

Statistical Analysis Plan for

**A RANDOMIZED PHASE 3 OPEN LABEL STUDY OF NIVOLUMAB VS.
TEMOZOLOMIDE IN COMBINATION WITH RADIATION THERAPY IN NEWLY
DIAGNOSED ADULT SUBJECTS WITH UNMETHYLATED MGMT (TUMOR 06-
METHYLGUANINE DNA METHYLTRANSFERASE) GLIOBLASTOMA**

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**STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT**

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METHYLGUANINE DNA METHYLTRANSFERASE) GLIOBLASTOMA**

PROTOCOL(S) CA209498

VERSION # 3.0

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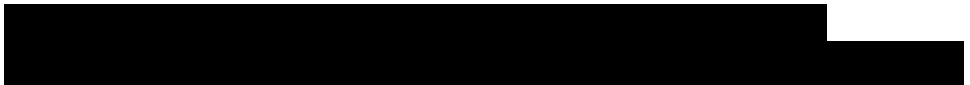
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[REDACTED]

[REDACTED]

[REDACTED]

2 STUDY DESCRIPTION

2.1 Study Design

This study will enroll subjects with newly-diagnosed glioblastoma (GBM), following surgical resection of the tumor. After informed consent is obtained, subjects will enter the screening phase. Tumor tissue will be evaluated for MGMT methylation by a central laboratory assay.

[REDACTED]

Post-operative baseline MRI following consensus recommendations, must be obtained prior to randomization. It is strongly recommended that this scan be obtained < 72hrs or > 14 days post-surgery in order to minimize artifact. There is no requirement that this baseline scan be performed on a “qualified” machine (a qualified MRI is one that meets the Imaging Manual specifications and has been validated with the required phantom scan). If a post-operative MRI is not available, a high-quality, contrast-enhanced CT scan may be performed initially, but in this case a contrast-enhanced MRI must be performed prior to randomization (> 2 weeks post-operative preferred).

Subjects with a central laboratory result of **un**methyated MGMT may continue in the **screening phase**, in which eligibility for randomization will be documented and baseline demographic and disease information submitted

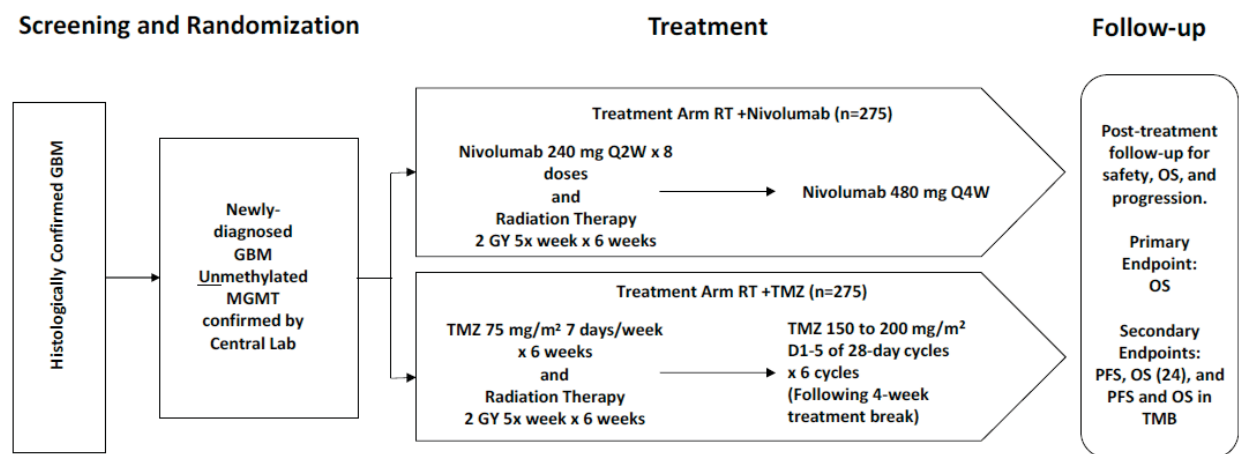
When ready to begin study treatment, subjects will proceed to the **treatment phase** of the study. The treatment phase will consist of an induction phase (chemoradiation therapy) followed by 4 weeks break and maintenance temozolomide therapy; for details, see Figure 2.1-1. All subjects who enter the treatment phase, i.e., all randomized subjects, will be followed for safety and tolerability, tumor progression and survival. A contrast-enhanced MRI should be performed 4 weeks (± 7 days) after completing radiation therapy, then every 8 weeks (± 7 days) until progression regardless of treatment schedule or dose delays. Tumor progression will be assessed using Radiologic Assessment in Neuro-Oncology criteria (RANO). Additional assessments will be performed for cognitive function, neurologic function, biomarkers and patient-reported quality of life outcomes.

After cessation of study treatment for any reason, all randomized subjects will enter a **follow up** phase. In the short-term, visits are defined for reporting of treatment-related adverse events. All subjects in whom disease progression had not been detected at the time study treatment is stopped will be followed closely for progression with contrast enhanced MRI every 8 weeks (± 7 days) until progression. After progression, subjects **MUST** be followed for survival (primary endpoint); subsequent treatments will be reported.

Baseline and all subsequent scans will be submitted to a blinded independent radiology review committee (BIRC) for archiving, once the subject is randomized and throughout the study period.

A Data Monitoring Committee (DMC) will meet regularly during the study to ensure that subject safety is carefully monitored.

Figure 2.1-1: Study Design Schematic



2.1.1 Screening Phase

Subjects will provide consent for enrollment and tumor submission in the peri-operative period, so that MGMT status can be determined, but consent for randomization and study treatment should

be deferred until MGMT unmethylated status and eligibility is established. The clinical circumstances should be considered with respect to the timing of consent.

Following informed consent, subjects with histologic diagnosis of GBM and no evident exclusions will be enrolled via a call to an IVRS system, in order to obtain a subject number, after which tumor tissue will be submitted to the central laboratory. For details, see a centralized tumor tissue assay for MGMT is required for randomization. Therefore, the tumor sample should be submitted as soon as possible.

Eligibility will be established and baseline information submitted for subjects with a central laboratory result of unmethylated MGMT. A subject cannot be randomized until the result of the central laboratory MGMT is entered into the IVRS. Subjects without a confirmed result of unmethylated MGMT will be considered screen failures and will not be eligible for randomization. If the assay result is methylated or indeterminate MGMT, they may be enrolled onto another BMS study (if available) based on the same MGMT assay.

It is expected that corticosteroid therapy will be tapered to the maximum extent possible during this phase. Subjects who cannot tolerate tapering of steroids to < 20mg prednisone or < 3mg dexamethasone per day (or equivalent) are not eligible for randomization.

