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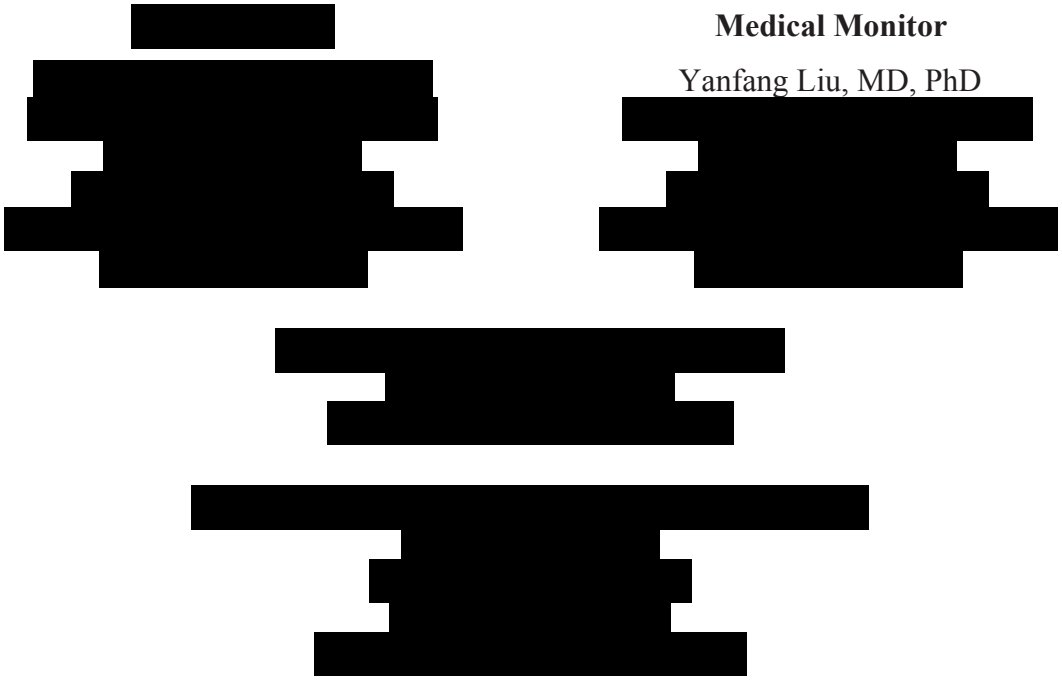
Date: 07-Oct-2015
Revised Date: 15-Nov-2017

Clinical Protocol CA209498

A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination with Radiation Therapy in Newly Diagnosed Adult Subjects with Unmethylated MGMT (tumor O-6-methylguanine DNA methyltransferase) Glioblastoma

CheckMate498: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 498

Revised Protocol Number: 05



Medical Monitor

Yanfang Liu, MD, PhD

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	15-Nov-2017	Incorporates Administrative Letters 04 and 05. In addition, the following major changes have been implemented in this Revised Protocol: 1. Removal of the interim analysis for superiority of the primary endpoint of OS 2. Addition of a secondary endpoint that evaluates, in newly diagnosed, unmethylated O-6-methylguanine DNA methyltransferase glioblastoma, any relationship between OS or PFS and tumor mutational burden in the radiation therapy (RT) + nivolumab arm compared to the RT + TMZ control arm
Administrative Letter 06	30-May-2017	Updated Study Director Credentials
Administrative Letter 05	08-May-2017	Updated Study Director and Medical Monitor
Administrative Letter 04	13-Jan-2017	Updated Study Director and removed incorrectly included pharmacokinetic and immunogenicity collections at the follow-up visits.
Revised Protocol 04	09-Nov-2016	Incorporates Amendment 08
Amendment 08	09-Nov-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. • Safety data from protocol CA209-143 added to the nivolumab clinical information in GBM. • 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 03	04-May-2016	Incorporates Amendment 06 and Administrative Letter 01
Amendment 06	04-May-2016	Major changes implemented in this Amendment include 3. Eligibility criteria a. Add exclusion for Gliadel® wafer b. Permit baseline MRI to be performed up to 72 hours post-operatively. If only CT is available, an MRI must be obtained prior to randomization. c. Modified language for women of child-bearing potential 4. Modify cutoff values used to define complete vs partial resection for purposes of randomization [redacted]

Document	Date of Issue	Summary of Change
		6. Update language throughout to conform with the Health Authority requests [redacted]
Administrative Letter 02	25-May-2016	[redacted]
Administrative Letter 01	26-Apr-2016	[redacted]
Revised Protocol 02	24-Feb-2016	Incorporates Amendment 04
Amendment 04	24-Feb-2016	Corrected the temozolomide dose modification guidance during maintenance temozolomide dosing; modified nivolumab dose delay and discontinuation criteria
Revised Protocol 01	12-Jan-2016	Incorporates Amendment 03
Amendment 03	12-Jan-2016	[redacted]

Document	Date of Issue	Summary of Change
Original Protocol	07-Oct-2015	Not applicable

SYNOPSIS

Clinical Protocol CA209498

Protocol Title: A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination with Radiation Therapy in Newly Diagnosed Adult Subjects with Unmethylated MGMT (tumor O-6-methylguanine DNA methyltransferase) Glioblastoma

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab (BMS-936558) 240 mg IV as a 30-minute infusion every 2 weeks for 8 doses followed by nivolumab 480 mg as a 30-minute infusion every 4 weeks beginning at Dose 9 until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever comes first, or Temozolomide 75 mg/m^2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide dosed on Days 1-5 at 150 mg/m^2 in cycle 1 increasing to 200 mg/m^2 as tolerated up to 6 cycles.

Study Phase: 3

Research Hypothesis: Treatment with radiation therapy plus nivolumab (RT + nivolumab) will improve overall survival (OS) compared with radiation therapy plus temozolomide (RT + TMZ) in subjects with newly diagnosed unmethylated MGMT glioblastoma (GBM).

Objectives:

Primary Objective:

To compare OS of nivolumab plus radiation therapy (RT + nivolumab) versus RT + TMZ in subjects with newly-diagnosed GBM and unmethylated MGMT tumors after surgical resection.

Secondary Objectives:

To compare investigator-assessed progression-free survival (PFS) of RT + nivolumab versus RT + TMZ

To estimate OS rate at 24 months (OS[24]) of RT + nivolumab versus RT + TMZ (final analysis only)

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]

Study Design:

This study will enroll subjects with newly-diagnosed 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] The screening number assigned in the CA209498 interactive voice response system (IVRS) will be the same subject number entered by the site to screen the subject into the CA209548 IVRS. Those with an MGMT status of methylated or indeterminate may be eligible to randomize in the CA209548 study. In order to randomize approximately 550 eligible subjects, a total of approximately 1200 subjects are expected to have tumor screening, of which approximately 600 subjects are anticipated to have unmethylated MGMT tumors.

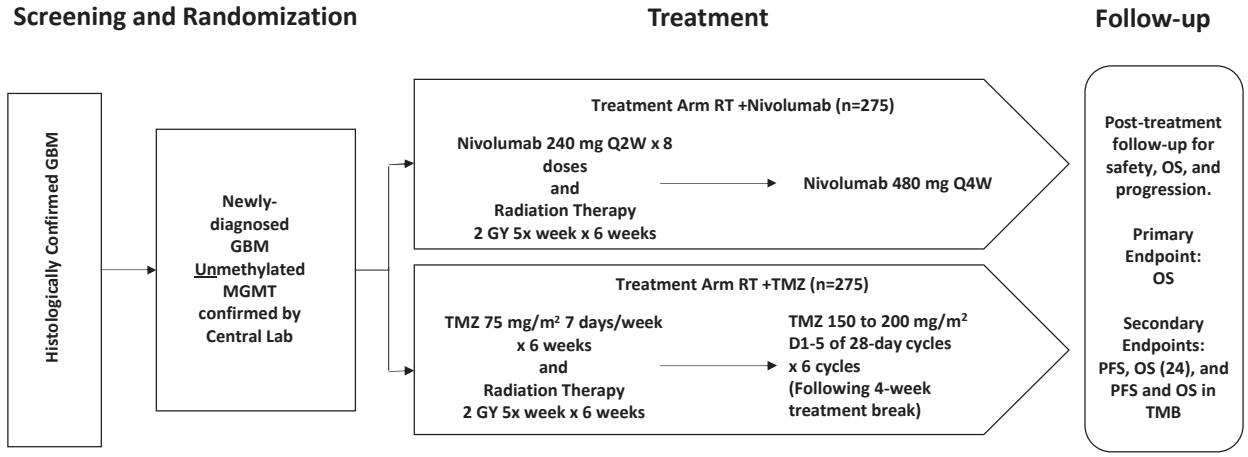
Subjects with a central laboratory result of unmethylated MGMT may continue in the screening phase, in which eligibility for randomization will be documented and baseline demographic and disease information submitted. During the screening phase a contrast-enhanced MRI should be obtained within 72 hours post-surgery (within 24 hours preferred).

