Official Title of Study:

A Randomized Phase 3 Single Blind Study of Temozolomide plus Radiation Therapy combined with Nivolumab or Placebo in Newly Diagnosed Adult Subjects with MGMT-Methylated (tumor O6-methylguanine DNA methyltransferase) Glioblastoma

PROTOCOL(S) CA209-548

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A RANDOMIZED PHASE 3 SINGLE BLIND STUDY OF TEMOZOLOMIDE PLUS RADIATION THERAPY COMBINED WITH NIVOLUMAB OR PLACEBO IN NEWLY DIAGNOSED ADULT SUBJECTS WITH MGMT-METHYLATED (TUMOR O6-METHYLGUANINE DNA METHYLTRANSFERASE) GLIOBLASTOMA

PROTOCOL(S) CA209548

VERSION # 6.0

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[redacted]

Research Hypothesis:

- Addition of nivolumab to standard radiotherapy (RT) plus temozolomide (TMZ) will increase overall survival (OS) in subjects with newly-diagnosed GBM of MGMT-methylated or indeterminate subtypes without baseline corticosteroids and regardless of baseline corticosteroids.
- Addition of nivolumab to standard radiotherapy (RT) plus temozolomide (TMZ) will increase progression free survival (PFS) in subjects with newly-diagnosed GBM of MGMT-methylated or indeterminate subtypes regardless of baseline corticosteroids.

Schedule of Analyses:

In this study, following are the planned formal efficacy analyses:

- For superiority of PFS in the first 558 subjects from all randomized subjects who were randomized to RT plus TMZ combined with nivolumab vs. subjects who were randomized to RT plus TMZ combined with placebo. One interim analysis will occur when 70% or 283 PFS events is reached, or when each of the 558 subjects reaches 12 months follow-up whichever comes first. The final PFS analysis is planned to be performed when at least 404 events in the first 558 subjects from all randomized population have been observed.

- For superiority of OS in all randomized subjects without baseline corticosteriods who were randomized to RT plus TMZ combined with nivolumab vs. subjects who were randomized to RT plus TMZ combined with placebo. One interim analysis will occur approximately 20 months after accrual is finished or when 70% or 236 OS events is reached which is estimated to occur at 45 months after study start. The final OS analysis is planned to be performed when at least 337 events in the sub-population of randomized subjects with no baseline corticosteroids have been observed.

The interim and final analyses for OS in all randomized subjects regardless of baseline corticosteroid are planned at the same time as the analyses in all randomized population with no baseline corticosteroid. An independent Data Monitoring Committee (DMC) will monitor the formal PFS and OS interim analyses and have access to periodic interim safety and efficacy reports to allow for a benefit/risk assessment. Details are specified in the DMC charter4.

If PFS or OS data crosses the pre-specified boundary at the time of planned interim analyses, the DMC will inform the sponsor, as described in the DMC charter4. If PFS data crosses the pre-specified stopping boundary the study will continue up to the final analysis.

If the pre-specified stopping boundary is not crossed at any of the formal interim analyses, the study will continue up to the final analysis.

Changes to the Planned Analyses:

- For this study, tumor scan measurements are reviewed by blinded independent radiologic review (BICR) in a batch read mode, i.e., independent reviews commence after all exams for each time point have been received. It is challenging to obtain data in real time. Due to delayed BICR data, the number of PFS events passed the pre-specified events required for interim analysis and it was close to the number of pre-specified PFS events required for final analysis. As a result, interim analysis for PFS will not be conducted.
- The Data Monitoring Committee (DMC) reviewed all available data on 09-Dec-2020 and agreed that there is no plausible scenario for this study to have a positive OS result at the final analysis based on either all randomized patients or on patients without baseline corticosteroids. This statement is based on the DMC’s review of the OS results to date, with over 80% of the final required number of events reached and related statistical considerations including conditional power (CP) of < 1% for a statistically significant final result. Therefore, the DMC recommended to unblind the sites and patients, which was approved by the sponsor. The study was officially unblinded on 22-Dec-2020.

  As a consequence, the timing of the primary OS analysis, originally planned when 337 and 494 events were to be reached respectively for the population without corticosteroid at baseline and the overall population, has been updated. It is no longer event-driven.

  To prevent any bias due to unblinding of patients, the primary OS analysis and the safety analysis will be conducted using the cut-off date of 22-Dec-2020, which is when the study was unblinded. The primary analysis of PFS per BICR will be conducted using the cut-off date of 14-Jun-2019 with a database lock date of 09-Aug-2019 (the primary PFS analysis assessed by

the DMC in 2019). The same analysis will also be conducted using the cut-off date of 22-Dec-2020.

- The efficacy analyses will be performed for the primary and secondary endpoints. All the secondary endpoints will be analyzed at the same time as the primary endpoints using the analysis methods already defined in the current SAP.

  The primary OS analysis in all randomized subjects without baseline corticosteroids and the primary PFS analysis in all randomized subjects will report a p-value as planned in the alpha recycling plan. Overall survival in all randomized subjects will be tabulated descriptively, as described in the Section 7.5.4. Potential subsets analyses will be presented descriptively.

- Based on CP calculation (<1%) for OS, there is no plausible scenario for this study to have a positive OS result. Therefore only selected analyses will be included in the primary CSR:

  Subject Disposition

  Demographics and Baseline Characteristics

  Prior Therapy

  Medical History

  Baseline Examinations

  Extent of Exposure

  - Administration of Study Therapy
  - Modifications of Study Therapy
  - Nivolumab Dose Delays
  - Nivolumab Infusion Interruptions and Rate Changes
  - Temozolomide Dose Modifications
  - Missing Radiotherapy
  - Dose Reductions/Escalation
  - Concomitant Medications

  Efficacy

  - Overall Survival
  - Consistency of Treatment Effect on OS in Subsets and PFS in subsets
  - Subject Follow-Up
  - Progression Free Survival + subsets

  Safety

  - Deaths

- Serious Adverse Events
- Adverse Events Leading to Discontinuation of Study Therapy
- Adverse Events Leading to Dose Delay of Study Therapy
- Adverse Events
- Select Adverse Events
- Immune-Mediated Adverse Events
- Immune Modulating Medication
- Multiple Events
- Clinical Laboratory Evaluations
- Hematology
- Serum Chemistry
- Vital Signs and Pulse Oximetry
- Pregnancy
- Biomarkers
- Distribution of PD-L1 Expression

- End of study analyses at study closure will be performed for subject disposition, duration of treatment and selected safety outputs.

2 STUDY DESCRIPTION

2.1 Study Design

This is a randomized phase 3 single blind study of temozolomide plus radiation therapy combined with nivolumab or placebo in newly diagnosed adult subjects with MGMT-methylated glioblastoma.

This study will enroll subjects with newly-diagnosed GBM, following surgical resection of the tumor. Tumor tissue will be evaluated for MGMT methylation by a central laboratory assay through the CA209498 study. After enrolling in the CA209498 study, the subjects may enroll in the CA209548 study and begin the screening process while they wait for the MGMT results. The screening number assigned in the CA209498 IVRS will be the same subject number entered by the site to screen the subject into the CA209548 IVRS. Those with a MGMT status of methylated or indeterminate may be eligible to randomize in the CA209548 study. In order to randomize 693 eligible subjects, a total of approximately 780 subjects will be evaluated. For details, see Section 2.1.1.

Subjects with a central laboratory result of MGMT-methylated or indeterminate may continue in the screening phase, in which eligibility for randomization will be documented and baseline demographic and disease information submitted; for details, see Section 2.1.1. A contrast-enhanced MRI should have been obtained within 72 hours post-surgery (within 24 hours

preferred) as part of the initial screening for the CA209498 study. If not obtained at that time, then a MRI must be performed prior to randomization (> 14 days post-op preferred).

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 Table 2.1-1. All subjects who enter the treatment phase, ie, all randomized subjects, will be followed for safety and tolerability, tumor progression and survival. The first on-study contrast-enhanced MRI should be performed 4 weeks (± 7 days) after completing radiation therapy, then subsequent scans should be every 8 weeks (± 7 days) up to 24 months post randomization, then every 12 weeks until progression regardless of treatment schedule or dose delays. Tumor progression will be assessed using RANO criteria. [redacted] For the purposes of this protocol, each cycle duration is 2 weeks until 8 doses of nivolumab/placebo are complete. The remaining subsequent cycles are 4 weeks in duration.

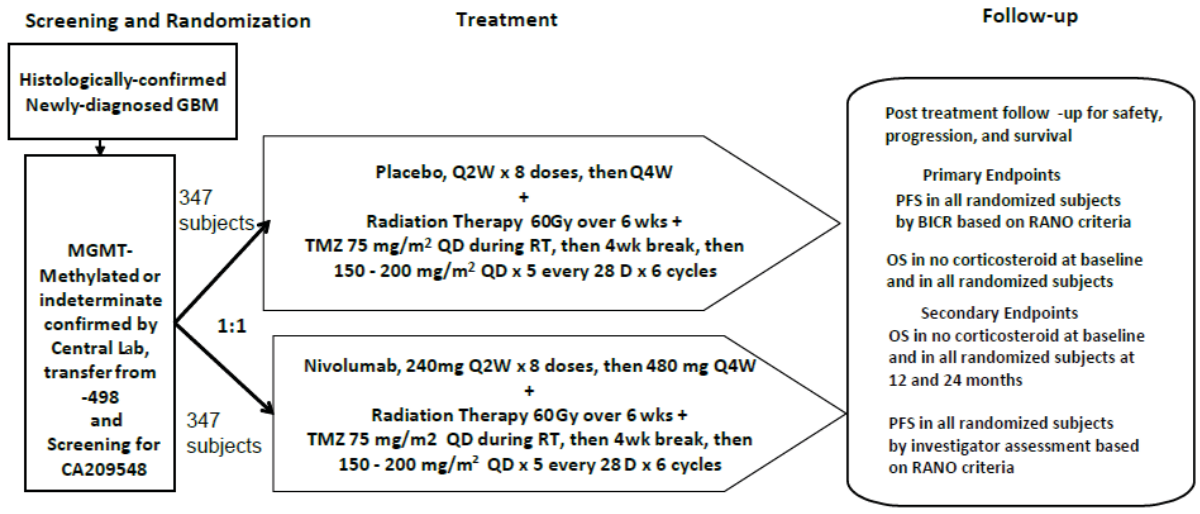
After cessation of all study treatment for any reason, all randomized subjects will enter a **follow-up** phase. In the short-term, visits are defined for reporting of treatment-related adverse events. Following study unblinding, subjects who discontinue all treatment will not be followed for progression per RANO criteria, or for survival.