RT should begin within 42 days of surgical resection, but may be delayed if clinically required. Typically, the time from screening procedure to treatment should not exceed 28 days, but may be longer if clinically indicated. If repeat resection to improve tumor control is performed for newly-diagnosed GBM prior to any other therapy (e.g., upon referral to research site), the 42-day interval should restart at the time of this second surgery and a new post-operative MRI must be performed.

2.2 Treatment Assignment

After informed consent has been obtained, the subject must be enrolled into the study by calling an IVRS to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth of subject
- Gender (at birth) of subject

CA209498 is a randomized study. Central lab confirmation of MGMT un-methylated status must be received prior to the IVRS randomization call. Once enrolled in IVRS, enrolled subjects who meet all eligibility criteria, and are clinically ready to begin treatment, will be randomized through the IVRS. The following information is required for randomization:

- Subject number
- Date of birth of subject

- Extent of tumor resection: Complete or Partial

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to receive radiotherapy + nivolumab (RT+ nivolumab) or radiotherapy + temozolomide (RT + TMZ). MGMT methylation status will be transferred from the testing laboratory to the IVRS database.

The exact procedures for using the IVRS are detailed in the IVRS manual.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

This SAP (version 3.0) incorporates the following amendments:

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
Revised Protocol 01 (Incorporate Amendment 03)	12-Jan-2016	Added exclusion for subjects with prior hypersensitivity to dacarbazine (DTIC); Added definition of Suspected, Unexpected Serious Adverse Event Reaction (SUSAR) and statement of SUSAR reporting responsibilities.
Revised Protocol 02 (Incorporates Amendment 04)	24-Feb-016	Corrected the temozolomide dose modification guidance during maintenance temozolomide dosing; modified nivolumab dose delay and discontinuation criteria
Revised Protocol 03 (Incorporates Amendment 06 and Administrative Letter 01)	04-May-2016	Major changes implemented in this Amendment include <ol style="list-style-type: none"> 1) Eligibility criteria <ol style="list-style-type: none"> a) Add exclusion for Gliadel® wafer b) Permit baseline MRI to be performed up to 72 hours postoperatively. If only CT is available, an MRI must be obtained prior to randomization. c) Modified language for women of child-bearing potential 2) Modify cutoff values used to define complete vs partial resection for purposes of randomization

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
<p>Revised Protocol 04 (Incorporates amendment 08)</p>	<p>09-Nov-2016</p>	<p>4) Update language throughout to conform with the Health Authority requests</p> <p>[REDACTED]</p> <p>6) Clarify treatment plan</p> <p>a) Insert guidance for radiation therapy as an appendix (referenced in Section 3.1.2.2)</p> <p>b) Switch from 240mg Q2 wk to 480mg Q4 wk after 8 doses (rather than 16 weeks)</p> <p>c) Aligned start of nivolumab and start of temozolomide to within 7 days of randomization</p> <p>d) Clarify that TMZ dosing is per institutional standards and update dose modification table to conform with SmPC</p>
<p>Revised Protocol 05</p>	<p>15-Nov-2017</p>	<p>This amendment updates the nivolumab clinical information in GBM and safety management algorithms as a result of most recent version of the Investigator Brochure (version 15). The amendment also clarifies several items as well as corrects minor errors.</p> <p>[REDACTED]</p> <ul style="list-style-type: none"> Renal, Pulmonary, Hepatic, and Skin safety management algorithms revised based on IBv.15 <p>Time windows and technical descriptions around assessments and administration schedule have been added or expanded to allow for flexibility at the site level while not affecting the conduct or the analysis of the data.</p>
<p>Major changes included are:</p>		

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
(Incorporates Administrative Letters 04 and 05 and amendment 09)		1) Removal of the interim analysis for superiority of the primary endpoint of OS. 2) Addition of a secondary endpoint that evaluated, in newly diagnosed, unmethylated MGMT GBM, any relationship between OS or PFS and TMB in the RT + nivolumab arm compared to the RT + TMZ control arm.

2.5 Data monitoring Committee

An independent Data Monitoring Committee (DMC) has been established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio. Following review, the DMC will recommend continuation, modification, or discontinuation of this study based on reported safety and efficacy data. Details of DMC responsibilities and procedures are specified in the DMC charter¹. Representatives of the Sponsor will serve only as coordinators of the committee, without having full member responsibilities or privileges. In addition, the Sponsor will independently review safety data in a blinded manner to ensure that any safety issues are identified and addressed.

3 OBJECTIVES

3.1 Primary

To compare OS of nivolumab in addition to radiation therapy versus temozolomide in addition to radiation therapy in subjects with newly diagnosed GBM with unmethylated MGMT tumors after surgical resection

3.2 Secondary

- To compare investigator-assessed PFS of RT + nivolumab versus RT + TMZ
- To estimate the OS rate at 24 months (OS[24]) of RT + nivolumab versus RT + TMZ
- To evaluate, in newly diagnosed, unmethylated MGMT GBM, any relationship between OS or PFS and tumor mutational burden (TMB) in the RT+nivolumab arm compared to the RT+TMZ control arm



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4 ENDPOINTS

4.1 Primary

The primary endpoint is OS. OS is defined as the time between the date of randomization and the date of death due to any cause. A subject who has not died will be censored at the last known alive date.