When ready to begin study treatment, subjects will proceed to the treatment phase of the study. All subjects who enter the treatment phase, ie, all randomized subjects, will be followed for safety and tolerability, tumor progression and survival. A contrast-enhanced MRI should be performed 4 weeks after completing radiation therapy, then every 8 weeks (± 7 days) until progression regardless of treatment schedule. 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). After progression, subsequent treatment will be reported. All randomized subjects MUST be followed for survival (primary endpoint).

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



Study Population: Subjects must meet all eligibility criteria specified in Sections 3.3.1and 3.3.2 of the protocol, including the following:

Key Inclusion criteria:

- Males and Females age ≥ 18 years old;
- Newly diagnosed histologically confirmed supratentorial GBM (Grade 4 malignant glioma by World Health Organization including gliosarcoma)
  - No treatment for GBM other than surgery;
  - Post-operative baseline MRI following consensus recommendations must be obtained prior to randomization. It is strongly recommended that this scan be obtained < 72 hours or > 14 days post-surgery in order to minimize artifact
- Substantial recovery from surgical resection
  - No major ongoing safety issues following surgery
  - Able to taper steroids (preferably discontinued). Dose at randomization must be ≤ 20 mg prednisone daily or ≤ 3 mg dexamethasone daily (or equivalent)
- Centrally confirmed tumor unmethylated MGMT
- Karnofsky performance status of ≥ 70
- Clinically appropriate for concomitant RT + TMZ based on investigator judgement

Key Exclusion Criteria:

- Prior treatment for GBM (other than surgical resection)
- Recurrent GBM
- Biopsy only of GBM at surgery, defined as < 20% resection of enhancing tumor

- Ongoing requirement for supraphysiologic steroid defined as >20 mg prednisone daily or >3 mg dexamethasone daily (or equivalent), due to intracranial mass effect
- CNS hemorrhage of Grade >1 on baseline MRI scan, unless subsequently documented to have resolved
- Any known metastatic extracranial or leptomeningeal disease
- Secondary GBM (ie, progression from prior low-grade or anaplastic astrocytoma)
- Known IDH mutated tumor (if available; test not required)
- Concomitant use of Gliadel® wafer

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for BMS-936558		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Temozolomide	20 mg, 100 mg, 140 mg	IP

Subjects randomized to nivolumab should begin treatment within 7 days of randomization and continue at a dose of 240 mg given as a 30-minute IV infusion on Day 1 of each treatment cycle every 2 weeks for 8 doses. The nivolumab dose will then change to 480 mg as a 30-minute IV infusion every 4 weeks with dose 9. Subjects will continue on study treatment until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever comes first.

Study Assessments:

Safety Evaluation: Adverse events will be assessed continuously during the study and for 100 days post-last treatment. Adverse events will be coded using the most current version of MedDRA and reviewed for potential significance and importance. Adverse events will be evaluated according to the NCI CTCAE Version 4.03. Subjects should be followed until all treatment-related adverse events have recovered to baseline or are deemed irreversible by the investigator.

Efficacy Assessments: Post-operative baseline MRI following consensus recommendations must be obtained prior to randomization. It is strongly recommended that this scan be obtained < 72 hrs or > 14 days post-surgery in order to minimize artifact. Tumor imaging assessments following recent consensus recommendations will occur 4 weeks (± 7 days) after completion of radiotherapy (baseline MRI) then every 8 weeks (± 7 days) until disease progression. Per RANO, assessment of disease progression during study requires that MRI scan be performed >12 weeks after RT; it is therefore recommended that second on-treatment scan be performed at least 84 days after completion of RT. Subjects will be treated until unacceptable toxicity or disease progression. Following discontinuation of therapy, safety will be assessed through post-treatment Follow Up visits 1 and 2 (~35 and 115 days from last dose). Survival status will be assessed every 3 months (± 14 days) after follow up visits are completed, and may be completed via telephone or in person visits.

Statistical Considerations:

Sample Size: 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.

This study requires at least 390 events (ie, death) to provide 90% power to detect a hazard ratio (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.

The secondary endpoint of only PFS will be tested hierarchically.

Endpoints: 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. OS will be followed continuously while subjects are on study drug and every 3 months (± 14 days) via in-person or phone contact during survival follow-up phase of the study.

The secondary endpoint of 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 die without a reported progression will be considered to have progressed on the date of death. Subjects who did not have disease progression or die will be censored at the date of last tumor assessment. Subjects who did not have any on study tumor assessment and did not 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 secondary endpoint of survival rate at 24 months, is defined as Kaplan-Meier survival probability at 24 months.

An additional secondary endpoint is OS and PFS assessed in the TMB-high population, as assessed in the TMB assay where the numerical cut-off for high versus low will be specified in the statistical analysis plan. Definition for OS and PFS for this endpoint will be the same as defined earlier.

Analyses:

The analyses of primary endpoint of OS and secondary endpoints of PFS and OS[24] will be based on all randomized subjects. If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the secondary endpoint of PFS will be used to preserve a study-wise type I error rate at 0.05. OS[24] will be estimated using Kaplan Meier method. OS and PFS will also be estimated for the TMB-high population.

OS and PFS distribution in all randomized subjects will be compared between treatment groups using a two-sided stratified log-rank test. The hazard ratio (HR) and corresponding two-sided 95% confidence intervals (CIs) will be estimated in a Cox proportional hazard model using treatment as a single covariate stratified by complete or partial resection at baseline.

OS and PFS curves will be estimated using the Kaplan- Meier product-limit method. Median OS and PFS along with the corresponding two-sided 95% CIs using the log-log transformation will be computed.

OS [24] and the corresponding 95% CIs using the log-log transformation will be computed after all subjects have follow-up of at least 24 months. OS and PFS in the TMB-high population will be estimated using the Kaplan-Meier method.

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[redacted]

1.2 Research Hypothesis

Treatment with radiation therapy plus nivolumab will improve OS compared with radiation therapy plus temozolomide in subjects with newly-diagnosed unmethylated MGMT GBM.

1.3 Objectives(s)

1.3.1 Primary Objective

To compare OS of nivolumab plus radiation therapy (RT + nivolumab) versus temozolomide plus radiation therapy (RT + TMZ) in subjects with newly-diagnosed GBM and unmethylated MGMT tumors after surgical resection.

1.3.2 Secondary Objectives

- 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 (final analysis only)
- To evaluate, 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.

[redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC), approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC, for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion

4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia), may only be enrolled in the study with the consent of a legally-acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but is capable of forming an opinion and assessing information, to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

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]

[redacted]

Post-operative baseline MRI following consensus recommendations,[52] must be obtained prior to randomization. It is strongly recommended that this scan be obtained < 72 hrs 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-op preferred).

Subjects with a central laboratory result of **un**methylated MGMT 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 3.1.1.

When ready to begin study treatment, subjects will proceed to the **treatment phase** of the study; for details, see section 3.1.2. All subjects who enter the treatment phase, ie, 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 RANO criteria described in Section 5.4.2. Additional assessments will be performed for cognitive function, neurologic function, biomarkers and patient-reported quality of life outcomes.

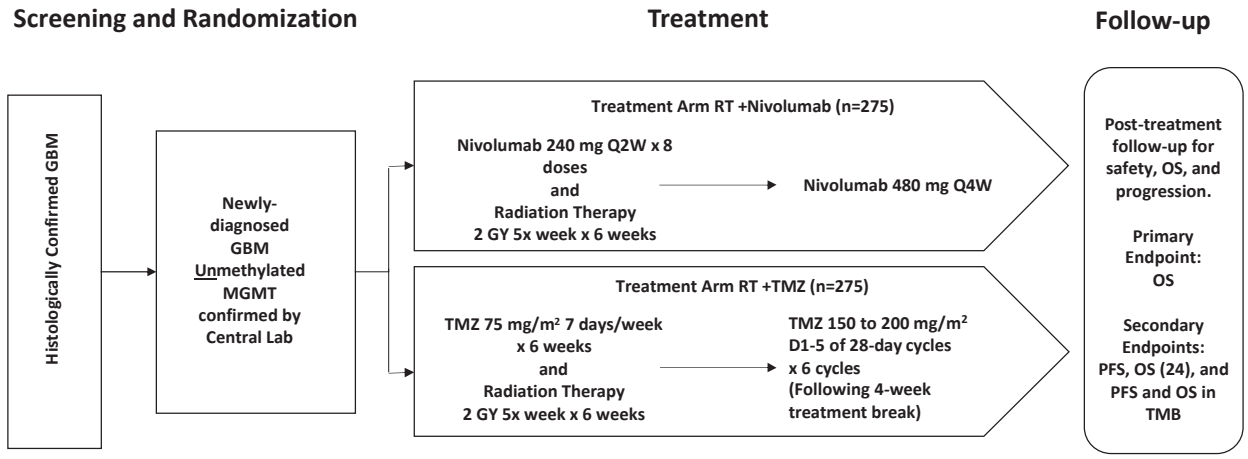
After cessation of study treatment for any reason, all randomized subjects will enter a **follow up** phase. In the short-term, visits are defined for reporting of treatment-related AEs. All subjects in whom disease progression had not been detected at the time study treatment is stopped will be followed 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. For details on the follow-up phase, see section 3.1.3.