Baseline and all subsequent scans will be submitted to an independent radiology review committee (IRC) for archiving, once the subject is randomized and until study unblinding on 22Dec2020. .

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

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

Table 2.1-1: Study Design Schematic

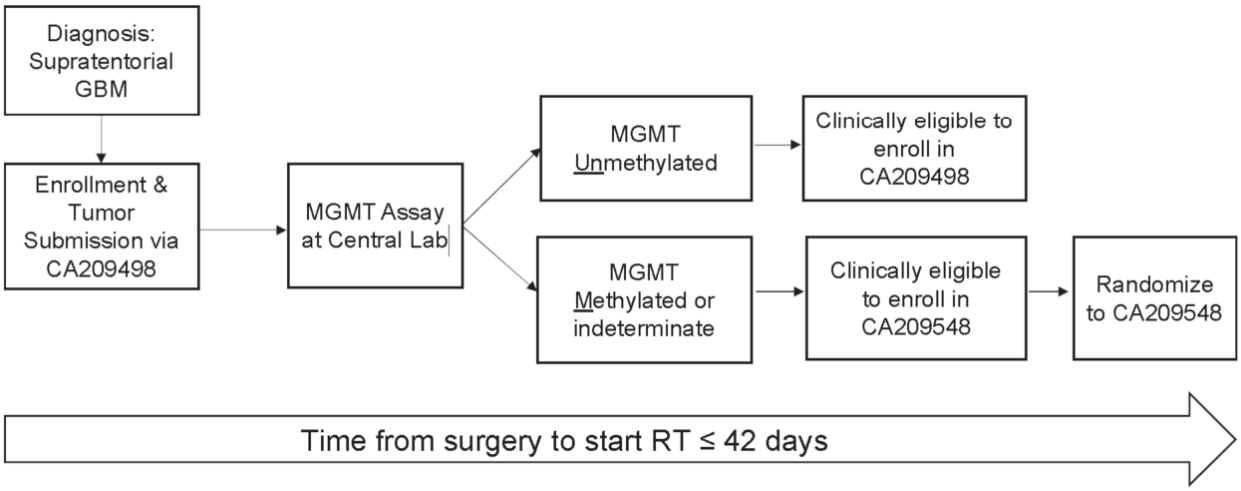


*Following unblinding subjects may continue on nivolumab and/or temozolomide (if applicable) treatment, following all protocol procedures.

2.1.1 Screening Phase

Subjects will provide consent for enrollment and tumor submission in the peri-operative period through the CA209498 study so that MGMT status can be determined. Consent for enrollment in the CA209548 study will occur while waiting for the MGMT results to be obtained and randomization and study treatment will occur once MGMT status of methylated or indeterminate is known and eligibility is established (Table 2.1.1-1).

Table 2.1.1-1: Screening and Randomization



A centralized tumor tissue assay for MGMT is required as part of the CA209498 MGMT testing. Subjects will consent to the MGMT testing and the CA209548 study simultaneously. Following informed consent for both studies, subjects will be enrolled via a call to an IVRS system for the CA209498 MGMT testing, in order to obtain a subject number. Immediately after the subject number is obtained from the CA209498 IVRS, the site will then screen the subject into the CA209548 IVRS. The original subject number from CA209498 must be entered into the eCRF.

When possible, subjects should not be on corticosteroids at Screening i.e. should be off corticosteroids at least 5 days prior to start of dosing. 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 < 20 mg prednisone or < 3 mg 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 (eg, 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 for both the CA209498 and CA209548 studies, the subject must first be enrolled into the CA209498 study by calling an interactive voice response system (IVRS) to obtain the subject number. The subject identification number in the CA209498 study will become the study number for the CA209548 study. Every subject that signs the informed consent form must be assigned a subject number in the 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
- Patient ID from the CA209498 study

Once enrolled in the IVRS, enrolled subjects who meet all eligibility criteria, and are clinically ready to begin treatment, will be randomized through the IVRS. Central lab confirmation of MGMT-methylated or indeterminate status must be received prior to the IVRS randomization call. 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 plus temozolomide combined with nivolumab or placebo. 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

The blinding strategy selected for the protocol is the single-blinding design, also called "site-subject blinded".[5] The subjects, investigator and site staff will be blinded to the study therapy administered. Access to treatment codes will be restricted from all participants, and site and BMS personnel prior to final database lock, with exceptions as specified below. Each investigative site must assign an unblinded pharmacist/designee. Designated staff of BMS Research & Development will be unblinded to facilitate drug supply and safety monitoring. [redacted]

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be

broken by the investigator. The subject's safety takes priority over any other considerations in determining if the treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the BMS Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made. Once the subject is unblinded, the decision to discontinue cannot be reversed.

For this study, the method of unblinding for emergency purposes is through the IVRS. For information on how to unblind for emergency, please consult the IVRS manual.

In cases of accidental unblinding, contact the BMS Medical Monitor and ensure every attempt is made to preserve the blind.

[redacted]

The DMC convened a pre-planned, periodic, routine review of all available data on 09-Dec-2020. The initial recommendation was that the study should continue unchanged, however subsequently the DMC notified BMS that they had deliberated further and unanimously agreed that based on the review of the OS results to date the study may not demonstrate an OS benefit for the investigational treatment arm, and after further discussion with the DMC the decision was made to unblind all study patients, and inform all investigators, ethics committees, and health authorities as required. This statement is based on the DMC's review of the OS results to date, with over 80% of the final required number of events reached and related statistical considerations including conditional power (CP) of < 1% for a statistically significant final result.

2.4 Protocol Amendments

The SAP is based on the protocol v.06 of 26-Feb-2021 which incorporates the following amendments:

Table 2.4-1: Protocol Revision History

Document	Date of Issue	Summary of change
Original Protocol	16-Dec-2015	Not applicable
Amendment 05	22-Apr-2016	The main purpose of the first global amendment is to provide additional clarification on several items in response to questions arising from investigators and IRB/IEC/HAs: • Add any ≥ 2 creatinine drug-related abnormality.

Table 2.4-1: Protocol Revision History

Document	Date of Issue	Summary of change
		• Delete provision regarding delay in subjects with baseline Grade 1 ALT, AST or total bilirubin toxicity to be allowed to continue dosing to Grade ≥ 3 toxicity, thus having all subjects delay for ≥ Grade 2 drug-related toxicity. • Modify criteria to specify that subjects with Grade 2 AST/ALT, or total bilirubin elevations may resume dosing when lab values return to baseline and management with corticosteroids is complete. • Modify criteria to specify subjects must discontinue for any Grade 3 non-skin, drug-related adverse event lasting > 7 days or which recurs with some exceptions. • Modify criteria for drug-related liver function test abnormality to discontinue for AST or ALT > 5 x ULN, Total bilirubin > 3 x ULN or concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN. • Add a definition for single blind. Additional modifications are as described below: • Revise resection cutoffs • Clarify time windows and technical descriptions around the infusion, examinations, and administration schedule • Remove exclusion criteria 2d for subjects with interstitial lung disease • Add exclusion criteria 2k to exclude subjects with prior hypersensitivity to dacarbazine (DTIC) • Add a Radiotherapy Guideline Appendix • Move Highly Effective Methods of Contraception to an Appendix • Incorporate other minor changes to correct and/or clarify protocol requirements
Revised Protocol 01	22-Apr-2016	Incorporates Amendment 05
Amendment 09	26-Oct-2016	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. [redacted] • Renal, Pulmonary, Hepatic, and Skin safety management algorithms revised based on IBv.15 • 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.
Revised Protocol 02	26-Oct-2016	Incorporates Amendment 09

Table 2.4-1: Protocol Revision History

Document	Date of Issue	Summary of change
Administrative Letter 04	08-May-2017	Change in Study Director
Amendment 11	03-Jun-2017	Changed to a Phase 3 trial with Primary Objective of OS
Revised Protocol 03	03-Jun-2017	Incorporates Amendment 11
Amendment 12	17-Jun-2017	Corrects an error in the Dose Delay Criteria and aligns the Dose Delay Criteria and Dose Discontinuation Criteria with the nivolumab program standards.
Revised Protocol 04	17-Jun-2017	Incorporates Amendment 12
Revised Protocol 05	8-Nov-2018	Major Changes • Progression Free Survival (PFS) is now a primary objective of the study, changed from secondary. In support of this change, blinded independent central review (BICR) has been added and may occur at any time during the study. • Overall survival (OS) rates at 12 and 24 months and PFS based on investigator assessment by RANO criteria are added as a secondary objective. • The statistical section has been revised to support changes in the study objectives. The study will now include 1 formal interim analysis for PFS and 1 formal interim analysis for OS for superiority. [redacted]
Revised Protocol 06	26-Feb-2021	• The study was officially unblinded on 22-Dec-2020 per DMC recommendation based on the DMC review conducted on 9-Dec-2020 and BMS approval. • The timing of the primary OS analysis has been updated. To prevent any bias due to unblinding of subjects, the primary OS analysis will be conducted using the unblinding date of 22-Dec-2020. • Study procedures for subjects remaining on treatment and in follow-up have been simplified. • Following study unblinding, subjects who discontinue study drug will only be followed for safety as required. • Protocol language per BMS standards for nivolumab studies and for COVID-19 has been incorporated. • Incorporates approved Administrative Letters 10 and 11.