4.2 Secondary

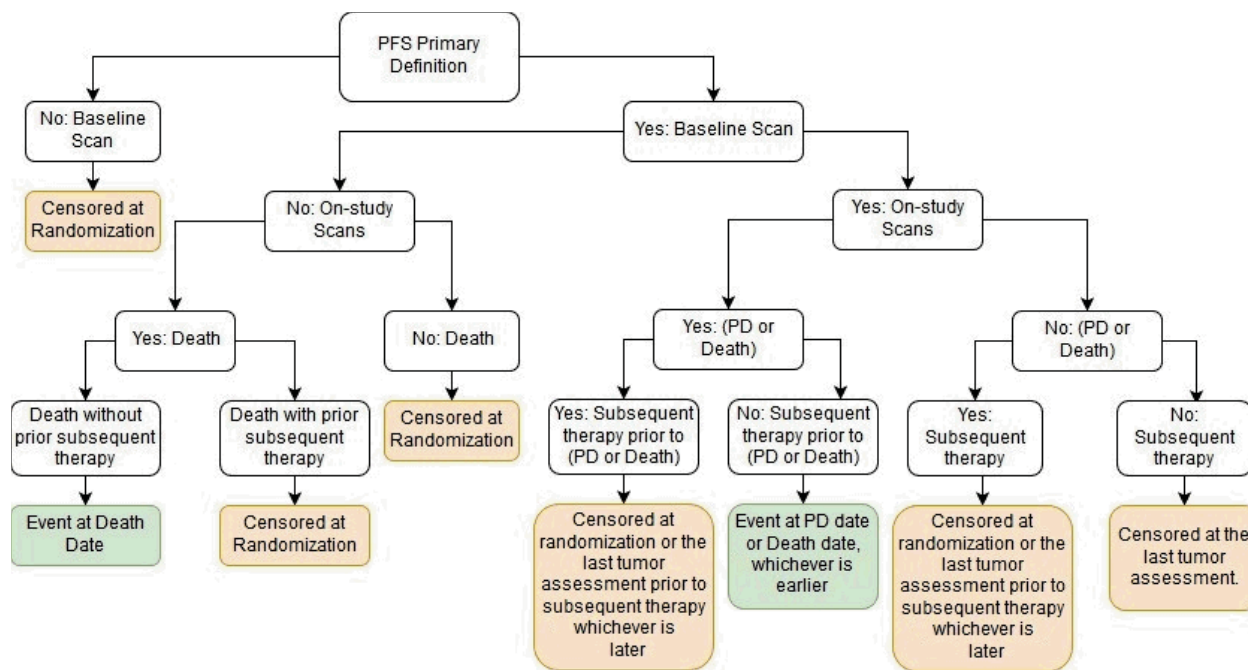
4.2.1 *Progression Free Survival*

PFS is defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. Subjects who did not have disease progression or who did not die will be censored at the date of last tumor assessment. Subjects who did not have any on study tumor assessment and did not have tumor progression or die will be censored at the randomization date. Subjects 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. Subjects who had surgical resection post start of study treatment will be censored at the last tumor assessment date prior to initiation of surgical resection. PFS will be determined by investigator reported response based on RANO criteria

The progression free survival rate at time T is defined as the probability that a subject has not progressed and is alive at time T following randomization.

Censoring rules for the primary analysis of PFS are presented in Figure 4.2.1-1 Alternate censoring rules for sensitivity analyses are specified in Section 7.5.3.2.

Figure 4.2.1-1: Graphic Display of PFS Primary Definition



4.2.2 Overall Survival at 24 months

Overall survival at 24 months is defined as probability of survival at 24 months based on Kaplan-Meier method. It will be estimated only when minimum follow-up is 24 months or more. In case the minimum follow-up is less than 24 months, but it is judged that data immaturity does not affect interpretability of the results, 24 months OS rate will be provided.



5 SAMPLE SIZE AND POWER

This is a Phase 3, randomized, open label, multicenter study of RT + nivolumab versus RT + TMZ in adult (≥ 18 years) subjects with newly diagnosed GBM subjects with unmethylated MGMT tumors.

Primary objective of the study is to compare the overall survival (OS) of RT+ nivolumab versus RT+TMZ in subjects with newly diagnosed GBM subjects with unmethylated MGMT tumors after surgery.

The sample size for this study is based on the following assumptions:

- 1) OS follows exponential distribution
- 2) Median OS in RT + TMZ arm is 13.0 months (Weller 2009⁵)
- 3) Hazard ratio (HR) of arm RT + nivolumab vs. RT + TMZ is 0.72, translated to median OS improvement of 5.0 months (13.0 months vs. 18.0 months for arm RT + TMZ and arm RT + nivolumab, respectively)

At least 390 events (i.e., death) provide 90% power to detect a hazard ration (HR) of 0.72 with an overall type 1 error of 0.05 (two-sided). This translates to an observed HR of 0.82 (median OS of 13.0 vs. 15.8 months) or less resulting in a statistically significant improvement.

Approximately 550 subjects will be randomized to the two arms (RT +nivolumab vs. RT + TMZ) in a 1:1 ratio stratified by complete or partial resection at baseline. Accrual will take approximately 10 months. The total duration of the study from start of randomization to final analysis of OS is expected to be approximately 33 months (10 months of accrual + 23 months of follow-up (Table 5-1)

Power calculations were done using East v 6.3.

Table 5-1: Key Parameters of Sample Size calculation

Assumptions	Analysis	Goal/Timing (from first subject randomized)	Significant Nominal p-value	Probability for declaring superiority Under HA/H0
$\alpha = 0.05$	Final	390	Superiority Observed nominal	90%/ 5%

Table 5-1: Key Parameters of Sample Size calculation

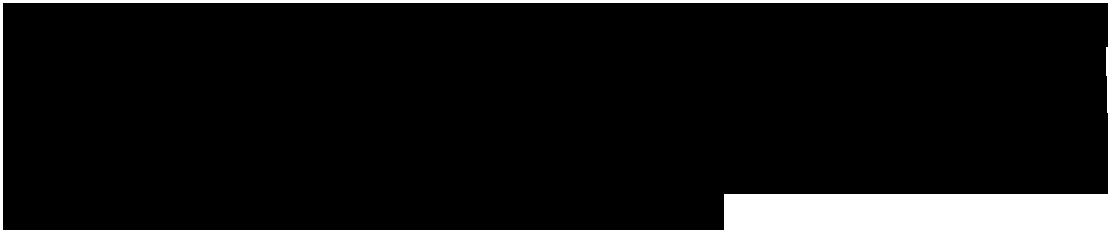


Assumptions	Analysis	Goal/Timing (from first subject randomized)	Significant Nominal p-value	Probability for declaring superiority Under HA/H0
Power = 90%	Superiority	OS events/ 33 months	p-value ≤ 0.05	
Control arm (RT+TMZ) median OS = 13.0 months;			No Superiority nominal p-value > 0.05	
Treatment arm (RT + Nivolumab) Median OS = 18.0 months HR = 0.72				

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

- 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. Evaluations (laboratory tests, pulse oximetry and vital signs) on the same date and time of the first dose of study treatment will be considered as baseline evaluations.
 - 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 on or prior to the first dose of study treatment:
 - ◆ For laboratory tests, the latest non missing labs value on or before first dose date (and time if collected) will be used as the baseline in the analyses. For 'LIPASE' and 'GLUCOSE', for treated subjects only, the last predose assessment with non-missing toxicity grade will be considered as baseline. If multiple assessments exist with the same collection date (and time if collected) and entry date and time, then the first observation is used as baseline.



- 
- 
- 
- Post baseline period:
 - On-treatment AEs will be defined as AEs with an onset date and time on or after the date and 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). For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment. No “subtracting rule” will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.
 - 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. For subjects who are off study treatment, evaluations should be within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment.

6.2 Treatment Regimens

The treatment group “**as randomized**” will be retrieved from the IVRS system

- Arm RT+TMZ: Radiotherapy + Temozolomide
- Arm RT+N: Radiotherapy + Nivolumab

The treatment group “**as treated**” will be the same as the arm as randomized by IVRS. However, if a subject received the incorrect drug for **the entire period** of treatment, the subject’s treatment group will be defined as the incorrect drug the subject actually received.

Unless otherwise specified, the safety analysis will be based on the treatment group “as treated”.

Unless otherwise specified, the efficacy analysis will be based on the treatment group “as randomized”.

6.3 Populations for Analyses

- All Enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- All Randomized subjects: All enrolled subjects who were randomized to any treatment arm.