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, see Section 7.

The study design schematic is presented in Figure 3.1-1.

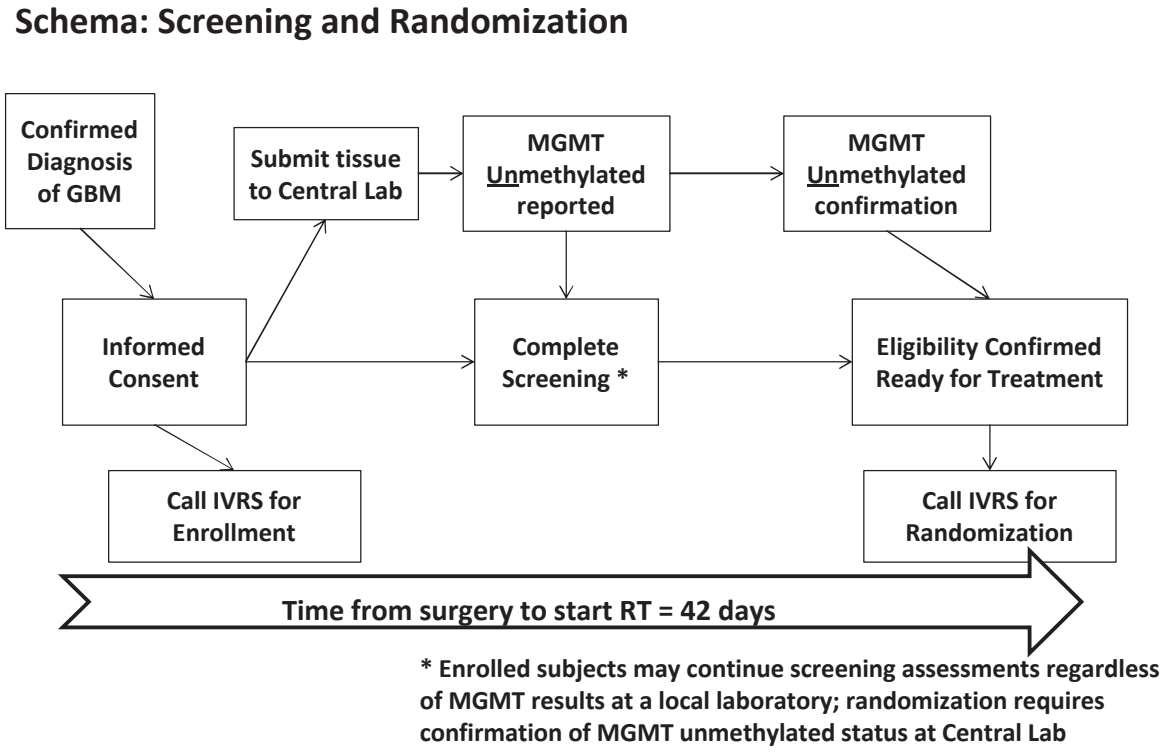
Figure 3.1-1: Study Design Schematic



3.1.1 Screening Phase

Subjects will provide consent for enrollment and tumor submission in the peri-operative period, so that MGMT status can be determined. Consent for randomization and study treatment may be deferred until MGMT unmethylated status and eligibility is established (or be obtained concurrently). However, consent for tumor submission only may be obtained pre-operatively based on a clinical/radiographic diagnosis of GBM. The clinical circumstances should be considered with respect to the timing of consent.

Figure 3.1.1-1: Screening and Randomization



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 Table 5.1-1.

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 < 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.

3.1.2 Treatment Phase

3.1.2.1 Randomization and Initiation of Treatment

After eligibility has been confirmed, subjects who are clinically ready to begin study treatment (ie, recovered from surgery) will proceed to the treatment phase of the study via a second call into the IVRS system. At this call, subjects will be randomized 1:1 to receive radiotherapy plus nivolumab (RT + nivolumab) or radiotherapy plus temozolomide (RT + TMZ).

Randomization will be prospectively balanced (ie, stratified) according to post-operative MRI finding of "complete" versus "partial" resection. For the purposes of this study, a complete resection will be defined as ≤ 5 mm of contrast enhancement on T1 images of the post tumor surgical region following surgical resection. A partial resection is defined as ≥ 10 mm of residual contrast-enhancing tumor tissue on T1 images following surgical resection. Resections with a residual of between > 5 and < 10 mm of enhancement will be defined as partial or complete by the investigator's best clinical judgment.

The total time elapsed from diagnostic surgery to initiation of RT should not exceed 42 days, including a maximum of 7 days from randomization to initiation of RT; however, treatment may be delayed if clinically required. Subjects in the RT + nivolumab arm should begin nivolumab within 7 days after randomization, and may be given at any time prior to RT start, as clinically appropriate. Subjects randomized to the RT + TMZ arm will begin combination chemoradiotherapy on the same day, within 7 days after randomization, as clinically appropriate.

See sections 4.5.1 and 4.5.2 for details of dosing for nivolumab and temozolomide; for an overview of the treatment phase, see Section 3.1.2.

3.1.2.2 Radiotherapy

Radiation therapy should begin after substantial recovery from surgical resection, preferably not more than 42 days after surgery; however, treatment may be delayed if clinically required. External-beam RT to a total dose of 60 Gy will be administered in daily doses of 2 Gy, typically on a 5 days on / 2 days off schedule as appropriate for scheduling, over 6-7 weeks. Patients considered clinically inappropriate for full dose RT (60 Gy ± 5%) are not eligible, eg, due to older age, tumor location. RT is administered to the post-operative tumor volume plus a 2-3 cm margin, as directed by a radiation oncologist.

Radiation therapy planning and administration should follow currently-accepted guidelines.[53] Additional details are provided in Appendix 2. RT may be administered at a facility more convenient to the patient, but approval from Sponsor or designee must be obtained if not part of the same practice group as the investigative study site. For AEs related to RT, see section 6.

Note: Suspected progression occurring within or during 12 weeks after RT may be "pseudoprogression"; in this setting, suspected progression should be confirmed prior to discontinuation of treatment. BMS Medical Monitor should be consulted.

3.1.3 Follow-up Phases

The follow-up phase begins when the decision is made to discontinue a subject from study treatment, including for AEs, for maximum clinical benefit (investigator decision), for subject request, for completion of TMZ maintenance therapy (6 cycles), disease progression, or another reason.

Subjects will be evaluated for AEs with visits at 35 days (± 7 days) and 115 days (± 7 days) after last dose; for details, see Table 5.1-3 and Section 6. All AEs must be documented for a minimum of 100 days after discontinuation, but drug-related toxicities should continue to be followed until they resolve, return to baseline or are deemed irreversible.

[redacted]

3.1.4 Overall Study Duration

The start of the trial is defined as first visit for first subject screened. End of trial is defined as last visit or scheduled procedure shown in Time and Events schedule for the last subject. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

Enrollment and randomization of 550 subjects is expected to require approximately 10 months. Final analysis is planned after at least 390 deaths have been reported. Depending on assumptions, this analysis is anticipated to occur at approximately 33 months after first subject is randomized, respectively; see Statistical Considerations, section 8 for details.

Data may be collected up to 12 months after the pivotal analysis has occurred, after which the study may be closed. At discretion of the Sponsor, survival data may continue to be collected for up to 5 years.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug. Study drug will be supplied via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Written informed consent and HIPAA authorization (applies to covered entities in the US only) obtained from the subject/legal representative prior to performing any protocol-related procedures;

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study;

2. Target Population

a) Newly-diagnosed histologically-confirmed supratentorial glioblastoma (Grade IV malignant glioma by World Health Organization, including gliosarcoma)[54]

i) No treatment for GBM other than surgery;

ii) Post-operative baseline MRI following consensus recommendations,[52] must be obtained prior to randomization. It is strongly recommended that this scan be obtained <72 hrs or >14 days post-surgery in order to minimize artifact;

b) Substantial recovery from surgical resection

i) No major ongoing safety issues following surgery;

ii) Able to taper steroids (preferably discontinued). Dose at randomization must be ≤ 20 mg prednisone or ≤ 3 mg dexamethasone daily (or equivalent);

c) Centrally confirmed (ie, third-party vendor) unmethylated MGMT;

d) Karnofsky performance status of ≥ 70 (Appendix 3)

e) Clinically appropriate for concomitant temozolomide plus radiation therapy based on institutional guidelines.

f) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized/has not been treated) is permitted. If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Males and Females, age ≥ 18 years old;

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study treatment (ie, 30 days [duration of ovulatory cycle] plus the time required for the investigational drug to undergo approximately five half-lives.

i) WOCBP randomized to receive temozolomide should use an adequate method to avoid pregnancy for 6 weeks (30 days plus the time required for temozolomide to undergo five half-lives) after last dose of temozolomide.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of the study treatment with nivolumab and for 7 months after the last dose of study treatment (90 days [duration of sperm turnover] plus the time required for the investigational drug to undergo approximately five half-lives).

   i) Males are encouraged to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with TMZ.

