Official Title of Study:

Phase Ib /II Clinical Trial of Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Pediatric Subjects with High Grade Primary CNS Malignancies CheckMate908: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 908

PROTOCOL(S) CA209-908

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 1B/2 CLINICAL TRIAL OF NIVOLUMAB AND NIVOLUMAB IN COMBINATION WITH IPILIMUMAB IN PEDIATRIC SUBJECTS WITH HIGH GRADE PRIMARY CNS MALIGANCIES

PROTOCOL CA209908

VERSION # 2.0

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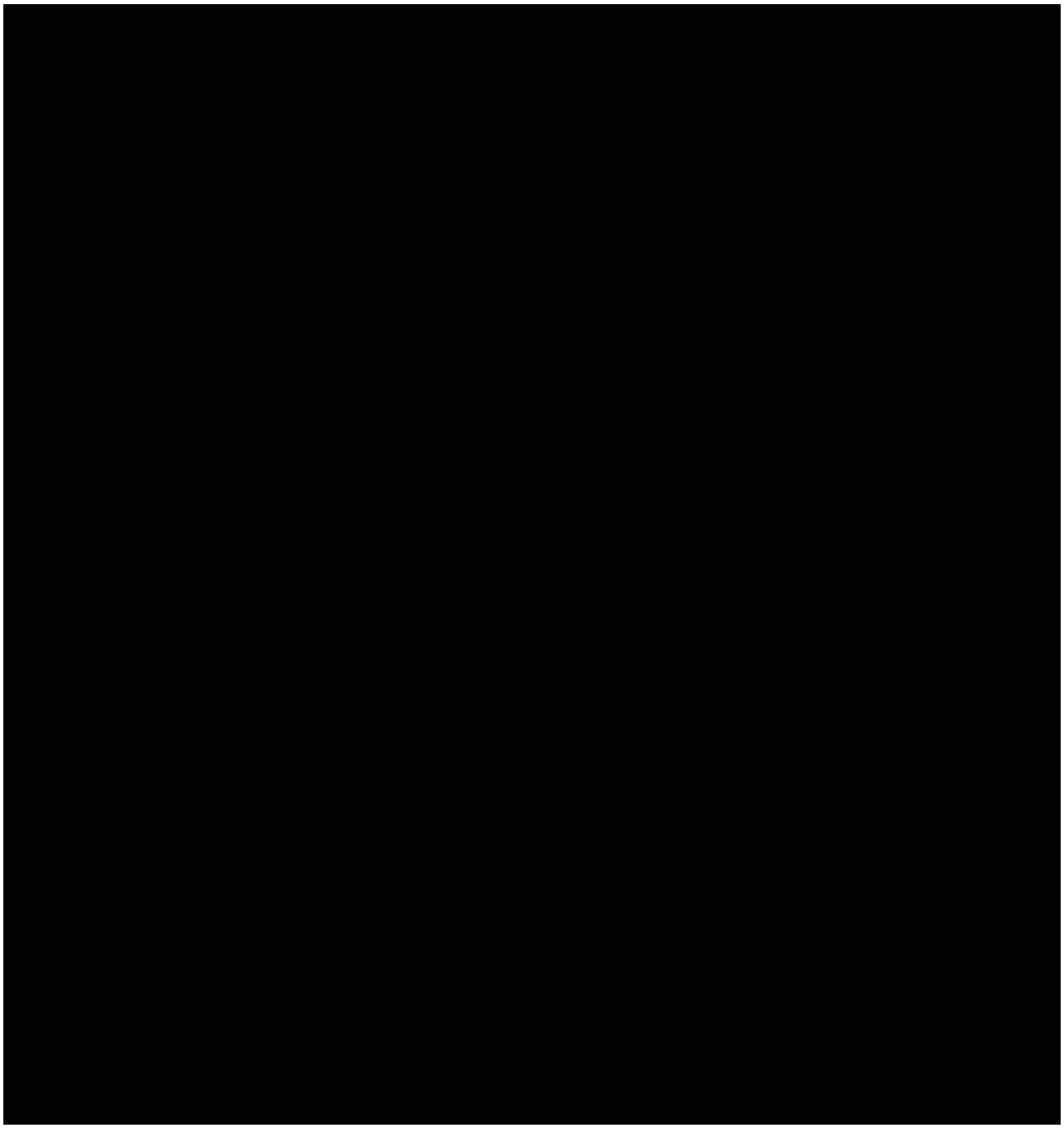


2 STUDY DESCRIPTION

2.1 Study Design

This is an open-label, sequential-arm Phase 1b/2 clinical trial of nivolumab monotherapy and of nivolumab plus ipilimumab in pediatric participants with high-grade primary CNS malignancies.

This study includes 5 cohorts and 2 modules as described below:

Cohorts are defined by tumor type (histology):

Cohort 1: N = 22 participants with newly-diagnosed DIPG, including midline glioma with H3K27M mutation

Cohort 2: N = 15 participants with recurrent or progressive non-brainstem HGG, regardless of mutation status, including glioblastoma

Cohort 3: N = 15 participants with relapsed or resistant medulloblastoma

Cohort 4: N = 10 participants with relapsed or resistant ependymoma

Cohort 5: N = 18 participants with other recurrent subtypes of high-grade CNS malignancy (eg, pineoblastoma, AT/RT, germ cell tumor, and others)

The above intended target numbers for each Module are approximate.

Molecular phenotype analyses will be performed according to institutional standard. Details on the molecular subtype of the individual tumors will be reported when they become available.

Treatments are defined by Module:

Module A: nivolumab 3 mg/kg every 2 weeks, as monotherapy, and

Module B: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks.

Enrollment to Module A will open in parallel for all cohorts. The first 6 participants in Cohort 1 who are treated and DLT evaluable will be evaluated for safety before additional participants are treated in that Cohort. Separately, the first 10 participants treated and DLT evaluable in the recurrent disease Cohorts 2-5 (combined) will be evaluated for safety before additional participants are treated (see Schema in Figure 2.1-1) in those Cohorts. At regularly-scheduled teleconferences, the Study Steering Committee (SSC) will review safety, assess potential DLTs, and make recommendations regarding reopening of enrollment. See additional details in Section 2.6.