- All Treated subjects: All randomized subjects who received at least one dose of study drug.
- TMB evaluable subjects: All randomized subjects who have a baseline TMB value.
- Response evaluable subjects: Randomized subjects with measurable lesions at baseline.

Unless otherwise specified, the safety analyses will include all treated subjects.

Unless otherwise specified, the efficacy analyses will include all randomized subjects.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, discrete variables will be tabulated by the frequency and proportion of subjects falling into each category, grouped by treatment. Percentages given in these tables will be rounded to the first decimal and, therefore, may not always sum to 100%. Percentages less than 0.1 will be indicated as '< 0.1'. Continuous variables will be summarized by treatment group using the mean, standard deviation, median, minimum, and maximum values.

Time-to-event variables (e.g. time-to resolution) will be analyzed using the Kaplan-Meier technique. When specified, the median will be reported along with 95% CI using Brookmeyer and Crowley method⁶ (using log-log transformation for constructing the confidence intervals⁷).

The conventions to be used for imputing missing and partial dates for analyses requiring dates are described in [Section 8](#).

7.1.1 Adverse Events, Serious Adverse Events, Multiple events, Select Adverse Events, Other Events of Special Interest and Immune-Mediated Adverse Events

Drug-related AEs are those events with relationship to study drug "Related", as recorded on the CRF. If the relationship to study drug is missing, the AE will be considered as drug-related.

Serious adverse events consist of AEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database.

Adverse events leading to study drug discontinuation are AEs with action taken regarding study drug(s) = "Drug was discontinued".

Adverse events leading to dose delay are AEs with action taken regarding study drug(s) = "Drug was delayed".

Adverse event that led to dose delay of the oral drug (similarly defined as dose omission or dose interruption) will be coded with action "Drug was interrupted".

Adverse events leading to dose reduction are AEs with action taken regarding study drug(s) = “Dose was reduced”.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the most recent version of the dictionary at the time of the database lock will be used. Adverse events results will be graded for severity using NCI Common Terminology Criteria for Adverse Events (CTCAE) and the most recent version of the criteria at the time of the database lock will be used.

In the AE summary tables, unless otherwise specified, subjects will be counted only once at the Preferred Term (PT), only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of subjects with an AE. The AE tables will be sorted by the SOCs and then PTs. SOC will be ordered by descending frequency overall and then alphabetically. PTs will be ordered within SOC by descending frequency overall and then alphabetically. The sorting will be done based on the ‘Any Grade’ column of the experimental arm when arms are presented side-by-side.

Unless otherwise specified, the AE summary tables will be restricted to on-treatment events regardless of the causality.

Analyses that take into account the multiple occurrences of a given adverse event will be conducted (see [Section 7.6.9](#)). To prepare these analyses, the CRF data will be processed according to standard BMS algorithms⁸ in order to collapse adverse event records into unique records based on the preferred term. These data will be presented as the rate per 100 person-years of exposure. These analyses will take into account all on-treatment events (allowing more than 1 event per subject) and the total exposure time. The person-year exposure will be computed as the sum over the subjects’ exposure expressed in years where the exposure time is defined as

- $(\text{Date of last dose of study treatment} - \text{date of first dose of study treatment} + 31 \text{ days (or 101 days, depending on the analysis)}) / 365.25$, for subject who are off study treatment and were followed for at least 30 days (or 100 days, depending on the analysis) after last dose of study treatment.
- $(\text{Last known alive date} - \text{date of first dose of study treatment} + 1) / 365.25$, for subjects who are still on-treatment or who are off study treatment and were followed less than 30 days (or 100 days depending on the analysis) after last dose of study treatment.

7.1.1.1 Select Adverse Events

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g. pulmonary events, gastrointestinal events categories, etc.). AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. Categories of select AEs may include subcategories (e.g. adrenal disorders, diabetes, pituitary disorders, and thyroid disorders are subcategories of the endocrine event category).

The list of MedDRA preferred terms used to identify select adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock will be provided by categories/sub-categories.

In addition to the frequency and worst severity of select AEs, time-to onset, time-to resolution, and time-to resolution where immune modulating medication was initiated will be analyzed for each specific category/subcategory when applicable.

Further details on the definitions of select adverse event, time-to onset and time-to resolution are described in [APPENDIX 1](#).

7.1.1.2 Other Events of Special Interest

Other events of special interest (OEOSI) consist of a list of preferred terms grouped by specific category (e.g. Myositis Event, Myocarditis Event, Demyelination Event, Guillain-Barre Syndrome, Pancreatitis Event, Uveitis Event, Encephalitis Event, Myasthenic Syndrome, Rhabdomyolysis Event, Graft Versus Host Disease). The list of MedDRA preferred terms used to identify OEOSI is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.1.3 Immune-Mediated Adverse Events

In order to further characterize AEs of special clinical interest analysis of immune-mediated AEs (IMAE) will be conducted. Immune-mediated AEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered as potential immune-mediated events by investigator, that meet the definition summarized below:

- those occurring within 100 days of the last dose,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).
- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

The list of MedDRA preferred terms used to identify Immune-Mediated adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

7.1.2 Laboratory Tests

Clinical laboratory parameters (hematology, serum chemistry and electrolytes) will be evaluated.

Laboratory tests will be graded using the NCI Common Terminology Criteria, and the most recent version of the criteria at the time of the database lock will be used.

Clinical laboratory data will be first analyzed using International System of Units (SI).

Analyses will be repeated using US conventional units.

In the laboratory summary tables, unless otherwise specified, subjects will be counted only once for each lab parameter according to their worst on treatment CTC grade (worst being the highest CTC grade). The laboratory tables and listings will be sorted by laboratory category, laboratory sub-category and laboratory test code sequence number.



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 randomized subjects. By subject listing of randomization date, first dosing date, country, investigational site will be provided.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized by treatment group for all randomized subjects. 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:

- Subjects receiving prior treatment for GBM other than Surgery
- Subjects with unknown or methylated MGMT status (using central lab)
- Subjects with KPS < 70



- Subjects with start of treatment more than 52 days after surgery.
- Subjects without baseline MRI scan

On-study:

- Subjects receiving anti-cancer therapy other than study therapy while on study therapy
- Subjects treated different than as randomized

Listings will also be provided.

7.3 Study Population

Unless otherwise specified, the following analyses will be presented by treatment group as “randomized” for all randomized subjects.

7.3.1 Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason for not being randomized. This analysis will be performed on the all enrolled subjects population only.

Number of subjects randomized but not treated along with the reason will be tabulated by treatment group as randomized.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group as treated. Reason for discontinuation will be derived from subject status CRF page. This analysis will be performed only on the all treated subjects population.

A subject listing for all treated subjects will be provided showing the subject’s off treatment date and whether the subject continue in the treatment period along with the reason for going off treatment period. A subject listing for all enrolled subjects will also be provided, showing the subject’s race, gender, age, consent date and reason for not being randomized (for those who were not randomized).