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However WOCBP must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise on the use of highly effective methods of contraception (Appendix 4), which have a failure rate of < 1% when used consistently and correctly.

4. Physical and Laboratory Test Findings

a) WBC ≥ 2,000/μL

b) Neutrophils ≥ 1,500/μL

c) Platelets ≥ 100 x10^3/μL

d) Hemoglobin ≥ 9.0 g/dL

e) Serum creatinine ≤ 1.5 x upper limit of normal (ULN), unless creatinine clearance (CrCl) ≥ 50 mL/min (measured or calculated using the Cockcroft-Gault formula)

   i) Female CrCl = $\frac{(140\text{-age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$

   ii) Male CrCl = $\frac{(140\text{-age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$

f) AST ≤ 3.0 x ULN;

g) ALT ≤ 3.0 x ULN;

h) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who may have a total bilirubin < 3.0 x ULN);

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Prior treatment for GBM (other than surgical resection)

b) Recurrent GBM

c) MGMT methylated, or indeterminate GBM

d) Biopsy-only of GBM at surgery, defined as <20% resection of enhancing tumor

e) Ongoing requirement for supraphysiologic steroid, defined as > 20 mg prednisone or > 3 mg dexamethasone daily (or equivalent), due to intracranial mass effect

f) Central nervous system (CNS) hemorrhage of Grade > 1 on baseline MRI scan, unless subsequently documented to have resolved

g) Any known metastatic extracranial or leptomeningeal disease

h) Secondary GBM (ie, progression from prior low-grade or anaplastic glioma)

i) Known IDH-mutated tumor (if available; test not required)

j) Concomitant use of Gliadel® wafer;

2. Medical History and Concurrent Diseases

a) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results

b) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways

c) Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll

d) Subjects with a co-existing condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone or equivalent, are permitted in the absence of active autoimmune disease

e) (Not applicable per Protocol Amendment 06)

f) Subjects with history of life-threatening toxicity, including hypersensitivity reaction, related to prior immunoglobulin treatment for another condition (except those considered unlikely to re-occur, with written approval of BMS medical monitor) or any other study drug component

g) History or evidence upon physical/neurological examination of other central nervous system condition (eg, seizures, abscess) unrelated to cancer, unless adequately controlled by medication or considered not potentially interfering with protocol treatment

h) Surgical procedure < 7 days prior to study treatment, vascular access device no restriction

i) Subjects unable (eg, due to pacemaker or ICD device) or unwilling to have a contrast-enhanced MRI of the head

j) History of allergy or hypersensitivity to study drug components

k) Unable to swallow oral medication or any gastrointestinal disease or surgical procedure that may impact the absorption of study drug

l) Subjects with prior hypersensitivity to dacarbazine (DTIC)

m) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast

3. Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, and/or detectable virus

b) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated by local regulation.

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required.)

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

3.4 Concomitant Treatments

It is expected that enrolled subjects will have systemic corticosteroids tapered as quickly as clinically appropriate during screening phase, and discontinued if possible prior to randomization.

Supportive care for all disease-related or treatment-related AEs should be maximized for all subjects on this study. See Section 4.5.2.4 for prophylaxis of Pneumocystis pneumonia.

3.4.1 Prohibited and/or Restricted Treatments

Concurrent anti-neoplastic therapy, including other chemotherapy, immunotherapy, additional radiation therapy or investigational agents for treatment of GBM are prohibited during the treatment phase. Use of any additional noninvasive medical device treatment of GBM (eg, novoTTF, Optune©) is prohibited. The following medications are prohibited during the study treatment (unless utilized to treat a drug related AE):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.3)

3.4.2 Other Restrictions and Precautions

Subjects with a coexisiting condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications (including within 14 days of randomization) are excluded. Subjects continuing to require supraphysiologic steroids (prednisone > 20 mg daily or > 3 mg dexamethasone per day or equivalent) for increased intracranial pressure may not be randomized. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone or equivalent, are permitted in the absence of active autoimmune disease.

Study-related MRI imaging of the brain will be performed using contrast materials. Subjects with severe renal insufficiency, who should not receive contrast materials (eg, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2) are excluded.

Certain surgically-implanted devices (pacemaker, deep brain stimulator, metallic implants, etc.) are incompatible with MRI imaging. The local imaging facility and investigator should determine the appropriate precautions or guidelines that should be instituted for subjects with tattoos, body piercings or other body art. For other locally performed imaging, it is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status, other contraindications), the appropriate imaging modality and contrast regimen for each subject. The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee.

In accordance with TMZ labeling, valproic acid should not be used concomitant with TMZ; at investigator discretion, alternative anticonvulsants should be used.

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Steroid use should be minimized prior to randomization. Systemic corticosteroid use or physiologic replacement doses of steroids are permitted, even if > 20 mg/day prednisone equivalents, for: a) treatment-related AEs b) symptoms related to GBM, including suspected tumor flare or pseudoprogression, or c) treatment of non-autoimmune conditions (eg, prophylaxis for contrast dye allergy, contact hypersensitivity). Details regarding corticosteroid use prior to and during the study will be collected (name of medication, doses utilized, start and stop dates, frequency of use, route of administration). Information regarding concomitant corticosteroid use may be analyzed with regard to study outcome measures.

Subjects requiring chronic treatment with corticosteroids may be treated with histamine-2-receptor antagonists or proton pump inhibitors as prophylaxis for potential gastrointestinal adverse reactions (ulceration, perforation, hemorrhage) unless otherwise contraindicated.

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Disease progression, except as described in Section 4.5.1.6
- Unacceptable toxicity requiring discontinuation of TMZ or nivolumab, see Sections 4.5.1.5 and 4.5.2.3
- Maximum clinical benefit, as determined by investigator
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject, see Sections 4.5.1.5 and 4.5.2.3
- Subject's request to stop study treatment (other than for an AE)
- Completion of 6 cycles of maintenance TMZ (for exception see Table 4.5-1)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Initiation of antineoplastic therapy other than as randomized

This is a survival study, therefore subjects discontinuing study treatment will **remain on study** for documentation of progression and death.

In case of pregnancy, the investigator must immediately notify the Sponsor or designee–of this event. In most cases, study drug will be permanently discontinued in an appropriate manner. Please call the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants re-initiation of study drug, after termination of the pregnancy and if allowed by local regulations, a discussion between the investigator and the Sponsor or designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Follow up

In this study, *OS is the primary endpoint of the study*. Post treatment follow-up is thus of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Table 5.1-3 until death or the conclusion of the study. Subjects who discontinue study drug will continue to be followed.

BMS may request that survival data be collected on all treated/randomized subjects outside of the 3 month (± 14 days) specified visit schedule. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, if possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational Medicinal Product (Non-IP/Non-IMP) and can consist of the following:

Table 4-1: Study Drugs for CA209498

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open-label	10 mL per vial (5 or 10 vials/carton Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing
Temozolomide Capsules[b]	20 mg	IP	Open-label	Wallet/blister card containing 5 capsules White opaque cap and body, imprinted in yellow ink. The cap is imprinted with '891.' The body is imprinted with '20 mg' and two stripes.	Do not store above 25 °C.
Temozolomide Capsules[b]	100 mg	IP	Open-label	Wallet/blister card containing 5 capsules White opaque cap and body, imprinted in pink ink. The cap is imprinted with '892.' The body is imprinted with '100 mg' and two stripes.	Do not store above 25 °C.
Temozolomide Capsules[b]	140 mg	IP	Open-label	Wallet/blister card containing 5 capsules White opaque cap and body, imprinted in blue ink. The cap is imprinted with '929'. The body is imprinted with '140 mg' and two stripes.	Do not store above 25 °C.

[a] May be labeled as either "BMS-936558-01" or "Nivolumab"

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. Although not a medicinal product, Radiation Therapy is also considered part of study treatment.

In this protocol, investigational products are:

- BMS-936558 (nivolumab)
- Temozolomide

4.2 Non-Investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

See Section 4.5 for details regarding study drug dosing in combination with RT.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

Infusion-related supplies (eg, IV bags, in-line filters (0.2-1.2 micron), 0.9% NaCl or 5% Dextrose solution) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab).[51]

4.3.1 Nivolumab (BMS-936558)

For details regarding drug storage, preparation, administration, and use time please refer to the BMS-936558 (nivolumab) Investigator Brochure and/or pharmacy reference sheets.

4.3.2 Temozolomide

For countries in which BMS is providing packaged/labeled temozolomide, please refer to package insert, summary of product characteristics (SmPC), or similar document for details regarding drug preparation, administration and use time.

For countries where local sourcing of temozolomide is permitted, product should be stored, prepared and administered in accordance to the package insert, summary of product characteristics (SmPC) or similar document.

4.4 Method of Assigning Subject Identification

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 will be detailed in the IVRS manual.