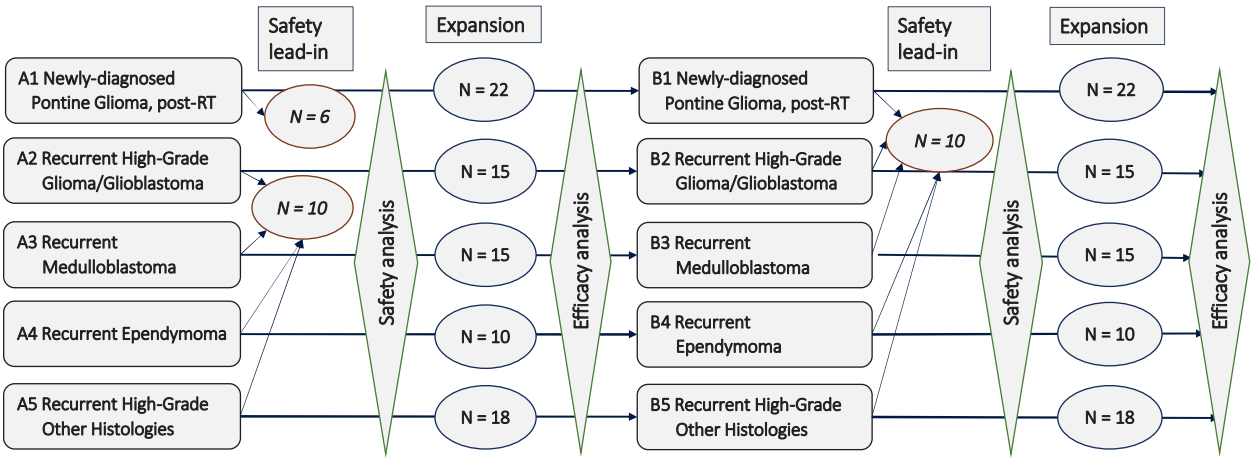
Based on determination of adequate safety, enrollment will re-open for evaluation of efficacy to complete the planned number of participants for each cohort in Module A expansion. Participants evaluated in the safety lead-in will be included for evaluation of efficacy (i.e., the 6 participants with DIPG evaluated for safety in Cohort 1 are included in the 22 planned participants).

Enrollment will begin in Module B, by cohort, based on completion of planned accrual in Module A or a decision of the SSC, therefore, accrual will not open in parallel for all cohorts into Module B. Investigators will be informed when Module B is open. For Module B, the first 10 participants treated and DLT evaluable in all cohorts combined will be evaluated for safety by the SCC before

additional participants are enrolled (see Schema in Figure 2.1-1) after which cohorts will be re-opened for full accrual in the expansion. (NOTE: An individual participant may not enroll in more than one Module.)

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Design Schematic



Notes:
- Cohorts are indicated by tumor type; Study Treatments are indicated as A = nivolumab and B = nivolumab + ipilimumab
- Safety is evaluated *across* cohorts (indicated as "lead-in), prior to expansion
- Efficacy is evaluated *by* cohort (indicated as Expansion), including lead-in population
- Module B opens, by cohort, when corresponding Module A is completed or upon decision of Steering Committee

.

2.2 Treatment Assignment

Subjects in Module A will receive nivolumab 3 mg/kg every 2 weeks, as monotherapy.

Subjects in Module B will receive nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

This SAP incorporates the following amendments:

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
Revised Protocol 01	11-Sep-2017	To clarify protocol text based on local reviews and investigator feedback.

2.5 Data Monitoring Committee

A Data Monitoring Committee will be established to provide oversight of safety and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of participants. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor participant safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. The DMC will meet at least every 6 months or more frequently as needed on an ad hoc basis. Information regarding DMC membership, responsibilities, and procedures are detailed in the DMC charter. The DMC will be informed should a safety signal emerge and may convene an ad-hoc meeting on its own initiative. Any major recommendation of the SSC (Section 2.6) will be communicated to the DMC. When required, adjudicated events will be submitted to the DMC and Health Authorities for review. The DMC will review all available data (safety and efficacy) data at each meeting. At the conclusion of each DMC meeting, the committee will provide the sponsor with a recommendation to continue, modify or terminate the study protocol based upon their review. Ultimately, decisions regarding the study protocol will be made by the sponsor in conjunction with advice from the SSC and the DMC.

2.6 Study Steering Committee

A Study Steering Committee (SSC) will be utilized. The SSC will be comprised of subject matter experts, with chairman representation from each of the Cooperative Groups (e.g., COG and ITCC). They will provide guidance for study design and input as needed throughout the course of the study including oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio in protocol CA209-908. Any major recommendation of the DMC will be communicated to the SSC. The Steering committee may recommend to:

- Terminate or continue accrual to any cohort for safety or efficacy reasons, and overall clinical risk/benefit considerations.
  a) a test for futility, as defined in Section 7.5.5.
  b) any of Cohorts 2-5 may be stopped at discretion of Steering Committee; for example, a cohort would be considered for closure if 0/9 evaluable participants experience an objective response
  c) keep accrual open beyond the stated target number of participants in any Cohort, for example, in order to study a sub-population with preliminary evidence of benefit
  d) proceed to Expansion phase based on safety criteria
- Open a newly-diagnosed HGG cohort, contingent on safety and preliminary efficacy in recurrent HGG, or another cohort based on new information
- Implement any clinically-indicated safety modifications (e.g., prolonging infusion duration) to be effective immediately.

Following review, the SSC will recommend continuation, modification, or discontinuation of this study based on reported safety and efficacy data.

3 OBJECTIVES

3.1 Primary

Safety Lead-in:

- To estimate the safety and tolerability of study treatment in pediatric participants with primary high-grade CNS tumors.