7.3.2 Demographics and Baseline Characteristics

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

- Age (descriptive statistics)
- Age category I (< 65, ≥ 65)
- Age category II (< 65, ≥ 65 - < 75, ≥ 75)
- Sex (Male vs. Female)
- Race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other)
- Region (US/Canada, Europe, Rest of the World)
- Disease diagnosis (Glioblastoma, Gliosarcoma)

- RPA Class (III, IV, V, Other)
- Type of Surgery (Complete Resection, Partial Resection, Other)
- Baseline Karnofsky performance status (100%, 95%, 90%, 80%, ...)
- Weight, BSA (descriptive statistics)
- Gene Promoter Methylation (Methylated, Unmethylated, Indeterminate, Not reported)
- Smoking Status (Current/Former, Never, Unknown, Not Reported)
- Baseline Corticosteroid Use (Based on average corticosteroid use 5 days prior to start of dosing (randomization date for subjects not treated))
- Time from Initial Disease Diagnosis to Randomization (in weeks) (Median, Range)
- All lesions (Investigator Tumor Assessments at Baseline): sites of disease, number of disease sites per subject.
- Measurable lesions (Investigator Tumor Assessments at Baseline): Presence of measurable lesions, site of measurable lesion, sum of products of perpendicular diameters of measurable lesions.
- Pre-treatment events: summarized by worst CTC grade presented by SOC/PT

Summary table (cross-tabulation) by treatment group for stratification factor (extent of tumor resection: complete vs partial) will be provided to show any discrepancies between what was reported through IVRS vs. CRF at baseline. This summary will be performed based on all randomized subjects.

A listing of randomization scheme presenting randomized treatment group and as treated treatment group will be provided for all randomized subjects.

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Therapy

The following will be summarized by treatment group.

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

Prior systemic cancer therapy agents and medication will be reported using the generic name. A summary table by ATC class and generic name and a listing by subject will also be provided including prior/current non study medication.

7.3.5 Baseline Examinations

Subjects with abnormal baseline physical examination will be listed by subject and will be tabulated by examination criteria (e.g. neck, cardiovascular, lungs, etc.), by treatment group.

7.4 Extent of Exposure

Listings will include all available exposure data. Analyses will be performed by 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 treatment group:

- Time from randomization and to first dose of study therapy (0 to 3 days, > 3 to 7, > 7 to 14, > 14 to 21, > 21 to 28, > 28)

Nivolumab

Dose (mg) is defined as total Dose administered (mg) and is collected on the CRF.

Cumulative Dose (mg) is sum of all the doses (mg) administered to a subject.

Duration of Treatment (in months): (Last dose date - Start dose date + 1) / 30.4375

Relative dose intensity (%): Sum of all relative dose intensity for all cycles/N where N is the number of cycles of nivolumab administered.

For each cycle i:

Cycle duration (i)(wk) = (dose date(i+1)-dose date (i))/7, when ith cycle is not the last.

Cycle duration (i)(wk) = 2, for the last cycle if ≤ 8 doses are taken.

Cycle duration (i)(wk) = 4, for the last cycle if > 8 doses are taken

Dose Intensity for cycle i (mg/wk) = Dose (i) / Cycle duration (i)

Relative Dose intensity for cycle i (%) = (Dose Intensity for cycle i (mg/wk) / 120(mg/wk))*100

The following parameters will be summarized (descriptive statistics) for subjects treated with nivolumab:

- 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. 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.

Temozolomide

Duration of Treatment (in weeks): (Dose end date - Dose start date + 1) / 7

Dose (mg/m²): total dose administered (in mg)/BSA at baseline (m²). Dose administered in mg at each dosing date is collected on the CRF

Cumulative dose (in mg/m²): sum of all the doses (mg/m²) administered to a subject

The following parameters will be summarized (descriptive statistics) by phase (induction and maintenance) for subjects treated with temozolomide:

- Duration of Treatment (in weeks)
- Cumulative dose (in mg/m²)
- Number of subjects that received less than 90% of planned dose

For maintenance phase only

- Number of subjects with dose escalation to 200mg/m²

For nivolumab and temozolomide: 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.

Radiotherapy

Duration of radiotherapy (in weeks): (Dose end date - Dose start date + 1) / 7

Cumulative dose (in Gy): sum of all the doses (Gy) administered to a subject as per CRF.

The following parameters will be summarized:

- Duration of radiotherapy (in weeks)
- Cumulative dose (in Gy)
- Number of subject that received less than 90% of planned dose

7.4.2 Modifications of Study Therapy

7.4.2.1 Nivolumab Dose delays

Each nivolumab infusion may be delayed. 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) for nivolumab. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized:

- 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 Nivolumab Infusion Interruptions and Rate Changes

Each nivolumab 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 for subjects treated with nivolumab:

- 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 Temozolomide Dose Modifications

The following parameters will be summarized by phase (induction and maintenance) for subjects treated with temozolomide:

- Number of subjects with at least one dose modification and reasons for dose modification.

7.4.2.4 Missing Radiotherapy

The number of subjects with at least one dose of radiotherapy missed and the reasons for missing dose will be tabulated for subjects treated with radiotherapy.

7.4.2.5 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 by treatment group will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term).

A by-subject listing will accompany the table.

[REDACTED]

[REDACTED]

[Redacted]

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

[Redacted]

- [Redacted]

[Redacted]

[Redacted]

7.4.3.3 Subsequent Cancer Therapy

Number and percentage of subjects receiving subsequent cancer therapies will be summarized. Categories include:

- Subsequent systemic therapy
- Subsequent surgery for treatment of tumors (restricted to tumor resection)
- Subsequent radiotherapy for treatment of tumors

A by-subject listing of subsequent cancer therapy will also be produced for all randomized subjects.

7.5 Efficacy

Unless otherwise specified, the primary population will consist in the all randomized subjects and the analysis will be performed by treatment group as “randomized”.

Unless stated otherwise, whenever a stratified analysis is specified, the following stratification factors (recorded at randomization as per IRT) will be used:

- Extent of tumor resection (complete or partial)

7.5.1 Overall Survival

7.5.1.1 Primary Analysis

The primary objective of the study is to compare the overall survival between treatment groups in all randomized subjects.

Overall survival will be compared between the treatment groups using stratified log-rank test (5% alpha level), the two-sided log-rank p-value will be reported. The stratified hazard ratio between the treatment groups will be presented along with the 95% CI.

OS will be estimated using the KM techniques. A two-sided 95% CI for median OS in each treatment group will be computed via the log-log transformation method. OS rates at fixed time points (e.g. 12, 18, 24 months, depending on the minimum follow-up) will be presented along with their associated 95% CIs. These estimates will be derived from the Kaplan Meier estimate and corresponding CIs will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. Minimum follow-up must be longer than the timepoint to generate the estimate. In case the minimum follow-up is less than the timepoint, but it is judged that data immaturity does not affect interpretability of the results, the estimate will be provided.