4.5 Selection and Timing of Dose for Each Subject

Dosing schedules for both arms are detailed in Table 4.5-1. All subjects will undergo surgical resection and radiotherapy as outlined in Sections 3.1. For the RT + nivolumab arm, the first dose of nivolumab is to be administered within 7 days of randomization. For the RT + TMZ arm, the first dose of temozolomide is to be administered at the beginning of radiotherapy. Treatment details

are described separately for each arm below; treatment modifications (eg, dose delay, reduction, or discontinuation) will be based on specific laboratory and AE criteria, as described in Sections 4.5.1 and 4.5.2.

Table 4.5-1: Selection and Timing of Dose

Drug	Dose	Frequency of administration	Route of administration	Duration
Arm RT + Nivolumab (BMS-936558)	240 mg, then 480 mg after 8 doses	Every 2 weeks, for 8 doses, then Every 4 weeks after 8 doses	30 minute intravenous (IV)	Until progression, unacceptable toxicity, or discontinuation from treatment
Arm RT + TMZ (Temozolomide)	75 mg/m^2 daily during RT then 150 mg/m^2 D1-5 for C1 and increased to 200 mg/m^2 D1-5 for C2-C6 as tolerated	Daily from first day of RT to last day of RT (not to exceed 49 days) then 4 week break followed by TMZ daily for 5 days every 28 days x 6 cycles[a]	Oral (PO)	Until completion of dosing, progression, unacceptable toxicity or discontinuation from treatment

[a] Additional cycles of temozolomide are permitted for subjects enrolled in Japan

4.5.1 Nivolumab Dosing

4.5.1.1 Nivolumab Dose and Schedule

Subjects randomized to nivolumab should begin treatment within 7 days of randomization, but RT should begin within 42 days after definitive resection, but may be delayed if clinically required. Subjects will continue on study treatment until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever comes first.

Subjects randomized to the RT + nivolumab arm will begin nivolumab at a dose of 240 mg, given as a 30-minute IV infusion on Day 1 of each treatment cycle Q2W for 8 doses. The nivolumab dose will then change to 480 mg as a 30-minute IV infusion Q4W with dose 9 (starting week 17, in the absence of delays). Nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. Nivolumab infusion must be promptly followed by a saline flush to clear the line.

Continuation of nivolumab treatment with suspected progression is permitted, see Section 4.5.1.6. Treatment will continue until discontinuation from study treatment for any of the criteria listed in sections 3.5 or 4.5.1.5.

There will be no dose escalations or reductions of nivolumab allowed. Subjects may be dosed no less than 12 days from the previous dose during Q2W cycles. A dose given more than 3 days after the intended dose will be considered a delay. For Q4W dosing cycles, subjects may be dosed within a ± 3 day window. Premedications are not recommended for the first dose of nivolumab.

Subjects should be monitored for infusion reactions during nivolumab administration. If an acute reaction is noted, subjects should be managed according to Section 4.5.1.8.

Doses of nivolumab may be interrupted, delayed or discontinued depending on how well the subject tolerates treatment. Dosing visits are not skipped, only delayed. Nivolumab should be delayed (see Section 4.5.1.3) for toxicities considered at least possibly-related to nivolumab. Nivolumab interruption refers to stopping the infusion, eg, for an infusion reaction (see Section 4.5.1.8).

No incompatibilities have been observed between nivolumab for injection and polyvinyl chloride (PVC), non-PVC/non-DHEP (di(2ethylhexyl)phthalate) IV components or glass bottles. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution because the product does not contain any antimicrobial preservative or bacteriostatic agent.

4.5.1.2 Dose Modifications for Nivolumab

Dose modification is not allowed for nivolumab; for dose delay, see 4.5.1.3.

4.5.1.3 Dose Delay Criteria for Nivolumab

Tumor assessments should continue per protocol schedule, even if dosing is delayed.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities
- Grade 3 skin drug-related AE
- Grade 3 drug-related laboratory abnormality with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 ALT/AST or total bilirubin will require dose discontinuation (see Section 4.5.1.5)
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated. Nivolumab dosing can be resumed on the established dosing schedule (q2 or q4 weeks) when retreatment criteria are met (Section 4.5.1.4).

4.5.1.4 Criteria to Resume Dosing for Nivolumab

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity

- For subjects with Grade 2 AST, ALT, and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.1.5) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor (or designee).
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

4.5.1.5 Treatment Discontinuation Criteria for Nivolumab

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurological toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurological toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT, or total bilirubin requires discontinuation*

      *In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 drug-related endocrinopathy AEs, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor (or designee).
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed, if approved by the BMS Medical Monitor (or designee).
  - Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

4.5.1.6 Continuing Nivolumab with Suspected Progression

Accumulating evidence indicates that a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of disease progression, eg, due to inflammatory reaction simulating progression ("tumor flare" or pseudoprogression). Subjects on the RT + nivolumab arm may, at investigator discretion, continue nivolumab in the setting of suspected progression until progression is confirmed. [Note: this is not the same as confirmation of progression occurring within 12 weeks after RT, which applies to both treatment arms.] Communication with the BMS Medical Monitor is strongly encouraged. If the investigator believes that the subject continues to derive clinical benefit by continuing treatment, the subject should continue assessments according to Table 5.1-2.

Subjects may continue nivolumab beyond initial (suspected) progression only if they meet the following criteria:

- Subject is tolerating nivolumab

- Treatment will not delay intervention to prevent imminent complications, eg surgery for relief of symptomatic intracranial mass effect
- Investigator-assessed overall clinical benefit

Radiographic assessment should be repeated after suspected progression as clinically required in order to determine whether there has been a decrease in the tumor size or continued progression. If possible, perfusion images should also be obtained. All MRI scans should be submitted to the imaging vendor as soon as possible.

Re-operation should be considered, if lesion is surgically accessible, to differentiate immune-treatment effects from progression. The BMS Medical Monitor should be consulted. Potential for clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive benefit from continued treatment with nivolumab. Nivolumab treatment should be discontinued permanently upon confirmation of RANO-assessed progression but prolonged observation (eg, 3 months) may be required, as suggested in Okada et al.[40]

4.5.1.7 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in Appendix 1 and in the nivolumab Investigator Brochure.

4.5.1.8 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For **Grade 1** symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For **Grade 2** symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further BMS-936558 will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For **Grade 3 or 4** symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.5.2 Temozolomide Dosing

4.5.2.1 Temozolomide Dose and Schedule

Subjects on RT + TMZ will be administered temozolomide (TMZ, Temodar®) daily during RT and as maintenance therapy for 6 cycles. TMZ dosing will be performed according to institutional standard; the following guidance is drawn from published literature.

Temozolomide (TMZ) will be dosed at 75 mg/m^2 once per day continuously throughout RT, typically for 42 days and with a maximum of 49 days. See Table 4.5.2.3-1 for dose modifications during concomitant RT + TMZ dosing. After completion of RT, there will be a 4-week break. Subjects will receive 6 cycles of temozolomide daily x 5 days every 28 days.

Table 4.5.2.1-1: Dose Levels for TMZ Maintenance Monotherapy

Dose Level	TMZ Dose in mg/m^2/day	Notes
-1	100 mg/m^2/day	Reduction for prior toxicity
0	150 mg/m^2/day	Dose during Cycle 1
1	200 mg/m^2/day	Dose during C2-6 in absence of TMZ-related toxicity

Source: adapted from Temodar® package insert (PI)

In the first maintenance cycle TMZ is given at a dose of 150 mg/m^2, and then increased to 200 mg/m^2 in cycle 2 as follows: If, during the first cycle, all non-hematologic AEs observed were grade ≤ 2 (except alopecia, nausea and vomiting) and with platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x10^9/L, then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. Doses of TMZ are not precise but are adjusted based on tolerance; rounding of up to 10% is entirely acceptable.

If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at Cycle 2, then the dose should not be escalated in further cycles based on AEs (see Table 4.5.2.3-2). If there was a prior dose reduction during the concomitant period with RT, then dose -1 should be the starting dose for subsequent cycles. Table 4.5.2.1-1 describes dose levels during temozolomide monotherapy.

4.5.2.2 Criteria to Start Temozolomide Maintenance Cycles

Maintenance treatment begins following a 4 week treatment break after RT. TMZ treatment may begin if blood count (obtained within the prior 3 days) shows ANC ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L and any Grade ≥ 3 non-hematologic AE (except alopecia) must have resolved to grade ≤ 1). If AEs persist, treatment should be delayed by 1 week for up to 4 consecutive weeks.

If, after 4 weeks of delay, all AEs have still not resolved to ≤ grade 1: then any further maintenance treatment with temozolomide should be discontinued.