2.5 Data Monitoring Committee

A Data Monitoring Committee will be established to provide oversight of safety and efficacy evaluation of the entire study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects. 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 subject 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. The DMC will review all available data (safety and efficacy) 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 feedback from investigators and the DMC.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

3 OBJECTIVES

3.1 Primary

- To compare PFS of subjects with newly-diagnosed MGMT-methylated or indeterminate GBM subtypes treated with RT plus TMZ combined with nivolumab or placebo. PFS will be determined by blinded independent central review (BICR) based on RANO criteria.
- To compare OS of subjects with newly-diagnosed MGMT-methylated or indeterminate GBM subtypes without baseline corticosteroids and regardless of baseline corticosteroids (ie, all comers) treated with RT plus TMZ combined with nivolumab or placebo.

3.2 Secondary

- To compare OS of subjects with newly-diagnosed MGMT-methylated or indeterminate GBM subtypes without baseline corticosteroids and regardless of baseline corticosteroids (ie, all comers) treated with RT plus TMZ combined with nivolumab or placebo at 12 and 24 months.
- To compare PFS based on investigator's assessment by RANO criteria of subjects with newly-diagnosed MGMT methylated or indeterminate GBM subtypes treated with RT plus TMZ combined with nivolumab or placebo.

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint(s)

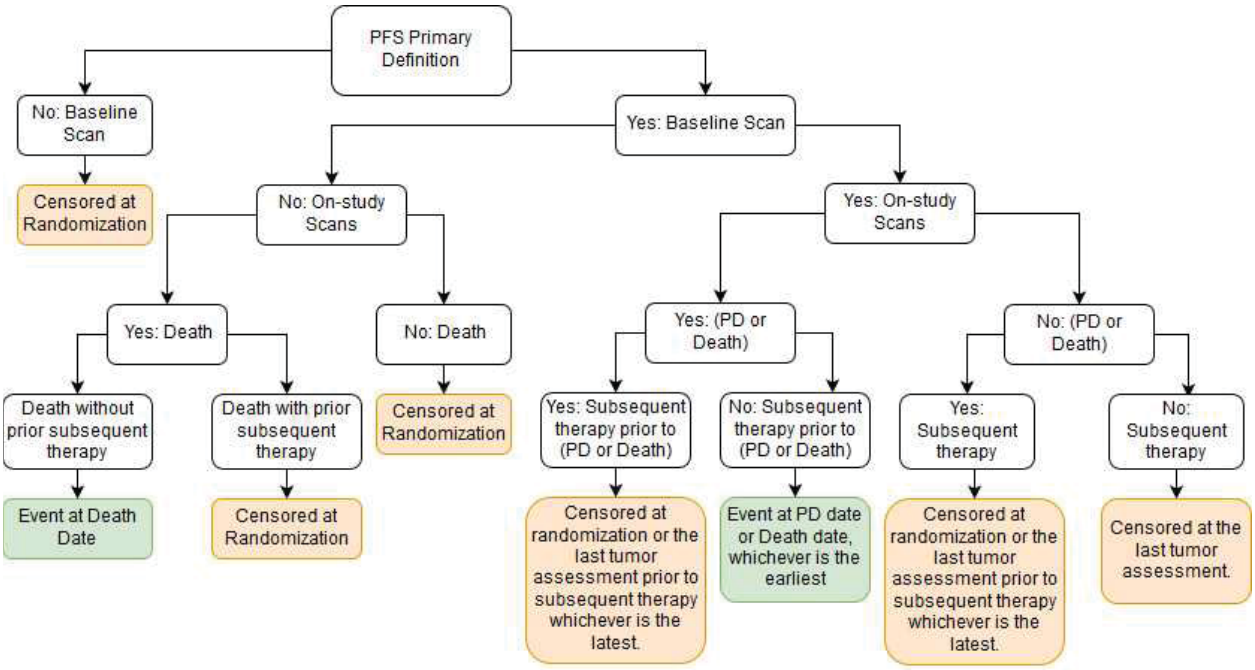
The primary endpoints of the trial will be assessed by OS and PFS.

OS is defined as time from the date of randomization to the date of death. Subjects who did not die by the end of the study will be censored to last known date alive. OS will be assessed in the randomized population with no corticosteroids at baseline and in the all randomized population.

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 die will be censored at the date of the last tumor assessment. Subjects who did not have any on study tumor assessment and did not die will be censored at the last tumor assessment. 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 anti-cancer therapy. Subjects who had surgical resection after start of study treatment will be censored at the last tumor assessment date prior to initiation of surgical resection. PFS will be determined by BICR, based on RANO criteria. PFS will be assessed in the first 558 subjects from all randomized population. 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 4.1-1. Alternate censoring rules for sensitivity analyses are specified in Section 7.5.2.2.

Figure 4.1-1: Graphic Display of PFS Primary Definition



4.2 Secondary Endpoint(s)

- OS rate at 12 months and 24 months derived Kaplan-Meier curve of OS
- PFS assessed by investigator based on RANO criteria

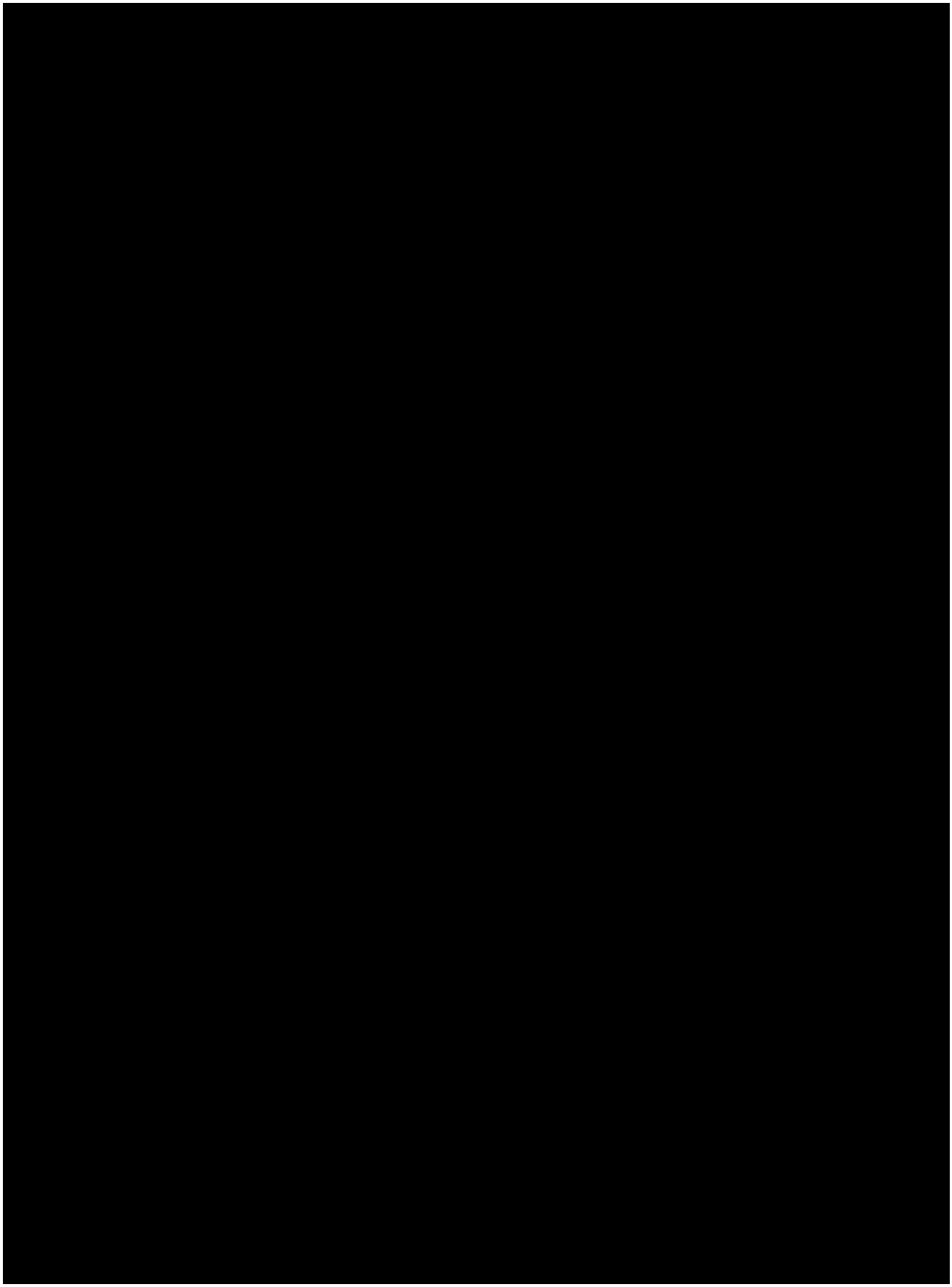
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

This is a Phase 3, randomized, single blinded, multicenter study of RT+TMZ+nivolumab or placebo in adult (≥ 18 years) subjects with newly diagnosed GBM and MGMT-methylated or indeterminate tumors.