The status of subjects who are censored in the OS KM analysis will be tabulated for each treatment group using the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdraw consent, never treated)

To examine the assumption of proportional hazards in the Cox regression model, in addition to treatment, a time-dependent variable defined by treatment by time interaction will be added into the model. A two-sided Wald Chi-Square p-values of less than 0.1 will indicate a potential nonconstant treatment effect. In that case, additional exploratory analyses may be performed.

A by-subject listing will be presented including treatment arm, OS, whether the subject was censored, and if censored, the subject’s status.

7.5.1.2 OS sensitivity Analyses

The following OS sensitivity analyses will be performed:

- 1) OS will be compared between treatment groups using a two-sided unstratified log-rank test.
- 2) OS will be compared between the treatment groups using the strata as determined at baseline (CRF source). This analysis will be performed only if stratification variable at IVRS and at baseline disagree for at least 10% of the randomized subjects.
- 3) OS will be compared between the treatment groups using a two-sided stratified log-rank test in All treated subject population, using arm, as randomized. This analysis will be performed only if the proportion of randomized but never treated subjects exceeds 5%.
- 4) A multivariate Cox regression model will be used to estimate the treatment effect after including the following covariates measured at baseline: Backward selection method will be used to eliminate non-significant covariates at level 0.15.
 - a) Age (continuous covariate)
 - b) Steroid Use (Yes, No)
 - c) Performance Status (Karnofsky scale) (≤ 80 , > 80)

The level of the covariate normally associated with the worst prognosis will be coded as the reference level. The hazard ratio associated with treatment and with each of the baseline covariates will be presented along with associated 95% CIs.

7.5.1.3 Consistency of Treatment Effect on OS in Subsets

To assess consistency of treatment effects in different subsets, a “forest” plot of the OS hazard ratio (and 95% CI) will be produced for the following variables, but not limited to:

- Baseline measurable lesion (yes vs. no) (source: CRF)
- Region (US/Canada vs. Europe vs. Rest of World)
- Age categorization (< 65 , $\geq 65 - < 75$, ≥ 75 , ≥ 65)
- Age categorization (< 50 , $\geq 50 - < 65$)
- Gender (Male vs. Female)
- Race (White, African American, Asian, Other)
- RPA class (III, IV, V, other)
- Smoking status (yes vs. no, unknown)
- Baseline Performance Status (Karnofsky scale) (≤ 80 , > 80)
- Baseline Pathology (Glioblastoma vs. Gliosarcoma)
- Baseline Corticosteroid use (No, Yes)

If a subgroup category has less than 10 subjects in a treatment group, then HR will not be reported for that subgroup.

7.5.1.4 Subject Follow-Up

The extent of follow-up defined as the time between randomization date 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) in months for all randomized 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 (defined by last patient last visit date), will be summarized in months 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.

Minimum follow-up for OS, defined as the time from cutoff date to last subject's randomization date, will be summarized in months for all randomized subjects.

7.5.2 Interim Analysis

No interim analyses is planned for this study.

7.5.3 Progression Free Survival

7.5.3.1 Primary Analysis

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

PFS will be compared between the two randomized arms using two-sided (5% alpha level) stratified log-rank test. This comparison will only be tested if OS comparison is positive.

In addition, a stratified Cox proportional hazards regression model will be used to estimate hazard ratio between treatment groups along with the 95% CI.

PFS rates at 6, 9, 12, and 18 months will be estimated using KM estimates on the PFS curve for each treatment group. Minimum follow-up must be longer than the time point to generate the rate. The associated two-sided 95% CI will also be calculated.

The source of progression (death vs. progression) will be summarized by treatment group.

The status of subjects who are censored in the PFS KM analysis will be tabulated for each treatment group using the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdrawn consent, never treated)
- No baseline tumor assessment
- No on-study tumor assessment and no death

- Received subsequent anti-cancer therapy

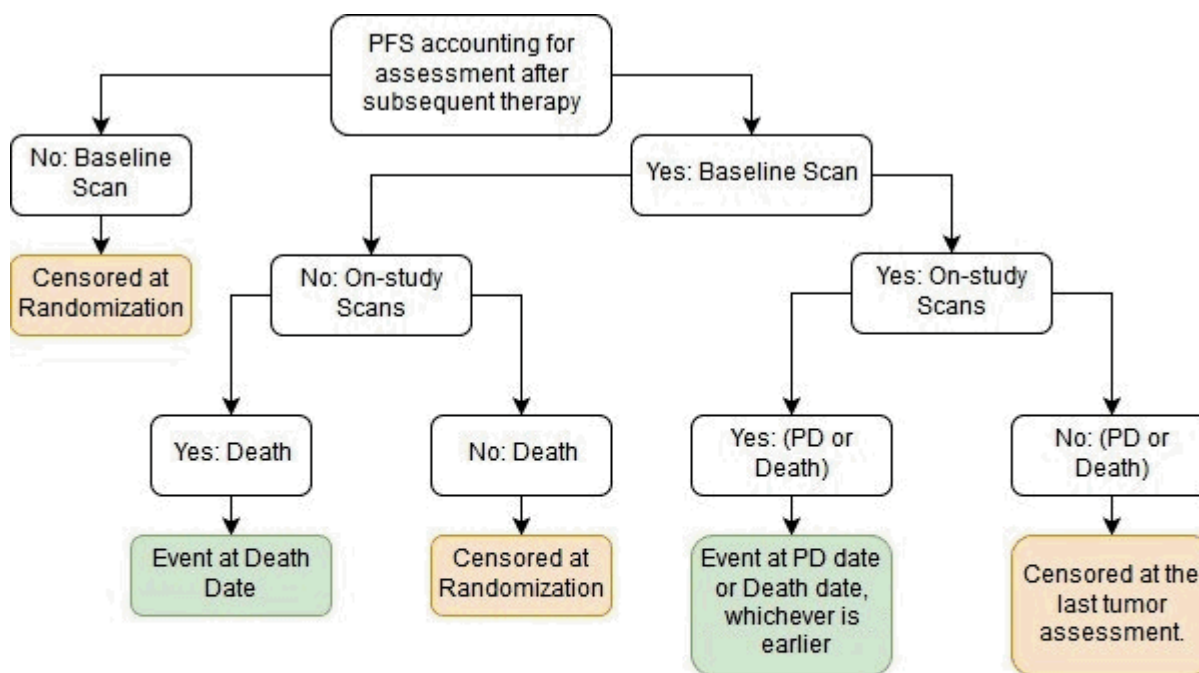
A by-subject listing will be presented including treatment arm, PFS, whether the subject was censored, and if censored, the subject’s status.