Expansion:

- To estimate the overall survival (OS) in pediatric participants with newly diagnosed DIPG. (Cohort 1)
- To estimate the progression-free survival (PFS) in pediatric participants with recurrent or progressive HGG. (Cohort 2)
- To estimate the PFS in pediatric participants with relapsed or resistant medulloblastoma. (Cohort 3)
- To estimate the PFS in pediatric participants with relapsed or resistant ependymoma. (Cohort 4)
- To estimate the PFS in pediatric participants with recurrent or progressive other rare CNS tumors (including pineoblastoma, atypical teratoid rhabdoid tumor (AT/RT), embryonic CNS tumors) (Cohort 5)

3.2 Secondary

Safety Lead-in:

- To describe any observed anti-tumor activity of study treatment in pediatric primary high-grade CNS tumors.

Expansion:

- To estimate the safety of study therapy in pediatric participants with newly diagnosed primary DIPG, recurrent or progressive HGG, recurrent or progressive primary medulloblastoma, recurrent or progressive primary ependymoma and recurrent or progressive other primary rare CNS tumors.
- To estimate the PFS and overall survival rate (OSr) in pediatric participants with newly diagnosed DIPG. (Cohort 1)
- To estimate the progression-free survival rate (PFSr), OS, and OSr in pediatric participants with recurrent or progressive HGG (Cohort 2)
- To estimate the PFSr, OS, and OSr in pediatric participants with relapsed or resistant medulloblastoma. (Cohort 3)

- To estimate the PFSr, OS, and OSr in pediatric participants with relapsed or resistant ependymoma. (Cohort 4)
- To estimate the PFSr and OS in pediatric participants with recurrent or progressive other rare CNS tumors (including pineoblastoma, AT/RT, other embryonic CNS tumors). (Cohort 5)

4 ENDPOINTS

4.1 Primary

4.1.1 Safety lead-in Phase

The primary objective of safety lead-in will be assessed by the incidence of DLTs, SAEs, and AEs leading to discontinuation.

A dose-limiting toxicity (DLT) is defined as a drug-related AE occurring in the first 6 weeks of study treatment. A participant will be considered evaluable for a DLT if study treatment was delayed > 2 weeks or was discontinued due to a related AE, or if planned study treatment (3 doses of nivolumab in Module A, 2 doses of nivolumab plus ipilimumab in Module B) was administered and safety evaluation after 6 weeks on study is available to the SSC. Participants who discontinue treatment for a reason other than toxicity (i.e., without DLT) are not evaluable for DLT and will be replaced in enrollment.

4.1.2 Expansion Phase

4.1.2.1 Overall Survival for Cohort 1

The primary endpoint of Cohort 1 is overall survival (OS). OS for Cohort 1 is defined as the time between the date of diagnosis and the date of death in Cohort 1. A participant who has not died will be censored at the last known alive date. OS will be followed continuously while participants are on study drug and every 3 months via in-person or phone contact during the survival follow-up phase of the study drug.

4.1.2.2 Progression Free Survival for Cohorts 2 to 5

The primary endpoints of Cohort 2-5 are progression-free survival (PFS).

PFS is defined as the time from first dose to the date of the first documented tumor progression or death due to any cause. Participants who die without a reported prior progression will be considered to have progressed on the date of death. Participants who did not have disease progression or die will be censored at the date of last evaluable tumor assessment. Participants who did not have any on study tumor assessment and did not die will be censored at the first dose date. PFS will be determined by investigators based on RANO criteria. First tumor assessments will occur at week 6 and 12, and will be at every 8 weeks for the first year and then every 12 weeks thereafter until disease progression is documented.

Table 4.1.2.2-1: Censoring Scheme used in Analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	First dose date	Censored
No on study tumor assessments and no death	First dose date	Censored
Documented progression	Date of the first documented progression per RANO	Progressed
Diagnostic surgical resection without documented progression prior or on the same day and without confirmed disease progression from tumor pathology	Date of last tumor assessment prior to initiation of the diagnostic surgical resection	Censored
No progression and no death	Date of last assessment for disease progression	Censored
Subsequent therapies, including new anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received, without progression reported prior or on the same day	Date of last assessment for disease progression prior to initiation of the subsequent therapy	Censored
Death without progression	Date of death	Progressed

4.2 Secondary

4.2.1 Safety

Incidence of AEs, SAEs, drug-related AEs, AEs leading to discontinuation, and death. Incidence of laboratory abnormalities.

4.2.2 Progression Free Survival for Cohort 1

Definition of PFS is the same as Section 4.1.2.2

4.2.3 Overall Survival Rate at 12 Months (OS(12)) for Cohorts 1 to 4

OS(12) is the proportion of subjects who are alive at 12 months, measured as the survival rate at 12 months from Kaplan-Meier product limit cumulative probability.