The familywise type I error rate for the primary comparisons will be set to 0.05, with 0.01 being allocated to the PFS comparison and 0.04 being allocated to the OS comparison.

The primary objectives on OS will test RT plus TMZ combined with nivolumab or placebo in the following hierarchy via a stratified log rank test:

1. OS in newly diagnosed MGMT-methylated or indeterminate GBM subtype without baseline corticosteroids.
2. If 1 is significant, OS in newly-diagnosed MGMT-methylated or indeterminate GBM subtype regardless of baseline steroid use (all comers).

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

- PFS and OS follows exponential distribution
- Median PFS in RT+TMZ arm is 10.0 months
- Hazard ratio (HR) of arm RT + TMZ + nivolumab vs RT + TMZ for PFS is 0.68, translated to median PFS improvement of 4.7 months (10.0 months vs 14.7 months for arm RT + TMZ and arm RT + TMZ + nivolumab, respectively)
- Median OS in RT+TMZ arm is 26.0 months[3]
- Hazard ratio (HR) of arm RT + TMZ + nivolumab vs RT + TMZ is 0.7 for the randomized population with no baseline corticosteroid, translated to median OS improvement of 11.1 months (26.0 months vs 37.1 months for arm RT + TMZ and arm RT + TMZ + nivolumab, respectively)
- Hazard ratio (HR) of arm RT + TMZ + nivolumab vs RT + TMZ is 0.75 for all randomized population, translated to median OS improvement of 8.7 months (26.0 months vs 34.7 months for arm RT + TMZ and arm RT + TMZ + nivolumab, respectively)

- Proportion of no baseline corticosteroid population within the entire newly-diagnosed MGMT-methylated or indeterminate GBM subtypes is 0.70

Approximately 693 subjects will be randomized in a 1:1 ratio, stratified by complete or partial resection. Of these 693 subjects, 485 subjects are assumed to be no baseline corticosteroids. Accrual is estimated to take approximately 25 months based on an observed monthly accrual in CA209548 of approximately 28 subjects per month; in the no baseline corticosteroids population, a piecewise accrual of 1, 4, 5, 8, 13, 16, 19, and then 23 subjects per month thereafter is assumed. At least 337 OS events (deaths) in the no baseline corticosteroid population are needed to achieve 88% power using a 2-sided Type 1 error of 4%. This number of events is projected to occur after an additional 44 months of follow-up (ie, at 69 months).

One interim analysis will be conducted on OS in the randomized population with no baseline corticosteroid. It will occur approximately 20 months after accrual is finished or when 70% or 236 OS events is reached which is estimated to occur at 45 months after study start, providing a 58% probability of stopping under H1. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the planned interim analyses occur exactly at the planned number of events, the projected alpha level will be 0.011 and 0.037. See Table 5-1. The interim analysis will also be conducted on OS in the overall randomized population. The interim analysis will be conducted at the same time as the interim for the no baseline corticosteroids population in a hierarchy with stopping boundaries at the interim and final analysis based on actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with Pocock boundaries[12].

The PFS comparisons will be based on first 558 randomized subjects in all-comers. At least 404 PFS events are needed to achieve 90% power using a 2-sided Type 1 error of 1%. Accrual is estimated to take approximately 23 months and this number of events is projected to occur after an additional 12 months of follow-up (ie, at 35 months).

One interim analysis on PFS is planned and it will occur when 70% or 283 PFS events is reached, providing a 54% probability of stopping under H1, or when each of the 558 subjects reaches 12 months follow-up whichever comes first. The stopping boundaries at the interim and final analyses will be based on the actual number of PFS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the planned interim analyses occur exactly at the planned number of events, the projected alpha level will be 0.002 and 0.009.

Due to delayed BICR data, the number of PFS events passed the pre-specified events required for interim analysis and it was close to the number of pre-specified PFS events required for final analysis. As a result, interim analysis for PFS will not be conducted and alpha of 0.01 will be fully allocated to the final analysis for PFS.

Power calculations were done using East v 6.3 and R.

Table 5-1: Key Parameters of Sample Size Calculation of PFS and OS

Primary Endpoint	PFS	OS	OS
Power	90%	88%	87%
Alpha	0.01	0.04	0.04
Hypothesized Median Control vs. exp (months)	10 vs 14.7	26 vs 37.1	26 vs. 34.7
Hypothesized Hazard ratio	0.68	0.7	0.75
Expected number of events for comparison towards primary objective	404	337	494
Accrual Duration (months)	23	25	25
Sample size	558 (all-comers)	485 (no baseline corticosteroids)	693 (all-comers)
Expected number of events at IA		236	346
FPFV to IA (months)		45	45
FPFV to LPLV (months)	35	69	69

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 (or date of randomization in case of no 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 30 days (or 100 days depending on analysis, see Core Safety SAP[6]) of the last dose of study treatment. 30 day and 100 day cut-off is only for subjects off-treatment and no 'subtracting rule' will be applied to AEs that occurred pre-treatment.

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

6.2 Treatment Regimens

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

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

The treatment group "**as treated**" will be the same as the arm as randomized by the 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.

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. This is the primary dataset for analyses of efficacy parameters and baseline characteristics.
- All Treated subjects: All randomized subjects who received at least one dose of study drug. This is the primary dataset for safety and exposure analyses.

[redacted]

- All Randomized subjects with no baseline corticosteroids: Randomized subjects who did not take corticosteroids for at least 5 days prior to start of dosing (or randomization for subjects not treated).
- Response evaluable subjects: Randomized subjects with measurable lesions at baseline

[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 treatment (with total). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by 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, time to response and duration of response) 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 24 months) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals[7]. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[8].

Unless otherwise specified, the stratified log-rank test will be performed to test the comparison between time to event distributions (OS and PFS). Stratification factor (complete resection or partial resection at baseline) will be as entered into the IVRS.

Unless otherwise specified, the stratified hazard ratio between 2 groups along with CI will be obtained by fitting a stratified Cox model with the group variable as unique covariate. Stratification factor (complete resection or partial resection at baseline) will be as entered into the IVRS.

P-values other than those provided for the PFS and OS primary analysis are for descriptive purpose only and not adjusted for multiplicity.

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.

<u>At Entrance:</u>

- Subjects receiving prior treatment for GBM other than Surgery
- Subjects with un-methylated MGMT status (using central lab)

- Subjects with KPS < 70
- Subjects on > 20 mg prednisone or > 3 mg dexamethasone at the time of randomization.
- 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.

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.

A subject listing for all treated subjects will be provided showing the subject's randomization date, first and last dosing date, off treatment date and reason for going off-treatment. 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 baseline characteristics will be summarized by treatment group. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age at the time of informed consent (descriptive statistics)
- Age category I (<65, ≥65)
- Age category II (<65, ≥65- <75, ≥ 75)
- Gender (male, female)
- Race (white, black, asian, 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%, 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 lesion.
- Pre-treatment events: summarized by worst CTC grade presented by SOC/PT
- Medical History

General medical history will only be listed by subject.

7.3.3 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 systemic cancer therapy agents and medication will be reported using the generic name.

A summary table by ATC class and generic name and a by-subject listing will also be provided for prior/current non study medication.

7.3.4 Baseline Examinations

Subjects with abnormal baseline physical exam results will be tabulated by examination criteria (eg neck, cardiovascular, lungs, etc), by treatment group, and by-subject listing will be produced for all measurements.

7.3.5 Discrepancies Between IVRS and CRF Stratification Factors

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

- Extent of tumor resection: Complete or Partial

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)/30.4327

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 i^{th} cycle is not the last.

Cycle duration (i)(wk)= 2, for the last cycle of the induction phase.

Cycle duration (i)(wk)= 4, for the last cycle of the maintenance phase

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 nivolumab treatment will be presented 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) for subjects treated with temozolomide:

- Duration of Treatment (in weeks)
- Cumulative dose (in mg/m2)

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 for subjects treated with radiotherapy:

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

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.

Analysis on extent of exposure will be restricted to the following populations, unless otherwise noted:

- All treated subjects
- All treated subjects without baseline corticosteroid
- All treated subjects in the first 558 subjects from all randomized population

7.4.2 Modifications of Study Therapy

7.4.2.1 Nivolumab Dose Delays

The following parameters will be summarized for subjects treated with nivolumab.

- 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 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.

Incidence of on-treatment corticosteroid use by average dose (in dexamethasone equivalents) received over time and by time periods will be presented for: all corticosteroids, corticosteroids used for disease, corticosteroids used for adverse events. The median average dose with the 1st and 3rd quartiles will also be presented by the time periods.

7.5 Efficacy

Efficacy analyses will be conducted in the first 558 subjects from all randomized subjects (PFS analysis only), all randomized subjects with no baseline corticosteroids, all randomized subjects regardless of corticosteroid use, and [redacted] unless specified otherwise. Analysis will be performed by treatment group as "randomized".

7.5.1 Overall Survival

7.5.1.1 Primary Analysis

OS will be analyzed in all randomized subjects without baseline corticosteroids and all randomized subjects regardless of baseline corticosteroids.