4.5.2.3 Dose Modifications or Discontinuation for Temozolomide

Table 4.5.2.3-1: Temozolomide Dose Modification Guidelines During Concomitant Radiotherapy and TMZ Dosing

Laboratory Value/Clinical Criteria:	Dose Modification	Additional Information:
ANC:		
≥ 0.5 and < 1.5 x10^9/L	Delay TMZ Dosing	Continue when ≥ 1.5 x10^9/L
< 0.5 x10^9/L	Discontinue TMZ	May restart at dose -1 in maintenance
Platelets:		
≥ 10 and <100 x 10^9/L	Delay TMZ Dosing	Continue when ≥ 100 x 10^9/L
< 10 x 10^9/L	Discontinue TMZ	May restart at dose -1 in maintenance
Any Non-Hematologic Toxicity (except alopecia, nausea, vomiting)		
CTC Grade 2	Delay TMZ dosing	Continue when ≤ CTC Grade 1 (except for alopecia, nausea, vomiting)
CTC Grade 3 or 4	Discontinue TMZ dosing	May restart at dose -1 in maintenance

Source: adapted from Temodar® package insert (PI)

Table 4.5.2.3-2: Temozolomide Dose Modification Guidelines During Maintenance TMZ Dosing

Laboratory Value/Clinical Criteria:	Dose Modification[a]	Additional Information:
ANC:		
< 1.0 x10^9/L	Reduce TMZ Dosing by 1 dose level per Table 5.4.2-1	
< 0.5 x10^9/L	Discontinue TMZ dosing	If Dose Level -1 (100 mg/m2) still results in unacceptable toxicity
Platelets:		
≥ 10 and < 100 x 10^9/L	Reduce TMZ Dosing by 1 dose level per Table 5.4.2-1	
< 10 x 10^9/L	Discontinue TMZ dosing	If Dose Level -1 (100 mg/m2) still results in unacceptable toxicity

Table 4.5.2.3-2: Temozolomide Dose Modification Guidelines During Maintenance TMZ Dosing		
Laboratory Value/Clinical Criteria:	**Dose Modification[a]**	**Additional Information:**
Any Non-Hematologic Toxicity (except alopecia, nausea, vomiting)		
CTC Grade 3	Reduce TMZ Dosing by 1 dose level per Table 5.4.2-1	
CTC Grade 4	Discontinue TMZ dosing	If Dose Level -1 (100 mg/m2) still results in unacceptable toxicity or the same Grade 3 non-hematologic toxicity recurs

[a] Dose reductions of temozolomide during maintenance should be based on the on the lowest blood count and worst non-hematologic toxicity during the prior cycle.

Source: adapted from Temodar® package insert (PI)

4.5.2.4 Supportive Care during Temozolomide

Subjects should be treated receive prophylaxis against Pneumocystis pneumonia (inhaled pentamidine [preferred], dapsone or oral trimethoprim–sulfamethoxazole) during concomitant treatment with RT plus TMZ and may be continued during maintenance at investigator discretion. Details regarding prophylactic agent use will be collected as concomitant medications.

Antiemetic prophylaxis with metoclopramide or a 5-hydroxytryptamine 3 antagonist is allowed prior to treatment with temozolomide.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Assessment of study medications will be performed at each study visit. For subjects receiving temozolomide, the subject should be instructed to bring all unused study drug to each visit as well as any empty containers. The dates and number of capsules dispensed and returned must be recorded on the drug accountability form maintained on-site. Unused or partially used study drug are returned to the subject and dosing should continue from the in-use container until it has been emptied. Subjects will be instructed to record dosing in a dosing diary which will be reviewed at each visit, in combination with drug accountability to confirm treatment compliance. Sites should discuss discrepancies between the diary and the drug log to reconcile actual dosing with the patient at each visit.

4.8 Destruction of Study Drug

For this study, IP (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

If...	Then...
IP supplied by BMS (including its vendors)	Any unused IP supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless IP containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If IP will be returned, the return will be arranged by the responsible Study Monitor.
IP sourced by site, not supplied by BMS (or its vendors) (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of IP provided by BMS (or its vendors). Destruction of non-IP sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

4.9 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedures (CA209498)

Procedure	Screening Visit 1	Notes
Informed Consent for Enrollment	X	Call IVRS to obtain subject number; see Section 3.1.1
Inclusion/Exclusion Criteria	X	**Must be confirmed prior to randomization**
Medical History	X	
Physical Examination, Vital Signs, Performance Status	X	Height, weight, BSA; Karnofsky performance status (Appendix 3), and full physical exam, BP, HR, RR, temperature, within 14 days prior to randomization
Tumor Sample Submission	X	Surgical biopsy (block or slides) Submission: See Laboratory Manual. Central Laboratory MGMT result must be available prior to randomization.
Baseline Tumor Assessment	X	Contrast-enhanced MRI[a] within 72 hours post-surgery (within 24 hours preferred); (see Imaging Manual). If not available, must be performed prior to randomization (> 2 weeks post-op preferred). See Section 5.4.
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
Concomitant Medication collection	X	Within 14 days prior to randomization, to include corticosteroid dose
Adverse Events Assessment	X	Serious Adverse Events from time of consent. See Section 6.1.1
Laboratory Tests	X	CBC w/differential; Chemistry panel including: AST, ALT, ALP, T.Bili, BUN or serum urea level, albumin, creatinine, phosphorus, Ca, Na, K, Cl, LDH, Glucose, within 14 days prior to randomization. TSH, T3 and T4 (Free or Total), Hep B/C (HBVsAG, HCV antibody or HCV RNA), within 28 days prior to randomization
Urinalysis	X	Dipstick, obtain within 14 days prior to randomization
Pregnancy Test [WOCBP only]	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours of first dose of study therapy
[redacted]	[redacted]	[redacted]

[a] Post-operative baseline MRI following consensus recommendations must be obtained prior to randomization. It is strongly recommended that this scan be obtained <72 hrs or >14 days post-surgery in order to minimize artifact. There is no requirement that MRI performed prior to randomization be on a "qualified machine." See section 5.4

Table 5.1-2: On-Treatment Assessments (CA209498)

Procedure	RT + TMZ	TMZ Maintenance	RT + Nivolumab	Notes: Windows refer to calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified.
IVRS Randomization call	Day 1		Day 1	Confirm eligibility criteria prior to randomization.
Targeted Physical Examination, Vital Signs	Q2 wks	Day 1 of each cycle	Q2 wks x 8 doses, then Q4 wks	Weight. BP, HR, RR, temperature, and Karnofsky Performance Status
Adverse Events Assessment	Continuously			Record at each visit
Review of Concomitant Medications	X	X	X	Record at each visit, including steroid dose
Radiation Therapy	See Note		See Note	Total dose 60 Gy over 6-7 weeks, see Section 3.1.2.2
CBC with Differential	Weekly	Day1&22 of each cycle	Within 3 days prior to each dose	Weekly if delayed and as clinically indicated
Chemistry panel	Q4 wks	Day 1 each cycle	Within 3 days prior to each dose	Chemistry panel: AST, ALT, ALP, T.Bili, albumin, BUN or serum urea, creatinine, Ca, Na, K, Cl, LDH, Glucose Additional tests, as clinically indicated, will also be submitted
Thyroid Function Test		X	X	TSH every 8 weeks, T3 and T4 (Free or Total, if TSH abnormal) and as clinically indicated
Pregnancy Test [WOCBP only]	Every 4 weeks			Serum or urine pregnancy test every 4 weeks (±3 days; minimum sensitivity 25 IU/L or equivalent units of HCG).
[redacted]			[redacted]	[redacted]
Tumor Assessment	X (See Note)			Contrast-enhanced MRI 4 weeks (± 7 days) after completing RT, then every 8 weeks (± 7 days)[a] until progression. See Section 5.4.1
[redacted]	[redacted]			[redacted]

Table 5.1-2: On-Treatment Assessments (CA209498)

Procedure	RT + TMZ	TMZ Maintenance	RT + Nivolumab	Notes: Windows refer to calendar days. Procedures must be done within 72h prior to dosing unless otherwise specified.
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
Health Care Resource Utilization	X (See Note)			Obtained prior to dosing Day 1 Week 1 and then with each MRI, (± 7 days) see Section 5.8.4
[redacted]	[redacted]			[redacted]
Dispense Nivolumab			X (see note)	Day 1 within 7 days of randomization, then every 2 weeks for 8 doses, then every 4 weeks
Dispense Temozolomide	D1, D15, D29 & D43 (if needed)	D1 each cycle		Temozolomide taken daily during RT then 4 week break, then daily x 5 in 28-day cycles x 6 cycles, see Section 4.5.2
Tumor Sample at time of progression or suspected progression	At time of PD or suspected PD			If biopsy or surgical resection is performed at progression or suspected progression, a tumor sample (block or slides) should be submitted for central neuropathologic review
Assess Temozolomide Compliance	X	X		Review medication diary

[a] Per RANO, assessment of disease progression during study requires that MRI scan be performed >12 weeks after RT; it is, therefore, recommended that second on-treatment scan be performed at least 84 days after completion of RT.