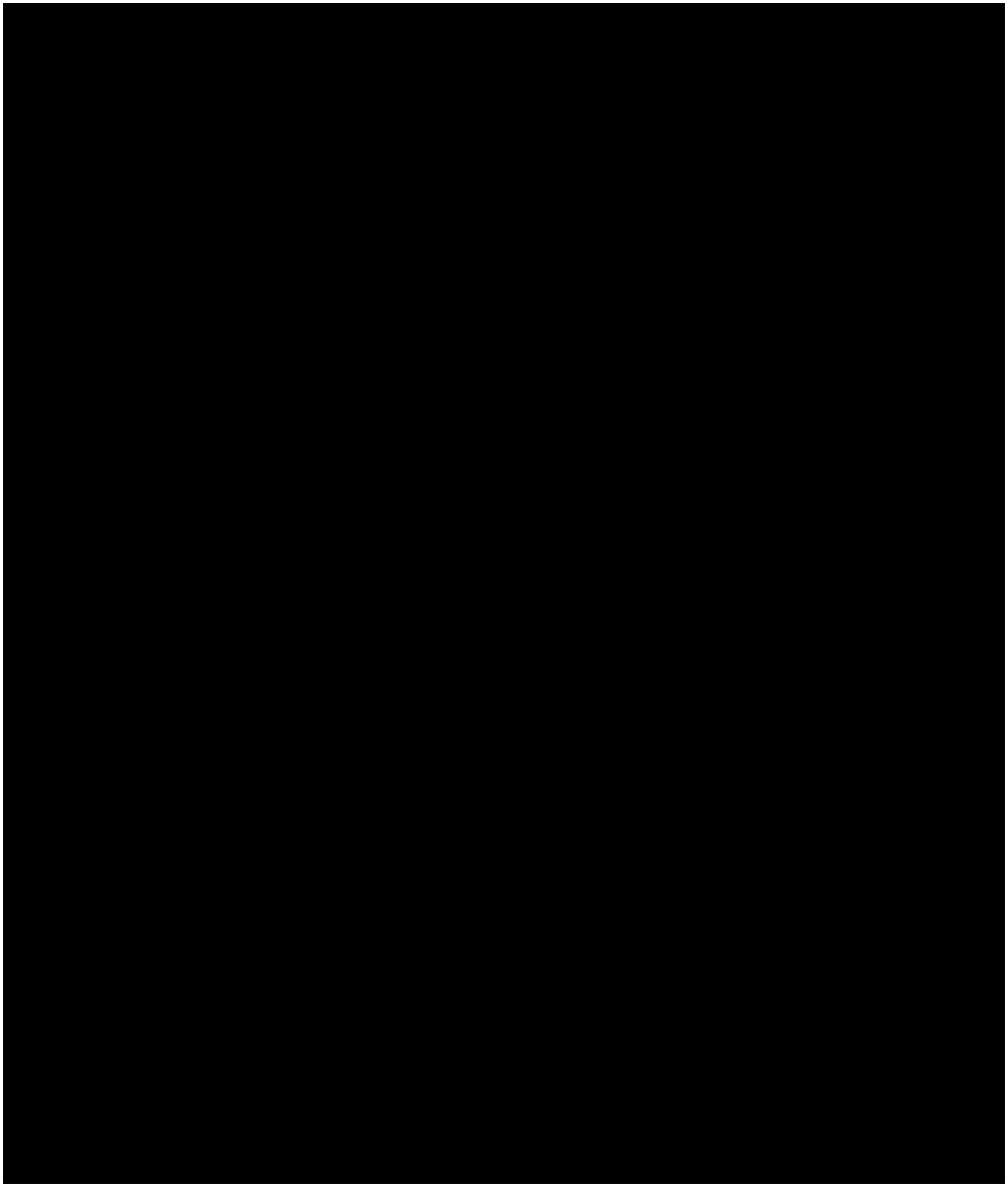
4.2.4 Progression Free Survival Rate at Time t (PFS(t)) for Cohort 2 to 5

PFS(t) is proportion of subjects who are progression free and alive at time t following first dose date, measured as the survival rate at time t from Kaplan-Meier product limit cumulative probability of progression free. PFS(6) will be assessed for Cohorts 2 to 4 and PFS(6) will be assessed for Cohort 5.

4.2.5 Overall Survival (OS) for Cohorts 2 to 4

OS for Cohort 2 to 4 is defined as the time between the randomization date and the date of death. A participant who has not died will be censored at the last known alive date. OS will be followed

continuously while participants are on study drug and every 3 months via in-person or phone contact during the survival follow-up phase of the study drug.



5 SAMPLE SIZE AND POWER

[redacted]

By applying the above methodology, the intended target number of participants (N) for cohort 1-4 are obtained as follows:

Cohort 1: 22 participants are required (17 events) for each cohort. This assumes 80% power with a one sided Type 1 error of 10%, a historical median OS of 9 months [redacted], 1-year accrual, 2-year follow-up, and a target effect size of median OS 15 months.

Cohort 2: 15 participants are required for each cohort. This assumes 80% power with a one-sided Type 1 error of 10%, a historical PFS(6) of 18% [redacted], one-year accrual, one-year follow-up, a target PFS(6) of 38%. An interim analysis based on PFS(6) for futility only will be conducted after at least 8 of the planned number of participants are enrolled with 6 months follow-up. In addition, all other available efficacy data will be evaluated in the futility analysis. [redacted] Details of the futility criteria and simulations will be contained in the Statistical Analysis Plan (SAP).

Cohort 3: 15 participants are required for each cohort. This assumes 80% power with a one-sided Type 1 error of 10%, 1-year accrual and 1-year follow-up, a historical median PFS(4) of 18% and a target PFS(4) of 38% ([redacted] equivalent to PFS(6) of 23%). An interim analysis based on PFS(6) for futility only will be conducted after at least 8 of the planned number of participants are enrolled with 6 months follow-up. In addition all other available efficacy data will be evaluated in the futility analysis.

Cohort 4: 10 participants are required for each cohort. This assumes at least 80% power with a one-sided Type 1 error of 10%, a historical median PFS of 2.1 months [redacted], 1-year accrual, 1-year follow-up, and a target median PFS of 4.4 months.

Cohort 5: 18 participants are required for each cohort. Sample sizes each of the expansion Cohorts A5 and B5 is not based on statistical considerations as these cohorts contain various tumor types. However, if the disease control rate at 12 months is 30%, 18 participants provide 21% precision for the estimate.

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.

[redacted]

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 100 days 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 100 days of the last dose of study.

6.2 Treatment Regimens

For each of the 5 cohorts, subjects in module A will receive nivolumab 3 mg/kg every 2 weeks; subjects in Module B will receive nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks.

6.3 Populations for Analyses

Population	Description
Enrolled	All participants who sign informed consent. This is the dataset for disposition.
Treated	All enrolled participants who received at least one dose of study drug. This is the dataset for safety evaluation.
Safety Lead-in participants	In Module A, the first 14 DLT-evaluable participants in Cohort 1 and the first 10 DLT-evaluable participants in Cohorts 2-5; in Module B, the first 10 DLT-evaluable participants.
Response-evaluable participants	All treated participants with measurable disease at a baseline tumor assessment (Source: CRF).
[redacted]	

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category, grouped by cohort and treatment (module). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by treatment group (with total) using the mean, standard deviation, median, minimum and maximum values. If a missing category is not being presented in the data display, only those subjects with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distributions (i.e. progression free survival, overall survival [redacted]) will be estimated using Kaplan Meier techniques. When appropriate, the median along with the corresponding log-log transformed 95% CI will be estimated. Rates at fixed timepoints (e.g. OS at 12 months) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals[10]. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[11].