OS curves for each of the randomized arms will be estimated using the Kaplan-Meier (KM) product-limit method and graphically displayed. Median OS and the corresponding two-sided 95% confidence intervals (CI) will be constructed based on the log-log transformed CI for survival function S(t). The distribution of OS will be compared between the two randomized arms via a two-sided stratified (complete or partial surgical resection at baseline) log-rank test at significance level α adjusted for the interim. In addition, a stratified Cox proportional hazards regression model

will be used to estimate hazard ratio (HR) between the two randomized arms along with the 100(1-α)% CI adjusted for the interim.

Survival rates at 12, 18 and 24 months will be estimated using KM estimates on the OS curve for each randomized arm. Minimum follow-up must be longer than the time point to generate the rate. Associated two-sided 95% CI will also be calculated using Greenwood's formula.

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

- On-study (on treatment and not progressed, on-treatment progressed, in follow-up)
- Off-study: (lost to follow-up, withdraw consent, other).

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-value of less than 0.1 will indicate a potential nonconstant treatment effect over time. [redacted]

7.5.1.2 OS Sensitivity Analyses

The following sensitivity analyses will be performed in all randomized subjects without baseline corticosteroids and all randomized subjects regardless of baseline corticosteroids. The same significance level as the corresponding primary analysis will be used (unless otherwise specified):

1. OS will be compared between treatment groups using a two-sided un-stratified 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 subjects in the analysis population.
3. OS will be compared between the treatment groups using a two-sided stratified log-rank test in all treated subject using arm as randomized. This analysis will be performed only if the proportion of randomized but never treated subjects exceeds 5% in the analysis population.
4. OS will be compared between the treatment groups using a two-sided stratified log-rank test in the subpopulation of subjects with MGMT methylated GBM subtype using arm as randomized. This analysis will be performed only if the proportion of subjects with indeterminate GBM subtype exceeds 10% in the analysis population.
5. 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), except for the analysis on OS in all randomized subjects without baseline corticosteroids

c. Performance Status (Karnofsky scale) (≤80, >80)

d. Prior Surgery (complete resection, partial resection, other), based on CRF source

The level of the covariate normally associated with the worst prognosis will be coded as the reference level i.e. "Yes" for steroid use, "≤80" for Karnofsky Performance Status, and "partial resection" for prior surgery. The hazard ratio associated with treatment and with each of the baseline covariates will be presented along with its two-sided 95% CI.

[redacted]

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, ≥ 65 - < 75, ≥ 75, ≥ 65)
- Age categorization (< 50, ≥ 50 - <65)
- Gender (male vs. female)
- Race (white, black, asian, other)
- Disease diagnosis (Glioblastoma, Gliosarcoma)
- RPA class (III, IV, V, other)
- Smoking Status (Current/Former, Never, Unknown)
- Type of Surgery (Complete Resection, Partial Resection, Other)
- Baseline Performance Status (Karnofsky scale) (≤ 80, > 80)
- Baseline corticosteroid use (Yes, No), except for the analysis on OS in all randomized subjects without baseline corticosteroids

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

The extent of follow-up is 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) 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, will be summarized by treatment group. Subjects who died and subjects with a Last Known Date Alive (LKDA) on or after data cut-off date 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.

7.5.1.5 Subsequent Therapy

Subsequent therapy will be summarized by treatment group for all randomized subjects with no baseline corticosteroids, all randomized subjects regardless of baseline corticosteroids use, [redacted].

- Subsequent Therapy
  - Systemic anti-cancer therapy by drug name
  - Surgery (restricted to tumor resection)
  - Subsequent Radiotherapy

In addition, a by-subject listing of follow-up therapy will be produced for subjects who had any subsequent therapy.

7.5.2 Progression Free Survival

PFS determined by BICR based on RANO criteria is the primary endpoint and the primary analysis will be based on the first 558 subjects from all randomized population. PFS based on investigator's assessment by RANO criteria is the secondary endpoint and will be analyzed similarly.

The analysis will also be performed on all randomized subjects without baseline corticosteroids, and all randomized subjects regardless of baseline corticosteroids, unless otherwise specified.

7.5.2.1 Primary Analysis

PFS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method and graphically displayed. Median PFS and the corresponding two-sided 95% confidence interval (CI) will be constructed based on the log-log transformed CI for survival function S(t). The distribution of PFS will be compared between the two randomized arms via a two-sided stratified (complete or partial surgical resection at baseline) log-rank test at significance level of 0.01 In addition, a stratified Cox proportional hazards regression model will be used to estimate hazard ratio (HR) between the two randomized arms along with the 99% CI.

PFS rates at 6, 9, 12, 18, and 24 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 using Greenwood's formula. 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)
- Received subsequent anti-cancer therapy

- No baseline tumor assessment
- No on-study tumor assessments

7.5.2.2 Sensitivity Analysis

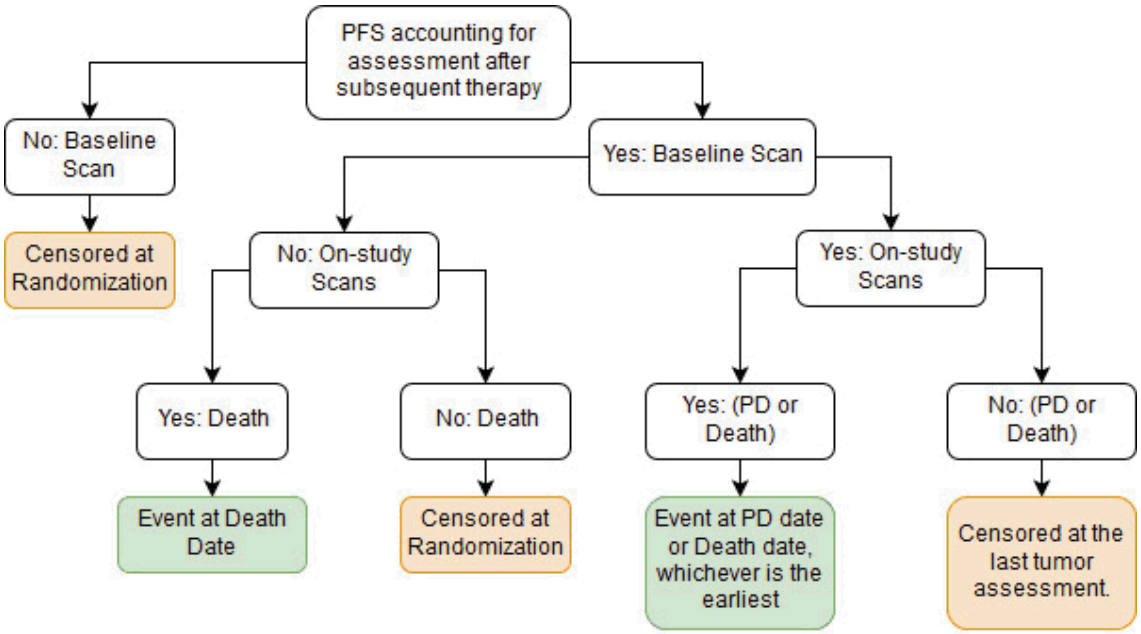
The following sensitivity analyses will be performed in the first 558 subjects from all randomized subjects, all randomized subjects without baseline corticosteroids and all randomized subjects regardless of baseline corticosteroids. The same significance level as the corresponding primary analysis will be used (unless otherwise specified):

1. PFS will be compared between treatment groups using a two-sided un-stratified log-rank test.
2. PFS 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 subjects in the analysis population.
3. PFS will be compared between the treatment groups using a two-sided stratified log-rank test in all treated subject using arm as randomized. This analysis will be performed only if the proportion of randomized but never treated subjects exceeds 5% in the analysis population.
4. PFS will be compared between the treatment groups using a two-sided stratified log-rank test in the subpopulation of subjects with MGMT methylated GBM subtype using arm as randomized. This analysis will be performed only if the proportion of subjects with indeterminate GBM subtype exceeds 10% in the analysis population.
5. 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), except for the analysis on OS in all randomized subjects without baseline corticosteroids
    c. Performance Status (Karnofsky scale) (≤80, >80)
    d. Prior Surgery (complete resection, partial resection, other), based on CRF source

    The level of the covariate normally associated with the worst prognosis will be coded as the reference level i.e. “Yes” for steroid use, “≤80” for Karnofsky Performance Status, and “partial resection” for prior surgery. The hazard ratio associated with treatment and with each of the baseline covariates will be presented along with its two-sided 95% CI.
6. Sensitivity analyses of PFS will also be performed using the following modification:
    - PFS accounting for assessment after subsequent therapy will be defined same as the primary definition except that events (progression or death) and tumor assessments that occurred on or after subsequent anticancer therapy or diagnostic surgical resection will

be taken into account (see censoring scheme for sensitivity analysis in Figure 7.5.2.2-1).

Figure 7.5.2.2-1: Graphic Display of PFS Accounting for Assessment after Subsequent Therapy



- PFS not considering clinical progression as an event will be defined same as the primary definition except not considering clinical progression as progression event.
- PFS not counting clinical progression as event will be defined same as the primary definition except that
  - clinical progression is not considered as progression event
  - events (progression or death) and tumor assessments that occurred on or after subsequent anticancer therapy or diagnostic surgical resection will be taken into account

[redacted]

7.5.3 Other Efficacy Analyses

7.5.3.1 Analyses of BOR, DOR, TTR

Best overall response (BOR) will be tabulated for each treatment group in all response evaluable subjects with no baseline corticosteroids and all response evaluable subjects regardless of baseline corticosteroids.