7.5.3.2 Sensitivity Analysis

Sensitivity analyses of PFS will also be performed using the following modification:

- 1) PFS accounting for assessment after subsequent therapy. It will be defined similar to the primary definition except that events (progression or death) and tumor assessments that occurred after subsequent anticancer therapy or diagnostic surgical resection will be taken into account (see censoring scheme 1 for sensitivity analysis in Figure 7.5.3.2-1).

Figure 7.5.3.2-1: Graphic Display of PFS Accounting for Assessment after Subsequent Therapy



- 2) PFS not considering clinical progression as event: It will be defined same as the primary definition except not considering clinical progression as progression event.
- 3) PFS accounting for assessment after subsequent therapy and not counting clinical progression as event: It will be defined same as sensitivity analysis #1 defined above except not considering clinical progression as progression event.

7.5.4 Overall Survival Rate at 24 Months

The OS[24] for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method and the corresponding two-sided 95% confidence intervals using log-log transformation will be computed. There will be no hypothesis testing for this endpoint.

7.5.5 Relationship between OS or PFS and TMB

This analysis will not be generated at the time of the primary lock, because - due to limited tissue availability and the need to use the samples for the MGMT promoter methylation bridging study - TMB analysis was put on hold.

7.5.6 Other Efficacy Analyses

7.5.6.1 Analysis of Objective Response Rate

The number and percentage of subjects in each category of BOR per investigator (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) will be presented, by treatment group. Estimates of response rate, along with its exact two-sided 95% CI by Clopper and Pearson⁹ will be presented, by treatment group. This analysis will be carried out on response-evaluable subjects.

A by-subject listing of best overall response will be presented including treatment group, best overall response per investigator and dates of CR/PR/progression.

A by-subject listing of per time point tumor assessments per investigator will be presented.

7.5.6.2 Time to Tumor Response and Duration of Response

Duration of response (DOR) and time to response (TTR) will also be evaluated for subjects who achieved confirmed PR or CR. The DOR for each treatment group will be estimated using the Kaplan-Meier (KM) product limit method and will be displayed graphically. A table will be produced presenting number of events, number of subjects involved, medians, and 95% CIs for the medians. The two-sided 95% CI in each treatment group will be computed based on a log-log transformation method.

TTR, which does not involve censoring, will be summarized by treatment group in all responders using descriptive statistics.

A by-subject listing will be presented including treatment group, time to response, duration of response, whether the subject was censored for duration of response, and, if so, the reason.

7.5.6.3 Analyses of Tumor Burden

The magnitude of reduction in tumor burden in response evaluable subjects with on-study tumor assessment will be summarized descriptively.

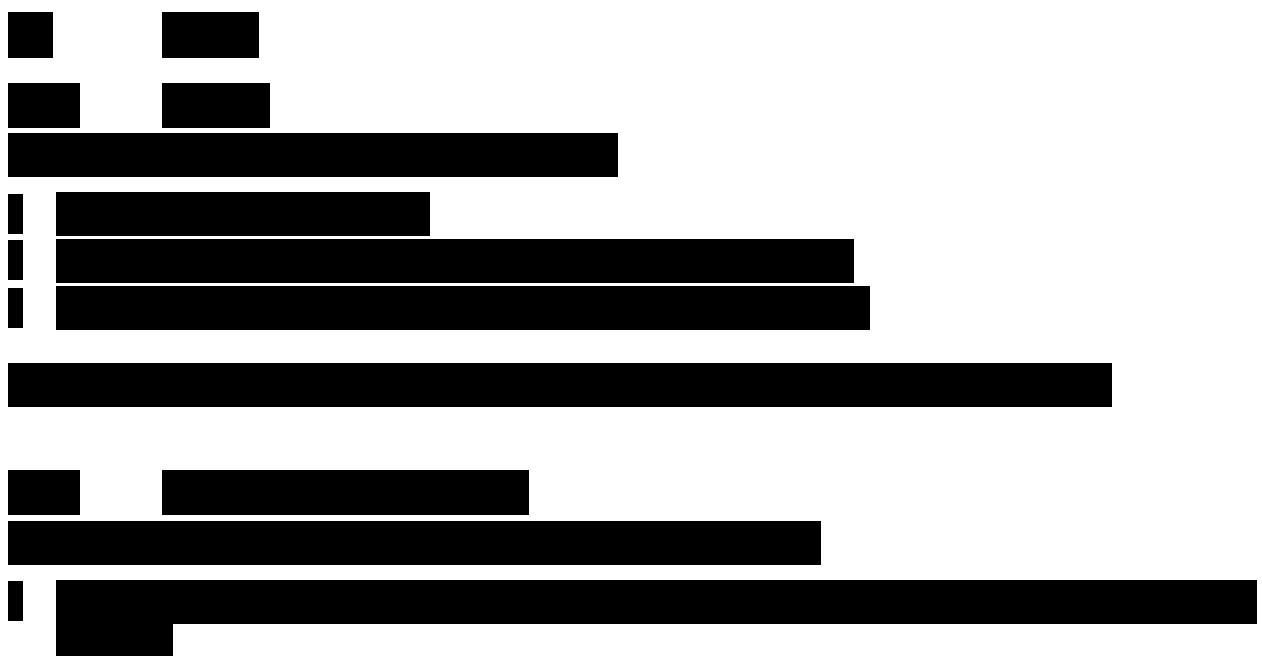
The following subject-level graphics will also be provided by treatment group as randomized:

- For all responders, time courses of the following events of interest will be graphically displayed: tumor response, progression, last dose received, and death.
- For response evaluable subjects with on-study tumor assessment, a waterfall plot showing the best reduction in measurable lesion based will be produced.
- For response-evaluable subjects with on-study tumor assessment, a plot of individual subjects' percent change in measurable lesion tumor burden from baseline will be produced.

7.5.6.4 Analysis of Subjects Treated beyond Progression

The following analysis may be conducted for subjects treated with RT plus nivolumab who are progressed:

- Summary of demographic and baseline characteristics by two groups (treated beyond initial progression or not treated beyond initial progression)
- Evaluation of survival for patients treated beyond initial progression vs. not treated beyond initial progression by a landmark analysis
- Plot of individual subjects' percent change in measurable lesion tumor burden from baseline.
- Time courses of the following events of interest will be graphically displayed in relation to OS: tumor response, progression, last dose received, on-treatment/subsequent surgery
- Summary of overall duration of treatment, number of doses received beyond initial progression, duration of treatment beyond initial progression.
- By-subject listing will include: overall duration of treatment, number of doses received beyond initial progression, duration of treatment beyond initial progression, OS



[REDACTED]

[REDACTED]

[REDACTED]