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all enrolled and treated subjects by cohorts and treatments. First dosing date, country, investigational site will be presented in a by subject listing of accrual for each cohort and treament.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized by cohort and treatment group. 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 [redacted] listings.

At Entrance:

- Subjects at age >= 22 or < 6 months
- Subjects have not received standard of care
- without previous first line treatment with at least radiotherapy and temozolomide (for Cohorts 1and 1b only)
- Subjects with prior treatment of an anti-PD-1, anti PD-L1 and L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co stimulation or checkpoint pathway
- Subjects without LPS (for subjects <=16 years old) or Karnofsky(for subjects >16 years old) performance status of 60 or higher
- Subjects with tumor size > 6 cm.
- Steroid (Dexamethasone or equivalent) use >0.05mg/kg/day

On-study:

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) other than study therapy while on study therapy.
- Subjects treated differently than as assigned (subjects who received the wrong treatment, excluding the never treated).
- Steroid (Dexamethasone or equivalent) use >0.05mg/kg

Listings will also be provided.

7.3 Study Population

Unless otherwise specified, the following analyses will be presented by cohort and treatment group as "treated"

7.3.1 Subject Disposition

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

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by cohort and treatment group as treated. Reason for discontinuation will be derived from subject status CRF page.

A subject listing for all treated subjects will be provided showing the subject's first and last dosing date, off study date and reason for going off-study. A subject listing for subjects not treated will also be provided, showing the subject's race, gender, age, consent date and reason for not being treated.

7.3.2 Demographics and Baseline Characteristics

The following baseline characteristics will be summarized by cohort and treatment group. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age category I (<18, ≥18)
- Age category II (<2, 2- <12, 12-<18, ≥ 18)
- Gender (male, female)
- Race (white, black, asian, other)
- Ethnicity (hispanic or non-hispanic, for US subjects only)
- Region (US/Canada, Europe, Rest of the World)
- Presence of a measurable lesion at baseline (Yes, No)
- Baseline performance status
- Height and Weight (descriptive statistics)
- Steroid Use (Yes, No)
- Time from Initial Disease Diagnosis to first dose date (<6 months,6-<12 months, 12-<18 months,18-<24 months, ≥24 months)
- All lesions (Investigator Tumor Assessments at Baseline): sites of disease, number of disease sites per subject.
- Target lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of longest diameter of target lesion.

[redacted]

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Therapy

The following will be summarized by cohort and treatment group.

- Prior systemic cancer therapy (yes/no)
- Prior agent received (generic name)
- Prior surgery related to cancer (yes/no)
- Prior radiotherapy (yes/no)

Agents and medication will be reported using the generic name. A listing by subject will also be provided including prior/current non study medication.

7.3.5 Baseline Examinations

Subjects with abnormal baseline physical exam results will be tabulated by examination criteria (eg neck, cardiovascular, lungs, etc), by cohort and by treatment group.

7.3.6 Discrepancies Between IVRS and CRF Cohorts

Summary tables (cross-tabulations) by treatment group for cohorts will be provided to show any discrepancies between what was reported through IVRS vs. CRF data (baseline).

7.4 Extent of Exposure

Listings will include all available exposure data. Analyses will be performed by cohort and treatment group "as treated" in all treated subjects, unless otherwise specified.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by cohort, study therapy (nivolumab and ipilimumab) and treatment group:

- Number of doses received
- Cumulative dose
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.

Duration of treatment will be presented by treatment group using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose changes) and a listing of batch numbers will be also provided.

The key parameters used to calculate dosing data are shown below.

Table 7.4.1-1: Study Therapy Parameter Definitions

Monotherapy of Nivolumab	
	Nivolumab
Dosing schedule per protocol	3 mg/kg every 2 weeks
Dose	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative Dose	*Cum dose (mg/kg) is* sum of the doses (mg/kg) administered to a subject.
Relative dose intensity (%)	Cum dose (mg/kg)/[(Last dose date - Start dose date + 14) x 3/14] x 100
Duration of treatment	Last dose date - Start dose date +1

Nivolumab combined with Ipilimumab		
	Nivolumab	**Ipilimumab**
Dosing Schedule per Protocol	3 mg/kg every 3 weeks for 4 doses followed by 3 mg/kg every 2 weeks	1 mg/kg every 3 weeks for 4 doses
Dose	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF	*Dose (mg/kg)* is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF
Cumulative Dose	Cum Dose (mg/kg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.
Cycle Duration$_{(i)}$ (wk)	(Dose date$_{(i+1)}$ - Dose date$_{(i)}$)/7	N/A
Cycle Intensity$_{(i)}$ (mg/kg/wk)	Dose$_{(i)}$/Cycle Duration$_{(i)}$	N/A
Relative Cycle Intensity $_{(i)}$ (%)	(Cycle Intensity$_{(i)}$/intended dose per week) * 100	N/A
Relative Dose Intensity (%)	Sum of all Relative Cycle Intensities divided by N	Cum dose /[(Last dose date - Start dose date + 21) x 1/21] x 100
Duration of Treatment	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

For nivolumab, treatment may be delayed for up to a maximum of 6 weeks from the last dose. Subjects receiving nivolumab may be dosed no less than 12 days from the previous dose.

Each study medication infusion may be delayed independently. 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) from previous dose for any given study medication. The length of delay for nivolumab is defined as (duration of previous cycle in days - 14). The length of delay for ipilimumab is defined as (duration of previous cycle in days - 42). Dose delays for each study medication will be divided into following categories: on-time, 4 - 7 days, 8 - 14 days, 15 - 42, > 42 days. Reason for dose delay will be retrieved from the respective CRF dosing pages for each study medication. If different reasons for delay are recorded (in the same cycle), both the reasons will be reported.

The following parameters will be summarized by cohort and treatment group.