Duration of response (DOR) will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method for each treatment group. Median DOR, corresponding two-sided 95% confidence interval constructed based on the log-log transformed CI for survival function, and range will also be calculated. In addition, the percentage of responders still in response at different time points (3, 6, 9 and 12 months) will be presented based on the KM plot.

Time to response (TTR) will be summarized for subjects who achieve confirmed PR or CR using descriptive statistics.

7.5.3.2 Analyses of Tumor Burden

The magnitude of reduction in tumor burden in response evaluable subjects will be summarized descriptively.

If enough tissue sample available, 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, a waterfall plot showing the best reduction in measurable lesion based will be produced.
- For response-evaluable subjects, a plot of individual subjects' percent change in measurable lesion tumor burden from baseline.

7.5.3.3 Analysis of Immune-Related Tumor Effects

A summary of surgeries for treatment of tumors (subjects with surgery, reasons for surgery) and results of histopathological examination will be presented for all treated subjects by treatments groups as treated.

7.5.3.4 Analysis of Subjects Treated beyond Progression

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

- Summary of demographic and baseline characteristics by two groups (treated beyond initial progression or not treated beyond initial progression)
- 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

7.5.4 Protection of Type I Error

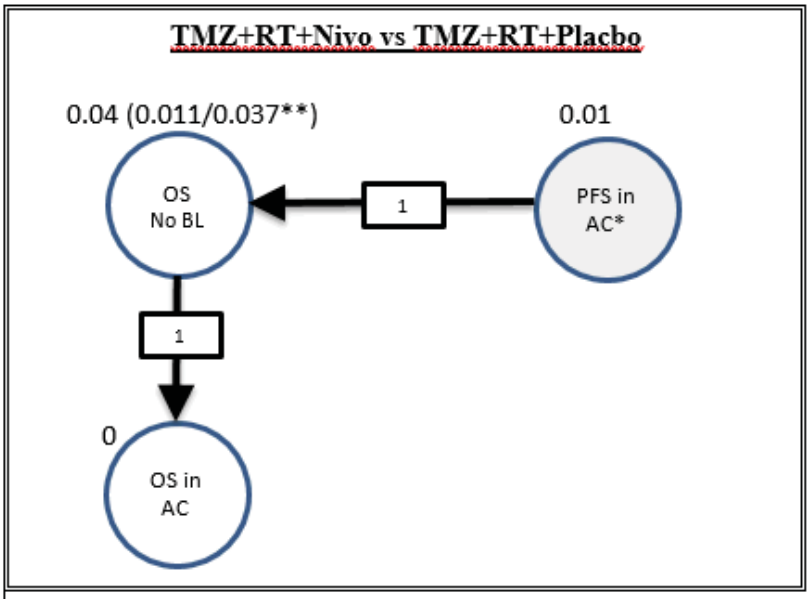
The main goals of the study include:

- to compare PFS in the first 558 subjects from all randomized subjects and to prove superiority of radiotherapy+TMZ+nivolumab arm over radiotherapy+TMZ+placebo.
- to compare OS in all randomized subjects without baseline corticosteroids and to prove superiority of radiotherapy+TMZ+nivolumab arm over radiotherapy+TMZ+placebo. OS in all randomized subjects will also be tested for superiority.

PFS will be tested at 1% type I error. OS will be tested at 4% type I error.

To strongly preserve the familywise type I error rate, Bonferroni-based graphical approach by Maurer and Bretz (2013)[7] will be employed: see Figure 7.5.4-1, for the graphical display of the multiple testing procedure. In this graph defining the test procedure, hypotheses together with their local significance levels are represented by weighted vertices and the propagation rule is represented by weighted directed edges. Algorithm 1 in Maurer and Bretz (2013) provides the rules for updating the local significance levels and the transition weights after rejecting an individual hypothesis. The resulting sequentially rejective testing procedure controls family-wise Type I error rate of 5% in the strong sense, and is uniquely determined by the graph in Figure 7.5.4-1.

Figure 7.5.4-1: Graphical Representation of the Testing Strategy



OS = Overall survival, PFS = Progression-free survival, No BL= all randomzied subjects without baseline corticosteroids, AC = all-comers (i.e, all randomized subjects)

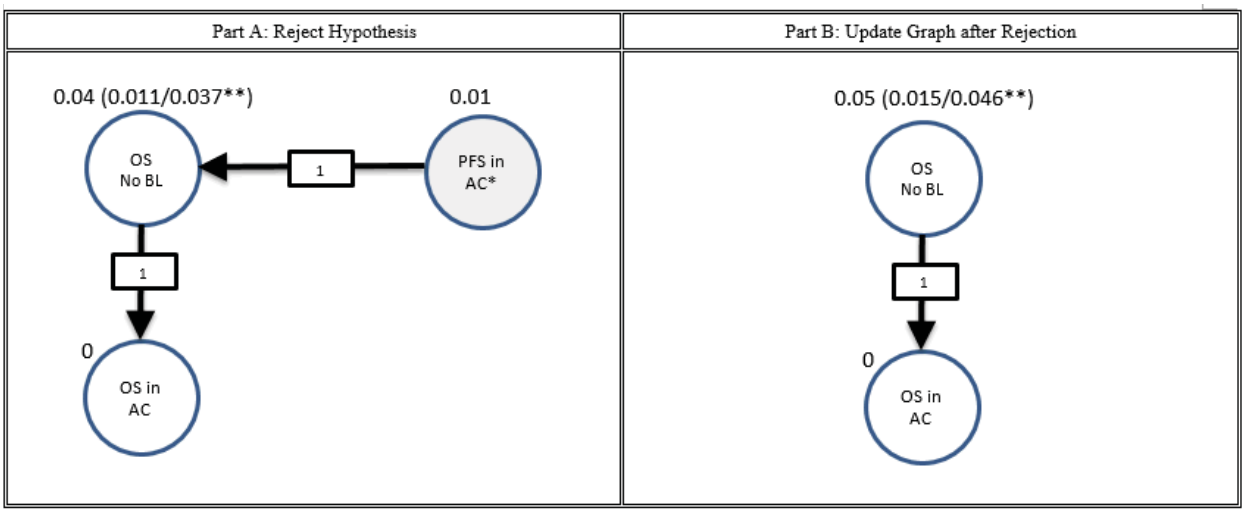
* first 558 subjects from all randomized population

In Figure 7.5.4-1, each vertex (circle) corresponds to a hypothesis to be tested. The numbers next to the vertices are the initially allocated (endpoint-specific) alpha levels. (Note that it is 0 for OS in all randomized subjects - meaning that they cannot be tested until alpha is passed to them from the OS in all randomized subjects without baseline corticosteroids). The weight (in rectangular frame) associated with a directed edge (line) between any two vertices indicates the fraction of the (local) significance level at the initial vertex that is added to the significance level at the terminal vertex, if the hypothesis at the tail is rejected.

At the time of the PFS analysis, PFS in the first 558 subjects from all randomized population will be tested, at alpha of 0.01.

If the hypothesis cannot be rejected, then the study continues to proceed to the OS analysis. If, however, the hypothesis can be rejected, graph will be updated as per Algorithm 1 of Maurer and Bretz (2013), the algorithm ensures that in case PFS in the first 558 subjects from all randomized population is rejected, its entire alpha level (i.e., 0.01) is passed to OS in all randomized subjects without baseline corticosteroids. A simple hypothetical example is illustrated in Figure 7.5.4-2 and Figure 7.5.4-3.

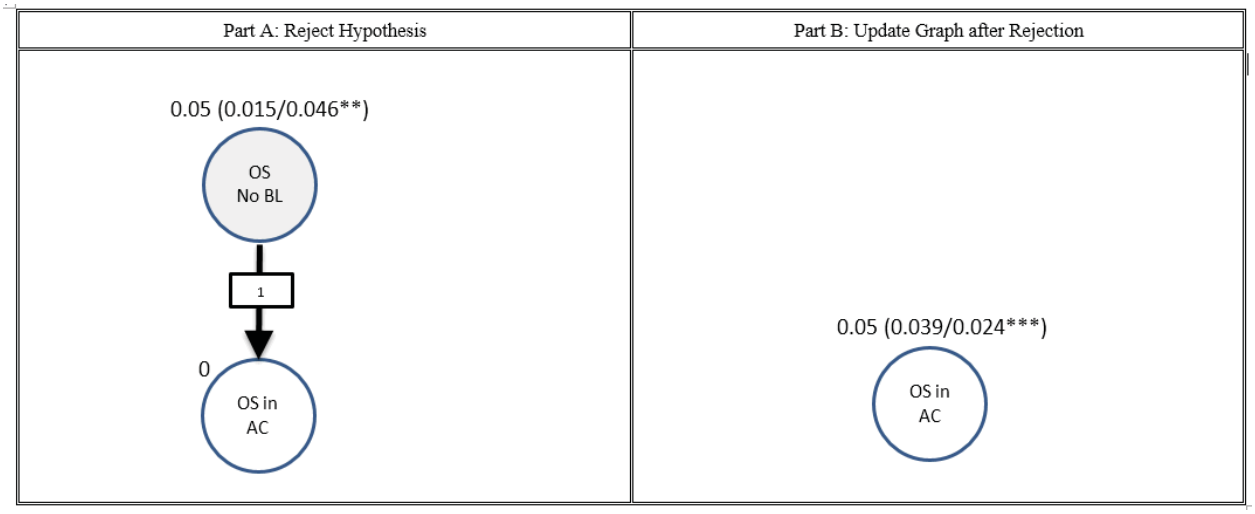
Figure 7.5.4-2: Rejection of PFS in the First 558 Subjects from All Randomized Population



* first 558 subjects from all randomized population
** Nominal significance levels for based on O'Brien-Fleming with 70% observed information fraction

Further, if OS in all randomized subjects with no baseline corticosteroid is rejected, its significance level is passed to the OS in all randomizes subjects (see Figure 7.5.4-3).