Table 5.1-3: Treatment Follow-up and Survival Follow-Up (CA209-498)

Procedure	Treatment Follow-up[a]	Survival Follow-up[b]	Notes
TIMING	35 and 115 days (±7 Days) after last dose	Q 3 Months (± 14 Days)	
Targeted Physical Examination	X		Weight. BP, HR, RR, temperature and Karnofsky Performance Status
Adverse Events Assessment	X	X	Beyond 100 days from the last dose of study treatment subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible or until lost to follow-up or withdrawal of study consent
Laboratory Tests	X		CBC w/differential, LFTs, BUN, creatinine and TSH at 35 days, repeat labs at 115 day visit if study drug-related toxicity persists.
Pregnancy Test [WOCBP only]	X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG).
Review of Concomitant Medications	X		
Tumor Assessment	X Q8 weeks (± 7 days) until PD		Required for subjects who did not progress on study treatment, eg, discontinued for AEs.
NANO scale	X	X	Completed by study physician with each MRI (± 7 days)
Cogstate		X	Cogstate Assessments should occur at Months 6, 12, 18, and 24 (± 15 days) and then continue every 12 months (± 15 days) as long as MRIs are performed. See Section 5.7.1.
Biomarker Sample	X		Serum and whole blood at time of progression; See Section 5.6.
Tumor Sample at time of progression	X	X	If biopsy or surgical resection is performed at the time of progression or suspected progression, a tumor biopsy sample (block or slides) should be submitted for central neuropathologic review.
EORTC QLQ-C30 and BN20	X		
EQ-5D	X	X	May be obtained through telephone call or clinic visit
Survival Status		X	Every 3 months (± 14 days) (clinic visit or telephone contact), during Survival phase, include documentation of subsequent chemotherapy.

[a] Subjects must be followed for at least 100 days after last dose of study treatment. Follow-up visit #1 (FU1) occurs approximately 35 days (± 7 days) after the last dose or coinciding with the date of discontinuation (± 7 days) if date of discontinuation is greater than 30 days after last dose. Follow-up visit #2 (FU2) occurs approximately 115 days (± 7 days) after the last dose

[b] Survival Follow-up visits to occur every 3 months (± 14 days) from Follow-up Visit 2. BMS may request that survival data be collected on all treated subjects outside of the 3 month specified window. At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within the Screening will be permitted (in addition to any parameters that require a confirmatory value). Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Any new result will override the previous result (ie, the most current result prior to randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.2 Study Materials

- NCI CTCAE version 4.03
- Nivolumab Investigator Brochure
- SMPC and/or USPI for Temozolomide
- Pharmacy Binder
- [redacted]
- Site manual for operation of IVRS, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- [redacted]
- Imaging Manual includes specifications for Radiology scan submission manual
- Dosing Diary for temozolomide

[redacted]

[redacted]

5.4 Efficacy Assessments

All subjects will undergo brain MRI at the time points specified in Table 5.1-1, Table 5.1-2, and Table 5.1-3. The baseline MRI will be used for stratification of randomization. If MRI is not available at study enrollment, a high-quality contrast-enhanced CT scan may be used; in this case, a MRI must be performed prior to randomization (> 2 weeks post-op preferred). Additional MRI scan may be obtained if clinically appropriate, eg for radiotherapy planning, but is not required; in this case the last scan prior to randomization will be considered the baseline MRI.

Subjects who are unable (due to existent medical condition, ie, pacemaker or ICD device) or unwilling to have a brain MRI at baseline are excluded from the study. Subjects who become unable to undergo MRI imaging after randomization may continue in the study for assessment of OS as long as there is no safety issue which would require monitoring by MRI.

Study sites will retain local access to the imaging results for safety and efficacy reading purposes. The study investigator will review the local MRI results as clinically appropriate to ensure that any potentially emergent clinical situations are addressed in a timely fashion. Clinically significant radiologic findings or changes from baseline scans will be coded as AEs or serious adverse events according to the criteria described below in Section 6. Additional radiographic findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled and handled by the Study investigator as per standard medical/clinical judgment.

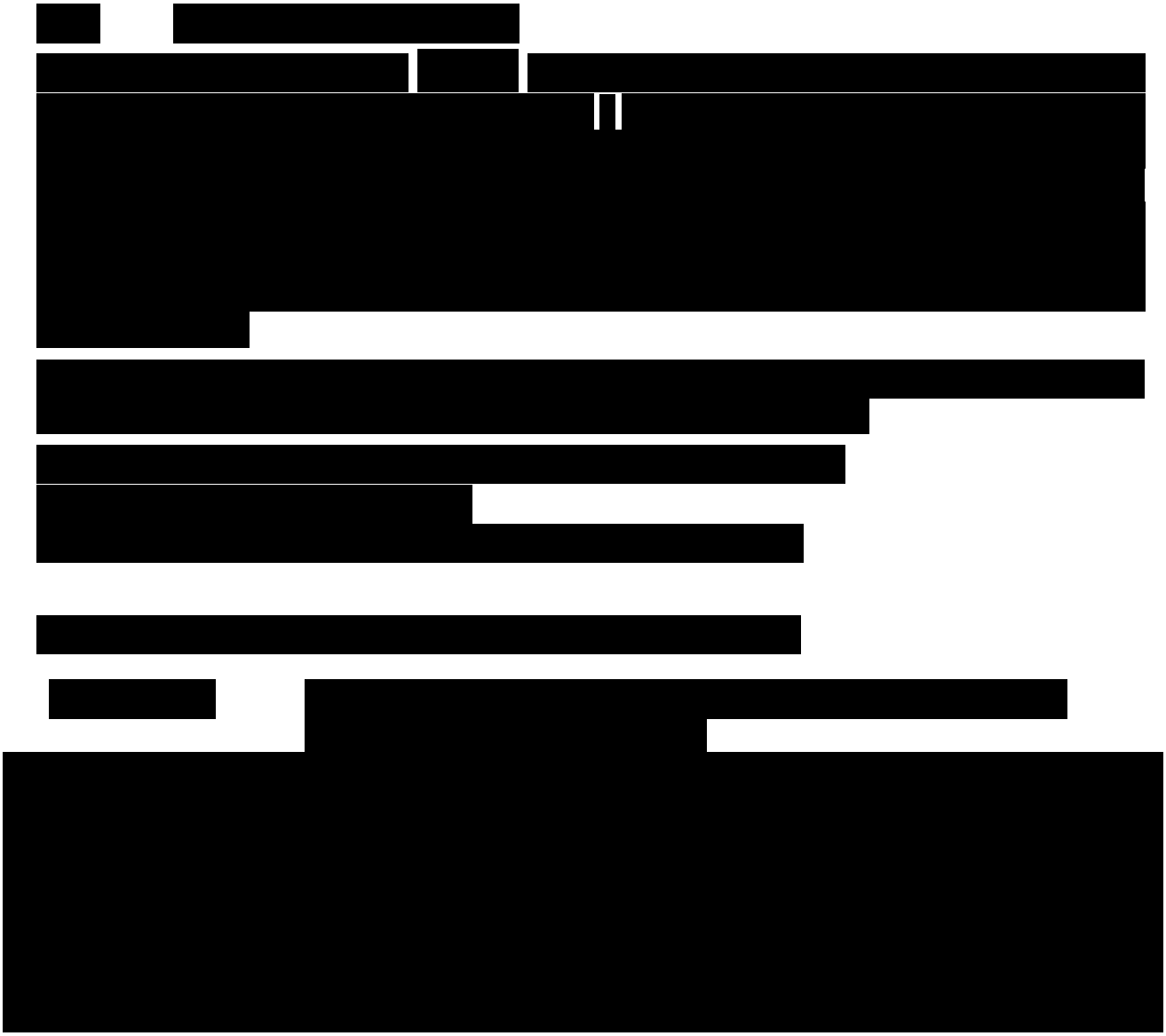
5.4.1 Suspected Progression

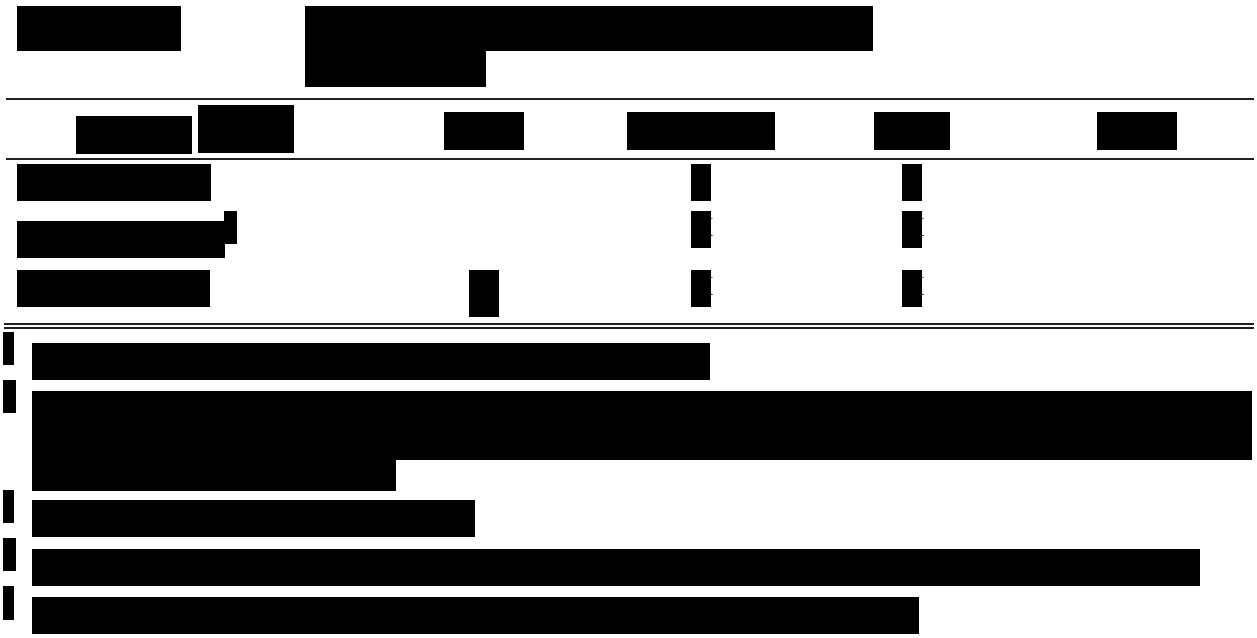
In order to distinguish potential treatment effects (or "pseudoprogression") from progressive disease and thus to minimize premature discontinuation of nivolumab or temozolomide, subjects who initially meet radiologic criteria for disease progression, but are tolerating study drug, may continue receiving study drug until confirmation of progression with an MRI performed approximately 8 weeks later. If possible, MRI perfusion images should also be obtained. If a determination cannot be made after an 8 week interval, then treatment may continue until either progression is confirmed or regression is observed, consistent with either pseudoprogression or