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

7.4.2.2 Infusion Interruptions and Rate Changes

Each nivolumab or ipilimumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages

The following parameters will be summarized by cohort and treatment group:

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

7.4.2.3 Dose Reductions/Escalation

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

[redacted]

7.5 Efficacy

The primary efficacy analyses will be performed on treated population for the final analysis. Unless otherwise specified, all analysis will be performed separately for each cohort and treatment group.

7.5.1 Overall Survival

7.5.1.1 Overall Survival for Cohort 1

As the primary efficacy endpoint of Cohort 1, the OS is defined as the time between the date of diagnosis and the date of death. A participant who has not died will be censored at the last known alive date.

The OS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. Median OS and the corresponding two-sided 80% confidence intervals using the log-log transformation will be computed.

The distribution of OS will also be compared against the historical control of an exponential distribution with median OS 9 months [redacted] using a one-sided one-sample log rank test when approximately 17 events have occurred or after each participant has been followed for at least 24 months.

As one of the secondary endpoints, survival rate at 12 months will be estimated using KM estimates on the OS curve and its corresponding 95% confidence interval will be derived based on Greenwood formula.

7.5.1.2 Overall Survival for Cohorts 2 to 4

As the secondary efficacy endpoints of cohorts 2 to 4, the OS is defined as the time between the first dose date and the date of death. A participant who has not died will be censored at the last known alive date.

The OS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. Median OS and the corresponding two-sided 95% confidence intervals using the log-log transformation will be computed.

Survival rate at 12 month will be estimated using KM estimates on the OS curve and its corresponding 95% confidence interval will be derived based on Greenwood formula.

7.5.1.3 Overall Survival for Cohort 5

OS will be listed. OS curve will be computed using Kaplan-Meier method for pooled indications and selected individual indications. The corresponding 95% confidence interval for median OS will be calculated via Brookmeyer and Crowley methodology using log-log transformation.

7.5.1.4 Subjects Follow Up

The extent of follow-up defined as the time between the first dose date (diagnosis date for cohort 1) and last known date alive (for subjects who are alive) or death date (for subjects who died). It will be summarized descriptively (median, min, max) for all treated subjects.

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 by treatment group. Subjects who died and subjects with a Last Known Date Alive on or after LPLV will have a value of '0' for currentness of follow-up. The currentness of follow-up will be categorized into the following categories: 0 days, 1-30 days, 31-60 days, 61-90 days, 91-120 days, 120-150 days, 151 or more days.

7.5.2 Progression Free Survival

For all cohorts, progression free survival (PFS) is defined as the time from first dose to the date of the first documented tumor progression or death due to any cause. Participants who die without a reported prior progression will be considered to have progressed on the date of death. Participants who did not have disease progression or die will be censored at the date of last evaluable tumor assessment. Participants who did not have any on study tumor assessment and did not die will be censored at the first dose date. PFS will be determined by investigators based on RANO criteria. First tumor assessments will occur at week 6 and 12, and will be at every 8 weeks for the first year and then every 12 weeks thereafter until disease progression is documented

7.5.2.1 Progression Free Survival for Cohorts 1

As one of the secondary endpoints of Cohort 1, PFS is estimated by Kaplan-Meier method and the corresponding 95% CI for median PFS will be calculated via Brookmeyer and Crowley methodology using log-log transformation. It will be analyzed at the time of the primary analysis.

7.5.2.2 Progression Free Survival for Cohorts 2 to 4

As the primary efficacy endpoints of cohorts 2 to 4, PFS curve will be estimated using the Kaplan-Meier (KM) method. Median PFS and the corresponding two-sided 80% confidence intervals using the log-log transformation will be computed.

The distribution of PFS for cohort 2 will be compared against the historical control of an exponential distribution with median PFS 2.25 months [redacted] using a one-sided one-sample log rank test when each participant has been followed for at least 12 months.

The distribution of PFS for cohort 3 will be compared against the historical control of an exponential distribution with PFS(4) equal to .18 using a one-sided one-sample log rank test when either 15 events have occurred or each participant has been followed for at least 12 months.

The distribution of PFS for cohort 4 will be compared against the historical control of an exponential distribution with median PFS equal to 2.1 months using a one-sided one-sample log rank test when either 10 events have occurred or each participant has been followed for at least 12 months.

In addition, as one of the secondary endpoints, PFS rate at 6 months will be estimated using KM estimates on the PFS curve and its corresponding 95% confidence interval will be derived based on Greenwood formula.

7.5.2.3 Progression Free Survival for Cohort 5

For each treatment group separately individual PFS will be listed by tumor type after each participant reaches 12 months follow-up. PFS curve will be estimated using the Kaplan-Meier (KM) method for all tumor types (pooled) and selected individual tumor types, if there is enough data. [redacted]

[redacted]

7.5.3 Subsequent Therapy

Subsequent therapy will be summarized and listed.

- Subsequent Therapy
  - Systemic anti-cancer therapy by drug name
  - Surgery

- Radiotherapy

A by-subject listing of follow-up therapy will be produced for subjects who had any subsequent therapy.

7.5.4 Interim Analyses

Cohorts A1 and B1: No interim analysis for futility is planned, as the Cohorts are expected to be fully enrolled when the OS endpoint becomes available. However, in Module A if other indications are stopped for futility, enrollment in Module B may be initiated based on recommendations of the Steering Committee.

Cohorts A2 and B2: The interim futility analysis for Cohorts A2 and B2 (HGG) will be conducted using PFS(6) and after at least 8 participants have been followed for 6 months. In addition, all other available efficacy data will be evaluated in the futility analysis.

Cohorts A3 and B3: An interim analysis based on PFS(6) for futility only will be conducted after at least 8 of the planned number of participants are enrolled with 6 months follow-up. In addition all other available efficacy data will be evaluated in the futility analysis.

Cohorts A4 and B4: No interim analysis for futility is planned as the sample size is too small.

Cohorts A5 and B5: No interim analysis for futility is planned as it is comprised of many diverse histologies. However, in Module A if other indications are stopped for futility enrollment in Module B may be initiated based on the recommendation of the Steering Committee.