Figure 7.5.4-3: Rejection of OS in All Randomized Population without Baseline Corticosteriods



** Nominal significance levels for based on O'Brien-Fleming with 70% observed information fraction
*** Nominal significance levels based on Pocock with 70% observed information fraction

Each time a hypothesis is rejected and the graph is updated, the alpha levels for IA and FA will be recalculated for each remaining OS endpoint using Lan-DeMets alpha spending function (O'Brien-Fleming boundaries will be used for OS in all randomized subjects without baseline corticosteriods, and Pocock boundaries will be used for OS in all randomized subjects). At the time of the final OS analysis, all events in the database at the time of the lock will be used.

Secondary endpoints are not included in a hierarchy of testing and, thus, these comparisons are not adjusted for multiplicity across endpoints. Analyses of the secondary OS and PFS endpoints (including p-values) will be performed for descriptive purpose only.

7.5.5 Interim Analysis

An independent statistician external to BMS will perform the analysis. In addition to the formal planned interim analyses for PFS and OS, the DMC will meet at least every 6 months or more frequently as needed on an ad-hoc basis. Details are included in the DMC charter.

PFS

The population for PFS analysis is the first 558 randomized subjects. A formal interim analysis for superiority of PFS will be performed when approximately 283 (70% of planned events or 283/404) events is reached, or when the 558 subjects reach 12 months minimum follow-up, whichever comes first, where an event is either progression or death. The stopping boundaries at the interim and final analyses will be based on the actual number of PFS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the planned interim analyses occur exactly at the planned number of events, the projected alpha level will be 0.002 and 0.009.

Due to delayed BICR data, the number of PFS events passed the pre-specified events required for interim analysis and it was close to the number of pre-specified PFS events required for final analysis. As a result, interim analysis for PFS will not be conducted and alpha of 0.01 will be fully allocated to the final analysis for PFS.

OS

A formal interim analysis for superiority of OS is planned when 70% or 236 OS events is reached in the population of no baseline corticosteroids, which is estimated to occur at 45 months after study start. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries to reject the null hypothesis of no treatment difference, controlling for a two-sided overall alpha of 4%. If the planned interim analyses occur exactly at the planned number of events, the projected alpha level will be 0.011 and 0.037.

OS in the all randomized subjects can be tested at the same time as the interim analysis of OS in the all randomized subjects without baseline corticosteriods and afterwards, provided analysis of OS in all randomized subjects without baseline corticosteroids is significant. The stopping boundaries at the interim and final analyses for all randomized subjects will be based on actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with Pocock boundaries.

The DMC will review the safety and efficacy data from the interim analyses and will recommend if the study should continue with or without changes or should be stopped. More details of the interim analyses are discussed in the Data Monitoring Committee Charter.

The chair of the DMC and the sponsor can call an unscheduled review of the safety data.

Implications of OS Interim Analysis

At the time of the formal interim analysis for superiority of OS, the DMC may recommend continuing or stopping the trial. If the trial continues beyond the interim look, the nominal critical point for the final OS analysis will be determined using the recalculated information fraction at the time of the interim analysis, as described above. The final OS hazard ratio and corresponding confidence interval will be reported whereby the confidence interval will be adjusted accordingly (i.e. using the recalculated nominal α level at the final analysis).

If the trial is stopped for superiority of OS at the interim, all the statistical analyses conducted at the time of interim analysis would be considered final.

7.6 Safety

For all safety related analyses, refer to the Core Safety SAP[6]. Safety will be summarized for: all treated subjects by treatment group as treated.

7.6.1 Deaths

See Core Safety SAP[6].

7.6.2 Serious Adverse Events

See Core Safety SAP[6].

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP[6].

7.6.4 Adverse Events Leading to Dose Delay of Study Therapy

See Core Safety SAP[6].

7.6.5 Adverse Events

See Core Safety SAP[6].

[redacted]

7.6.7 Immune-Mediated Adverse Events

See Core Safety SAP[6].

7.6.8 Immune Modulating Medication

See Core Safety SAP[6].

7.6.9 Multiple Events

See Core Safety SAP[6].

7.6.10 Clinical Laboratory Evaluations

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

7.6.10.1 Hematology

See Core Safety SAP[6].

7.6.10.2 Serum Chemistry

See Core Safety SAP[6].

[redacted]

7.6.12 Vital Signs and Pulse Oximetry

See Core Safety SAP[6].

7.7 Pregnancy

See Core Safety SAP[6].

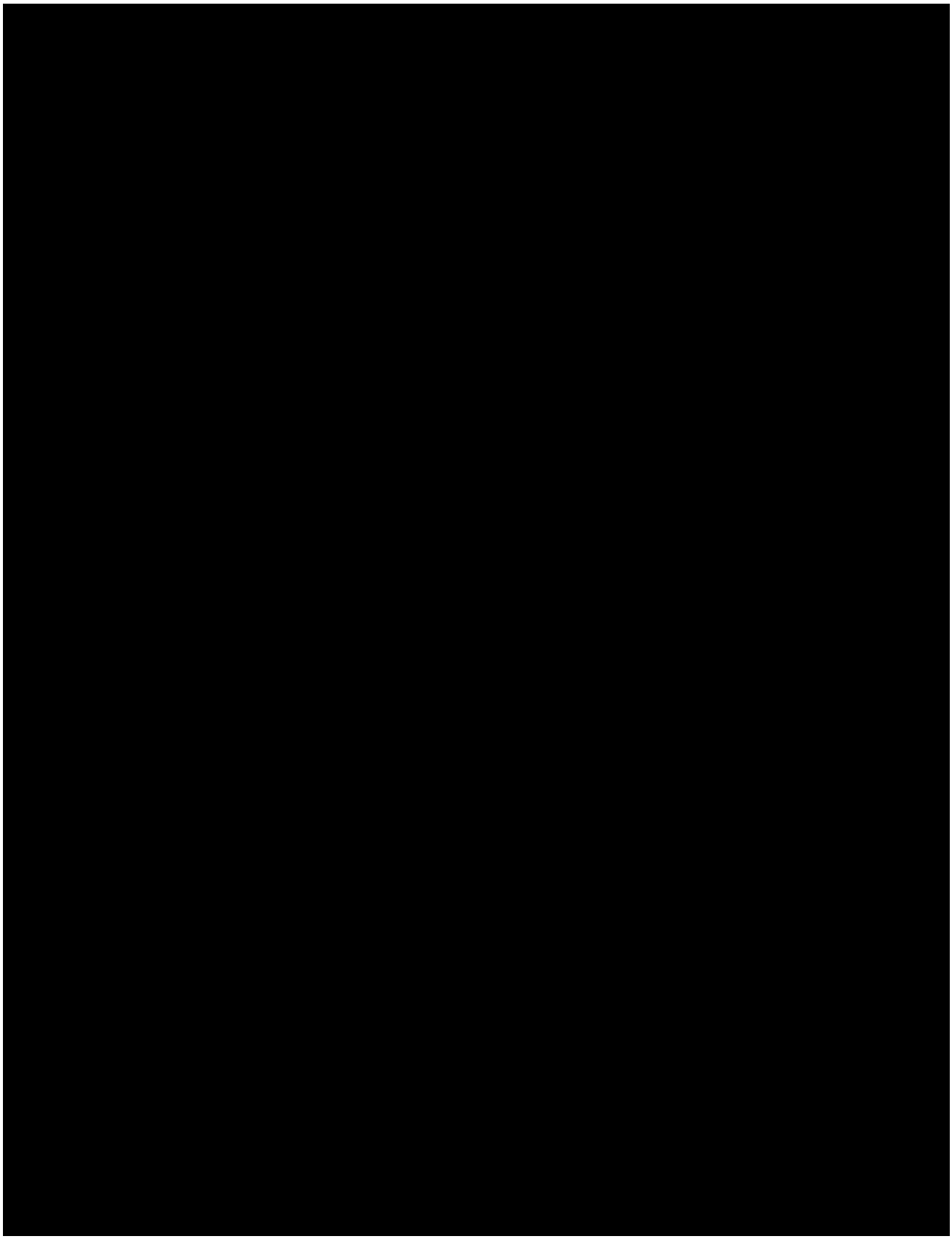
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

7.13 End of Study Analyses at Study Closure

Subjects who have continued on study treatment following the study unblinding will be followed per protocol through treatment discontinuation and safety follow-up.

The end of study analyses will be performed for the selected safety data and duration of treatment using all randomized subjects.

Data to be reported:

- Subject disposition
- Duration of treatment (Nivolumab, Temozolomide)
- Death
- Adverse events
- Serious adverse events

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[9]. 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[10].

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.