7.6.14 *Pregnancy*

A by-subject listing of pregnancy tests results will be provided for randomized female subjects.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Additional exploratory analyses may be performed. 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	Description
3.0	[REDACTED]	<p>Revision Date: 15-Jan-2019</p> <p><u>Section 2 Study Description</u>: Multiple changes are made in section 2 Study description in accordance with the amendments of the protocol.</p> <p><u>Section 2.1 Study Design</u>: “The treatment phase will consist of an induction phase (chemoradiation therapy) followed by 4 weeks break and maintenance temozolomide therapy” is added to define induction and maintenance phase for exposure analysis.</p>

Table 10-1: Document History

Version Number	Author	Description
		<p>[REDACTED]</p> <p>Sections 4.2.2 Overall Survival at 24 months, 7.5.1.1 Primary Analysis: A text is added that survival rate estimates can also be produced for timepoints beyond the minimum follow-up if it is judged appropriate.</p> <p>Section 4.3 Exploratory Endpoint(s) is restructured: Subsection for [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Section 5 SAMPLE SIZE AND POWER: “The progression free survival (PFS) , overall survival at 24 months (OS[24]), and OS and PFS in TMB-high patients are secondary endpoints. OS[24] is included as secondary endpoint to evaluate the improvement in long term survival.” is deleted as irrelevant in this section.</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

Table 10-1: Document History

Version Number	Author	Description
		<p>Section 7.2.2 Relevant Protocol Deviations: new deviation “Subjects without baseline MRI scan”.</p> <p>[REDACTED]</p> <p>Section 7.3.1 Subject Disposition: Analysis population is specified; description of listings is updated to be compliant with the CRF and support the tables.</p> <p>[REDACTED]</p> <p>Section 7.3.4 Prior Therapy: Summaries of agents by name and by ATC class are specified.</p> <p>Section 7.4.1 Administration of Study Therapy: The denominator for duration of treatment in months is corrected to 30.4375; definition of the last cycle length is corrected; terms “Dose Intensity”, “Relative Dose intensity” and the definitions are made compliant; populations for exposure analysis are restricted to subjects treated with a particular drug; definition of TMZ Dose (mg/m2) is corrected to be defined via BSA instead of weight; the following analyses for TMZ maintenance phase is removed: Cycles of treatment, Number of subjects completing 6 cycles; structure of the section is improved.</p> <p>Section 7.4.2 Modifications of Study Therapy: Populations for exposure analysis is restricted to subjects treated with a particular drug.</p> <p>Section 7.4.2.1 Nivolumab Dose delays: Definition of a delayed dose is added.</p> <p>Section 7.4.2.3 Radiotherapy and Temozolomide is split to 7.4.2.3 Temozolomide Dose Modifications and 7.4.2.4 Missing Radiotherapy for compliance of the analyses with the CRF</p> <p>[REDACTED]</p> <p>Section 7.4.3.3 Subsequent Cancer Therapy is moved from 7.5. Efficacy; subsequent surgeries for “Other” reason and with a specification which includes ‘RESECTION’ will be accounted for subsequent therapy.</p> <p>Section 7.5. Efficacy: Use of the stratification factor is specified.</p>

Table 10-1: Document History

Version Number	Author	Description
		<p>Section 7.5.1.1 Primary Analysis: a by-subject listing is added.</p> <p>Section 7.5.1.2 OS sensitivity Analyses: The covariate of prior surgery is delete from the multivariate analysis since the model is stratified by IVRS resection which would correlate with the covariate.</p> <p>Section 7.5.3.1 Primary Analysis: Censoring categories are added; a by-subject listing is added.</p> <p>Section 7.5.3.2 Sensitivity Analysis: Table 7.5.3.2-1 is replaced by figure 7.5.3.2-1.</p> <p>Section 7.5.5 Relationship between OS or PFS and TMB: new analysis.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Section 7.6 Safety: Reference to Core Safety SAP is replaced by the appropriate text due to retirement of Core Safety SAP.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

Table 10-1: Document History

Version Number	Author	Description
		<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p><u>Throughout the document:</u></p> <p>Multiple changes in the structure and language were made for the sake of compliance with the IO core SAP and without modification of the text meaning;</p> <p style="text-align: center;">Multiple editorial changes.</p>
2.0	[REDACTED]	<p style="text-align: center;">Revision Date: 19-Sep-2018</p> <p>Revised SAP according to protocol amendment 09. Major changes included in this amendment are:</p> <p style="text-align: center;">Removal of the interim analysis for superiority of the primary endpoint of OS.</p> <p style="text-align: center;">Addition of a secondary endpoint that evaluated, in newly diagnosed, unmethylated MGMT GBM, any relationship between OS or PFS and TMB in the RT + nivolumab arm compared to the RT + TMZ control arm.</p>
1.0	[REDACTED]	<p style="text-align: center;">Initial version dated 05-Jan-2017</p>

APPENDIX 2 MISSING AND PARTIAL RADIOTHERAPY AND SURGERY DATES IMPUTATION ALGORITHMS

Procedures – Imputation Rules.

If reported procedure start date is a full valid date then set start date equal to the date part of procedure start date.

In case of partial date use imputation rules described below:

- If only day is missing then
 - If month and year of procedure match month and year of first dose date then impute as date of first dose;
 - If month and year of procedure don't match month and year of first dose date then impute as first day of that month and year.
- If both day and month are missing, then impute as maximum between 01JAN of the year and date of the first dose;
- If date is completely missing or invalid then leave missing.

Note: Imputation is not applicable to data where start date is not collected (for example "PRIOR RADIOTHERAPY" CRF). Set start date to missing in this case.

If reported end date is a full valid date then set end date equal to the date part of the reported end date.

In case of partial date use imputation rules described below:

- If reported end date is partial then set end date equal to the last possible reported end date based on the partial entered reported end date.
- If reported end date is missing, continuing, unknown or invalid then set end date equal to the most recent database extraction date.

If end date was imputed then compare end date to the death date or last known alive date if subject is not dead. If posterior then end date should be imputed to death date (or last known alive date if subject not dead).

Note: Imputation of partial dates only applies to data entered on "RADIOTHERAPY" CRF page. For other CRF pages in case of partial dates set end date to missing.

Surgeries – Imputation Rules.

If reported surgery date is a full valid date then set start date equal to the date part of surgery date.

In case of partial date, use one of the two imputation rules described below:

- 1) For data collected on "PRIOR SURGERY RELATED TO CANCER" CRF page:
 - a) If only day is missing then impute as the first day of the month;
 - b) If both day and month are missing then then impute as 01JAN of the year;

- c) If date is completely missing or invalid then leave missing.
- 2) B. For data collected on other CRF pages (deemed to be on-treatment/subsequent surgeries):
- a) If only day is missing then
 - i) If month and year of surgery match month and year of first dose date then impute the missing date as the date of first dose;
 - ii) If month and year of surgery don't match month and year of first dose date then impute as first day of that month and year;
 - b) If both day and month are missing then impute as maximum between 01JAN of the year and date of the first dose;
 - c) If date is completely missing or invalid then leave missing.