Cohort 4 has a smaller sample size than the other cohorts (n=10) so it is not appropriate to add an interim analysis for futility.

For Cohorts 2 and 3: The Bayesian statistical methodology is described in Bayesian Adaptive Methods for Clinical Trial by Berry et al published in Chapman and Hall (2011) and is outlined here with adaptations from [redacted].

1) Once 8 subjects have been followed for at least 6 months a Cox proportional hazards model will be fit to interim data and estimate of hazard rate obtained.
2) Based on memoryless property of exponential survival times will be generated for each subject conditional on the observed data using the estimated hazard rate and one-sample log rank test applied to the fully enrolled cohort. The simulated trial will be declared success if log rank is significant.
3) Simulations will be repeated 1000 times. The predictive probability of success is defined as the proportion of simulated trials that are declared success based on observed interim data.
4) If predictive probability of success is <20%, futility may be declared. The totality of data will be considered in any decision to stop the cohort.

7.5.5 Final Analysis

The final analysis (study closure analysis) will be conducted once the last subject was followed for 100 days post treatment dose and 36-month survival follow up from study entry has been

conducted for each subject where applicable. The study will be closed after the final analyses, which include but not limited to updated safety analyses and OS, are completed.

7.6 Safety

Primary safety analyses will be performed for safety lead-in participants which includes 3 groups: in Module A, the first 14 DLT-evaluable participants in Cohort 1, and the first 10 DLT-evaluable participants in Cohorts 2-5;in Module B, the first 10 DLT-evaluable participants.

Secondary safety analyses will be performed for all treated subjects and summarized by cohort and treatment.

7.6.1 Deaths

See Core Safety SAP[1].

7.6.2 Serious Adverse Events

See Core Safety SAP[1].

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP[1].

7.6.4 Adverse Events Leading to Dose Delay of Study Therapy

See Core Safety SAP[1].

7.6.5 Adverse Events

See Core Safety SAP[1].

7.6.6 Select Adverse Events

See Core Safety SAP[1].

7.6.7 Immune-Mediated Adverse Events

The immune-mediated adverse events (IMAE) consist of a list of preferred terms grouped by specific category (e.g. pneumonitis, diarrhea/colitis, see Core Safety SAP for select adverse events). The IMAE categories and terms are defined by the Sponsor and the list that is the most current at the time of analysis will be used. This list will be based on the most current version of MedDRA at the time when integrated database will be built. The final list will be included as appendix in CSR.

Table 7.6.7-1: Immune-Mediated Adverse Events

Class Name of IMAE	PT TERM	Order in the output
PNEUMONITIS	PNEUMONITIS Interstitial lung disease	1
DIARRHEA/COLITIS	COLITIS DIARRHEA ENTEROCOLITIS	2
HEPATITIS	HEPATOTOXICITY HEPATITIS HEPATITIS ACUTE AUTOIMMUNE HEPATITIS ASPARTATE AMINOTRANSFERASE INCREASED ALANINE AMINOTRANSFERASE INCREASED BLOOD BILIRUBIN INCREASED HYPERBILIRUBINAEMIA BLOOD ALKALINE PHOSPHATASE INCREASED	3
ADRENAL INSUFFICIENCY	ADRENAL INSUFFICIENCY	4
HYPOTHYROIDISM/THYROIDITIS	HYPOTHYROIDISM THYROIDITIS ACUTE AUTOIMMUNE THYROIDITIS THYROIDITIS	5
HYPOTHYROIDISM	HYPOTHYROIDISM	6
THYROIDITIS	AUTOIMMUNE THYROIDITIS THYROIDITIS THYROIDITIS ACUTE	7
HYPERTHYROIDISM	HYPERTHYROIDISM	12
HYPOPHYSITIS	HYPOPHYSITIS	13
DIABETES MELLITUS	DIABETES MELLITUS DIABETIC KETOACIDOSIS	8
NEPHRITIS AND RENAL DYSFUNCTION	NEPHRITIS NEPHRITIS ALLERGIC TUBULOINTERSTITIAL NEPHRITIS RENAL FAILURE ACUTE RENAL FAILURE BLOOD CREATININE INCREASED	9
RASH	RASH Rash maculo-papular	10

Table 7.6.7-1:	Immune-Mediated Adverse Events	
Class Name of IMAE	**PT TERM**	**Order in the output**
HYPERSENSITIVITY	HYPERSENSITIVITY INFUSION RELATED REACTION	11
OTHER	Myasthenic Syndrome Myasthenia Gravis Myasthenia Gravis Crisis Myasthenic Syndrome Demyelination Event Demyelination Guillain-Barre Syndrome Guillain-Barre Syndrome Miller Fisher Syndrome Pancreatitis Event Autoimmune Pancreatitis Pancreatitis Pancreatitis Acute Pancreatitis Necrotising Uveitis Event Chorioretinitis Cyclitis Intermediate uveitis Iridocyclitis Iritis Uveitis	14

All summaries in the following subsections for IMAEs based on extended follow-up (100 day window after the last dose).

7.6.7.1 Incidence of IMAEs

Immune-Mediated AEs by worst CTC grade (both classifications, that are, "Any Grade, Grade 3-4, Grade 5" and "Worst CTC Grade", unless noted otherwise) will be summarized by Category/PT for each category:

- Summary of any endocrine IMAE
- Summary of IMAE where immune modulating medication was initiated
- Summary of IMAEs [only by Worst CTC Grade]
- Summary of endocrine serious IMAEs
- Summary of serious IMAEs where immune modulating medication was initiated
- Summary of any endocrine IMAEs leading to dose delay or reduction
- Summary of IMAEs leading to dose delay or reduction where immune modulating medication was initiated
- Summary of endocrine IMAEs leading to discontinuation
- Summary of IMAEs leading to discontinuation where immune modulating medication was initiated

7.6.7.2 Management of IMAEs

Following summaries will be presented

- Summary of duration of immune modulating concomitant medication for IMAE management
- Summary of immune modulating concomitant medication for IMAE management
- Summary of immune modulating concomitant medication for Grade 3 to 5 IMAEs management

7.6.7.3 Time to Onset and Resolution of IMAEs

Time to onset and resolution for IMAEs will be analyzed. Following summaries will be presented

- Summary of time to onset of endocrine IMAE
- Summary of time to onset of IMAEs where immune modulating medication was initiated
- Summary of time to resolution of endocrine IMAEs
- Summary of time to resolution of endocrine IMAEs where immune modulating medication was initiated

7.6.7.4 Re-Challenge

Subjects who had infusion of nivolumab after the onset of IMAE were considered re-challenged subjects. Following summary will be presented for re-challenged subjects.