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

Duration = (Last date - first date + 1)

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

9 CONTENT OF REPORTS

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Initial version dated 05-Jan-2017
2.0	[redacted]	Section 2 Study Description: Multiple changes we made in section 2 Study description in accordance with the amendments of the protocol, the history of protocol amendments is added on section 2.4. Section 2.1 Study Design: "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. Section 3 Objectives: The section is modified in accordance with the protocol update. Section 4.1 Primary Endpoint(s): two-co-primary endpoints were set in accordance with the protocol update. Section 4.2 Secondary Endpoint(s): Endpoints are modified to 3 secondary endpoints in accordance with the protocol update; sentence "Subjects who die without a reported progression will be considered to have progressed on the date of death" is removed; "PFS will be determined by investigator reported response based on *radiographic and clinical findings in accordance with* RANO criteria" text in italic is added for clarity; censoring rules in Figure 4.1-1: Graphic Display of PFS Primary Definition were corrected for cases when subjects have PD/death and on-study scans (event and censoring had been mixed up) and when subsequent therapy started before an event (possibility to censor by randomization date is added). [redacted]

Table 10-1: Document History

Version Number	Author(s)	Description
		Section 5 SAMPLE SIZE AND POWER: Sample size justification is updated in accordance with the protocol; a clarifying statement "The co-primary objectives of the study will be tested hierarchically, therefore, the first endpoint in the hierarchy, i.e. OS in subjects wthout baseline corticosteroids will be primarily used to investigate the hypothesis of superiority of RT+TMZ+nivolumab treatment compared to RT+TMZ+placebo" is added; statement about secondary endpoint of PFS is removed as no longer relevant for the sample size. Section 6.1.1 Baseline Period: "Evaluations on the same date and time of the first dose of study treatment will be considered as baseline evaluations." is removed since it is not precise and the precise rules are defined in the next paragraph. Section 6.3 Populations for Analyses: New populations are defined: [redacted], All Randomized subjects with no baseline corticosteroids, Response evaluable subjects, [redacted]. Section 7.1 General Methods: "P-values other than those provided for the OS primary analysis ~~and *PFS*~~ are for descriptive purpose only" Section 7.2.2 Relevant Protocol Deviations: Deviation "Subjects with methylated MGMT status" is corrected to "Subjects with *un*-methylated MGMT status". Section 7.3.1 Subject Disposition: description of listings is updated to be compliant with the CRF and support the tables. Section 7.3.2 Demographics and Baseline Characteristics: "Age *at the time of informed consent*" is clarified; BSA is added for analysis; "Time from Initial Disease Diagnosis to ~~*start of treatment randomization*~~"; "Target" lesions are changed to "Measurable, "longest diameter" is changed to "products of perpendicular diameters" in accordance with RANO Section 7.3.4 Baseline Examinations: "and by-subject listing will be produced for all measurements" is added Section 7.4.1 Administration of Study Therapy: definition of the last cycle length is corrected; terms "Dose Intensity", "Relative Dose intensity" and the definitions are made compliant; populations for exposure analysis is restricted to subjects treated with a particular drug; definition of TMZ Dose (mg/m2) is corrected to be defined via BSA instead of weight; TMZ Cumulative planned dose for induction phase is defined; the following analyses for TMZ maintenance phase is removed: Cycles of treatment, Number of subjects completing 6 cycles; Duration of Treatment is added to analyses for TMZ maintenance phase; structure of the section is improved. Section 7.4.2 Modifications of Study Therapy: populations for exposure analysis is restricted to subjects treated with a particular drug. 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 Section 7.4.3 Concomitant Medications: "Incidence of on-treatment corticosteroid use by average dose (in dexamethasone equivalents)

Table 10-1: Document History

Version Number	Author(s)	Description
		received over time and by time periods will be presented for: all corticosteroids, corticosteroids used for disease, corticosteroids used for adverse events. The median average dose with the 1st and 3rd quartiles will also be presented by the time periods." is added Section 7.5 Efficacy: "Efficacy analyses will be conducted in all randomized subjects with no baseline corticosteroids, all randomized subjects regardless of corticosteroid use, [redacted]. Analysis will be performed by treatment group as "randomized"." is added. Section 7.5.1.1 Primary Analysis: "OS will be analyzed in all randomized subjects without baseline corticosteroids, all randomized subjects regardless of baseline corticosteroids, [redacted]." is added for compliance of the analysis with the updated study design; graphical display of OS curves is added to the analysis; wording is improved. Section 7.5.1.2 OS sensitivity Analyses: added that the analysis is to be conducted "for each of the co-primary endpoints"; wording is improved and is made applicable for each of the co-primary endpoints; clarified that Steroid Use will not be included in multivariate Cox regression model for the analysis of OS in subjects with no baseline corticosteroids; the levels of the covariate normally associated with the worst prognosis are detailed; Section 7.5.1.3 Consistency of Treatment Effect on OS in Subsets: "The analysis will be performed for both co-primary endpoints" is added; Disease diagnosis, Type of Surgery, Baseline corticosteroid use are added to subsets for the analysis; Baseline Pathology, Prior Corticosteroid use are excluded from subsets for the analysis; subsets for Race and smoking status are corrected Section 7.5.1.4 Subject Follow-Up: minimum follow-up analysis is added Section 7.5.1.5 Subsequent Therapy: populations for the analysis are specified: "for all randomized subjects with no baseline corticosteroids, all randomized subjects regardless of baseline corticosteroids use, [redacted]; clarification "Surgeries with the following reasons for surgery will not be considered subsequent therapy: Excisional biopsy, Incisional biopsy, Fine Needle Aspiration, Fluid Aspiration, Other" is added; clarified that *Subsequent* Radiotherapy is to be summarized; wording is improved. Section 7.5.5 Interim Analysis is moved at the end of the Section 7.5 Efficacy Section 7.5.2.1 Primary Analysis: population is defined: "PFS will be analyzed in all randomized subjects without baseline corticosteroids and in all randomized subjects regardless of baseline corticosteroids."; wording is improved; PFS rates timepoints are completed for compliance with the protocol; censoring status is completed with No baseline tumor assessment, No on-study tumor assessments categories

Table 10-1: Document History

Version Number	Author(s)	Description
		Section 7.5.2.2 Sensitivity Analysis: populations for the analysis are defined: "all randomized subjects without baseline corticosteroids and in all randomized subjects regardless of baseline corticosteroids"; wording is improved; Table 7.5.3.2-1: Censoring Scheme 1 for Sensitivity Analysis of PFS is replaced with Figure 7.5.2.2-1: Graphic Display of PFS accounting for assessment after subsequent therapy for clarity; "Subjects with no baseline or on-study tumor assessment and no death will be censored on the date of randomization." is removed from definition of PFS not considering clinical progression as not applicable Section 7.5.3 Other Efficacy Analyses is split to Subsections 7.5.3.1 Analyses of BOR, DOR, TTR, 7.5.3.2 Analyses of Tumor Burden, 7.5.3.3 Analysis of Immune-Related Tumor Effects, 7.5.3.4 Analysis of Subjects Treated beyond Progression; analysis of integrated data from -548 and -498 (-143) studies is removed. Section 7.5.3.1 Analyses of BOR, DOR, TTR: populations for analysis are defined: "all response evaluable subjects with no baseline corticosteroids and all response evaluable subjects regardless of baseline corticosteroids"; Time to response (TTR) analysis is added; wording for DOR analysis is improved. Section 7.5.3.2 Analyses of Tumor Burden: population for analysis is defined: "in response evaluable subjects"; "target" lesions are changed to "measurable" in accordance to RANO criteria. Sections 7.5.3.3 Analysis of Immune-Related Tumor Effects, 7.5.3.4 Analysis of Subjects Treated beyond Progression are added Section 7.5.4 Hierarchy for Efficacy Endpoints is added Section 7.5.5 Interim Analysis is changed to describe interim analyses for two co-primary endpoints in accordance with the updated protocol; Hierarchy of efficacy testing is added for clarity; details about control of type I error for second co-primary endpoint are added as well as projected nominal alpha levels are estimated. Section 7.6.7 Immune-Mediated Adverse Events: the analysis is to be conducted according to the Core Safety SAP, there for "See Core Safety SAP" replaced the repeat text [redacted]

Table 10-1: Document History

Version Number	Author(s)	Description
		[redacted] Multiple editorial changes
3.0	[redacted]	Section 1: Research hypothesis and schedule of analyses are modified in accordance with the protocol update. Section 2: Table 2.1-1 Study design schematic is modified in accordance with the protocol update. Section 3: Objectives are modified in accordance with the protocol update. Section 4: Primary and secondary endpoints are modified in accordance with the protocol update. Section 5: Sample size considerations are modified in accordance with the protocol update. [redacted] Section 7.4: Analysis on TMZ by phase is removed. Section 7.5.2: Statistical analysis on PFS is modified in accordance with the protocol update. Section 7.5.3.4: Statistical analysis on treatment beyond progression is updated. Section 7.5.4: Details on alpha recycling is added. Section 7.5.5: Interim analysis is modified in accordance with the protocol update. [redacted]

Table 10-1: Document History

Version Number	Author(s)	Description
		Multiple editorial changes
4.0	[redacted]	Section 1, Section 5 and Section 7.5.5 are updated on the change of removing interim analysis for PFS Section 2.5 is added. Section 4.3.7, Section 4.3.8 and Section 4.3.9 are updated on the analysis time window to be consistent with I-O core SAP. Section 7.5.3.2 is updated. Multiple editorial changes
5.0	[redacted]	Section 5: Replacing "O'Brien-Fleming" with "Pocock" in order to keep consistency with stopping boundary specified in sections 7.5.4 and 7.5.5 for all randomized population Section 7.5.4: Minor editorial changes on page 42 to add clarity Section 7.5.5: Minor editorial changes on page 43 to add clarity [redacted]
6.0	[redacted]	Section 1: Changes to the Planned Analyses section is updated to reflect the unblinding on 22-Dec-2020 per DMC recommendation. The timing of the OS primary analysis has been modified by the unblinding decision. It is not anymore, an event driven analysis. Only selected analyses will be performed for the primary CSR analysis and the end of study analysis at study closure.