- Summary of subjects who were re-challenged with nivolumab by IMAE category

Listings of IMAEs will also be provided

7.6.8 Immune Modulating Medication

See Core Safety SAP[1].

7.6.9 Multiple Events

See Core Safety SAP[1].

7.6.10 Clinical Laboratory Evaluations

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test. ALT and AST ULN provided by the external vendor will be used rather than the protocol specified fixed ULN of 45 for clinical laboratory toxicity grading for consistency across Nivo program.

7.6.10.1 Hematology

See Core Safety SAP[1].

7.6.10.2 Serum Chemistry

See Core Safety SAP[1].

[redacted]

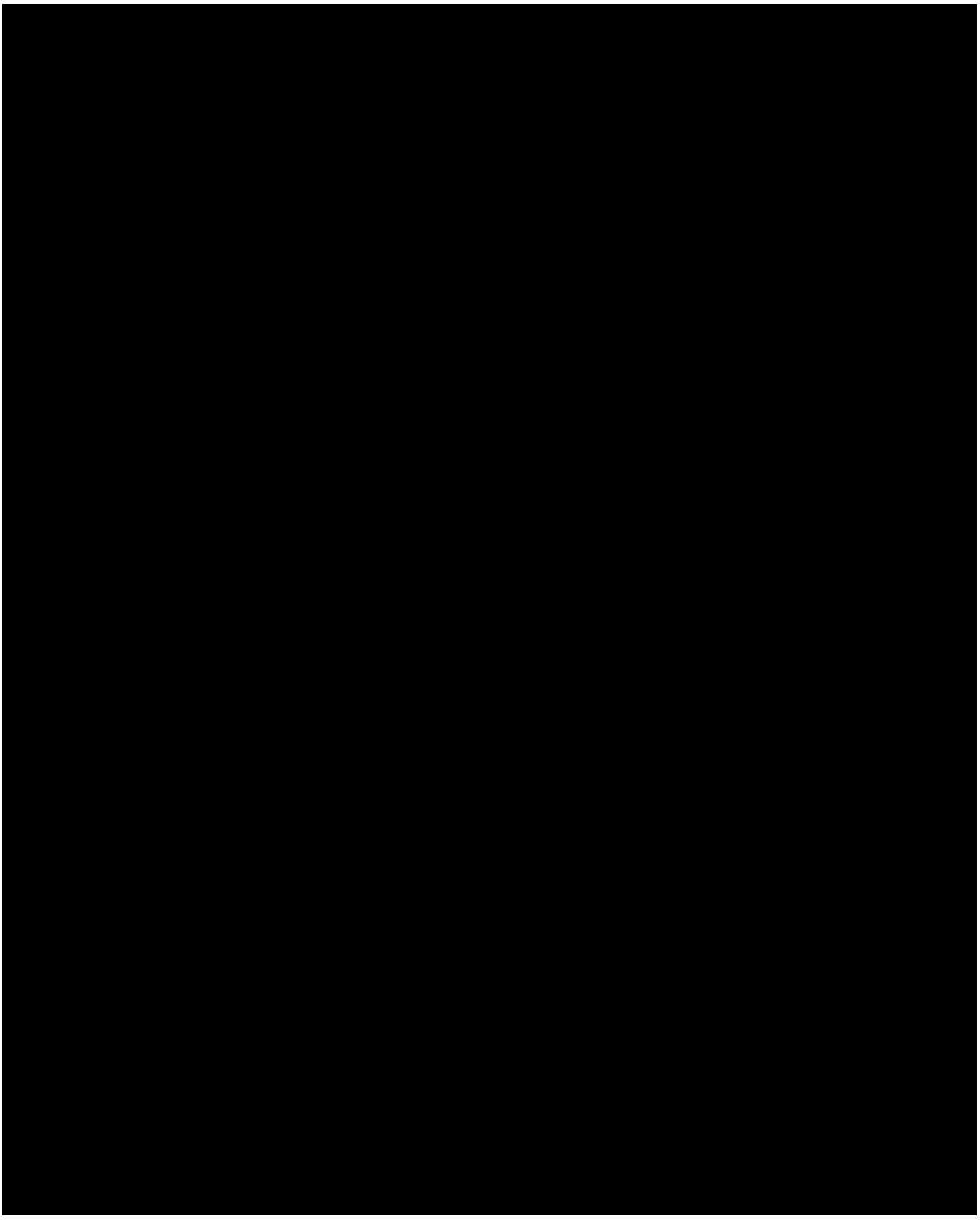
7.6.12 Vital Signs

See Core Safety SAP[1].

7.7 Pregnancy

See Core Safety SAP[1].

[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[12]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[13].

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 date alive day 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 date alive day
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive day

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 cases where 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 may 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.

[redacted]

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

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. [redacted] Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Initial version dated 18-Apr-2018
2.0		Section 4.2.4 - updated to PFS(6) from PFS(12) to be consistent with table 4-1 of protocol Section 7.2.2- Added "=" to ">=22" in first criteria Section 7.3.2 - Removed baseline pathology (gliobastoma, gliosarcoma) as it is not relevant for this study Section 7.3.6 - Removed "Presence of a measureable lesion at baseline (Yes, No) since this study was not stratified by presence of measurable disease" Section 7.4.1 - Changed dose of ipi from 3 to 1 in formula for relative dose intensity Section 7.5.6 - New Section Section 7.6.10 Added statement regarding use of vendor ULN for ALT and AST [redacted]