immune-treatment effect. Consultation with the BMS Medical Monitor is recommended but not required.

Confirmation of progression is mandatory if recurrence occurs within 12 weeks of completion of RT. Suspected disease progression within 12 weeks after the end of RT must be confirmed by subsequent MRI performed within 8 weeks after the initial radiological assessment of progression. Prior to 12 weeks after RT, progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling.[39] Note: in the absence of radiographic or histologic confirmation of progression, clinical decline alone is not sufficient for definition of progressive disease.

If the follow-up assessment confirms that progression has occurred, the date of progression will be the date at which progression was first determined. If the follow-up assessment does not confirm progression, then the original time point response will be assessed as SD.





5.6.1 Tumor Samples

Tumor specimens will be obtained from consenting subjects prior to treatment to characterize immune cell populations and expression of selected tumor markers. Tumor tissue (block or slides) must be available for submission prior to randomization. If a block is not available, a minimum of twenty (20) unstained slides of good quality is required. In situations where on-treatment biopsies or surgeries are performed, tumor sample should be sent for central pathology reading.

5.6.1.1 Tumor sample collection details

Collection of tumor tissue at diagnostic surgery is required for study eligibility. If clinically appropriate, additional biopsies obtained at any time, eg, if progression is suspected, may also be collected.

Biopsy samples from neurosurgical resections should be fixed in 10% Neutral-buffered formalin for 24 – 48 hours prior to paraffin embedding. Tumor tissue samples should not be shipped in formalin as the temperature and length of fixation cannot be controlled during shipping.

In order to provide adequate tissue for MGMT testing and exploratory analyses, two paraffin blocks are requested (1 minimum). If only slides are available, they should be unstained, have a recommended tissue section thickness is 4 microns and must be positively charged. Slides should be shipped refrigerated at 2-8° C.

An assessment of tissue quality by a pathologist is strongly encouraged at the time of the procedure. The tumor tissue that is obtained will be divided in the following priority order: 1) into formalin for fixation and paraffin-embedding, 2) into RNALater for RNA/DNA extraction.

Sample shipments should include a completed requisition form containing collection date, collection method, primary/met, site, fixation conditions, and a copy of Pathology report, if available.

Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Procedure Manual at the time of study initiation.

5.6.1.2 MGMT status

Randomization to this study is limited to subjects with established unmethylated MGMT status. Testing will be performed using a centralized RT-PCR assay. Details regarding MGMT testing are provided in Section 5.6.1.1.

[redacted]

5.6.1.4 Characterization of T cell repertoire

As described above, DNA sequencing may be performed on pre-and post-treatment tumor tissue to assess the composition of the T cell repertoire. DNA will be isolated from either the FFPE tumor block or from RNAlater or equivalent preparations.

5.6.1.5 Gene expression profiling

Tumor tissue collected in RNAlater or equivalent fixative will be examined for mRNA gene expression by Affymetrix gene array technology and/or quantitative real-time polymerase chain reaction (qPCR) to detect expression of selected immune related genes.

5.6.1.6 Tumor genotyping, mutational analysis, and tumor antigen profiling

DNA and RNA from tumor samples will be analyzed using whole-exome and transcriptome sequencing to determine the number of mutations found within a given sample relative to a normal host tissue, such as adjacent non-transformed cells or PBMC. Mutations that are detected will be analyzed for their ability to bind the MHC I and MHC II proteins using prediction algorithms, such as NetMHC. Evaluating the ability of tumor mutations to bind MHC molecules will provide evidence that these mutations are serving as antigens that are recognized by the immune system and are potential rejection antigens.

[redacted]

5.8 Other Assessments

5.8.1 Results of Central Pathology Reading

In situations where on-treatment biopsies or surgeries are performed, tumor sample should be sent for central pathology reading. Instructions for shipping biopsy samples/slides can be found in the lab manual. Investigators will receive central pathology results.

[redacted]

5.8.3 Results of Central Radiology Assessments

The clinical management of subjects during the study protocol and secondary outcomes (PFS) will be based upon local radiologic tumor measurements and the investigator-assessed RANO response criteria described in Section 1.2. Radiologic imaging from this study will be also be transmitted to a centralized imaging core lab for storage and for analysis by blinded independent central review as determined by the Sponsor. The site will be informed of quality issues or need for repeat scanning via queries from the core lab.

5.8.4 Healthcare Resource Utilization

Healthcare resource utilization data associated with hospitalizations and non-protocol specified medical visits related to either study therapy or disease will be collected for all randomized subjects. The healthcare resource utilization will be collected prior to dosing on day 1 week 1 and then at a convenient clinical visit near the time of the MRI scan.

[redacted]

confusion, seizure, weakness, vomiting, aphasia, hydrocephalus, etc (depending on tumor site). Use of "tumor flare" as a single aggregate AE term is preferable to reporting each individual neurologic finding. (Note: MRI findings per se are not AEs.)

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

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.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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 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 2009[34])
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 (ie, death) provides 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 8.1-1).

Power calculations were done using East v 6.3.

Table 8.1-1: Key parameters of Sample Size Calculation of OS

Assumptions	Analysis	Goal/Timing (from first subject randomized)	Significant Nominal p-value	Probability for declaring superiority Under HA/H0
$\alpha = 0.05$ Power = 90% Control arm (RT+TMZ) median OS = 13.0 months; Treatment arm (RT + Nivolumab) Median OS = 18.0 months HR = 0.72	Final Superiority	390 OS events/ 33 months	Superiority Observed nominal p-value ≤ 0.05	90%/5%

The 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. Only PFS will be tested using a hierarchical testing procedure. (Section 8.4.2).

8.2 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.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

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. OS will be followed continuously while subjects are on study drug and every 3 months (± 14 days) via in-person or phone contact during survival follow-up phase of the study.

8.3.2 Secondary Endpoint(s)

The first secondary objective (comparing PFS between arm RT + nivolumab and RT + TMZ) will be measured by the endpoint of PFS. 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 die without a reported progression will be considered to have progressed on the date of death. Subjects who did not have disease progression or die will be censored at the date of last tumor assessment. Subjects who did not have any on study tumor assessment and did not 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 (Section 5.4.3).

The secondary objective (estimate the overall survival rate at 24 months (OS[24]) of RT + nivolumab) will be Kaplan-Meier probability of survival at 24 months.

The secondary objective is OS and PFS assessed in the TMB-high population, as assessed in the TMB assay where the numerical cut-off for high versus low will be specified in the statistical analysis plan (SAP). Definition for OS and PFS for this endpoint will be the same as defined earlier.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all randomized subjects by treatment group, as randomized, using descriptive statistics.

8.4.2 Efficacy Analyses

The analyses of primary (OS) and secondary (PFS, OS[24]) endpoints will be based on all randomized subjects. Safety summaries will be based on all treated subjects. If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the secondary endpoint of PFS will be used to preserve a familywise type I error rate at 0.05.

The formal statistical testing for PFS will take place only if OS is statistically significant. Secondary endpoints of OS[24] and OS and PFS in the TMB-high population will be estimated using the Kaplan Meier method.

8.4.2.1 Analyses of Primary Endpoint

The distribution of OS in all randomized subjects will be compared in arms RT + nivolumab and RT + TMZ at the final analysis via a two-sided, log-rank test, stratified by complete resection or partial resection at baseline. The Kaplan-Meir product limit method will be used to estimate the survival curve in each arm including medians and its 95% CI, OS rates at pre-specified time points. The HR and the corresponding two-sided 95% CIs will be estimated in a Cox proportional hazards model with treatment arm as a single covariate stratified by corresponding stratification factor (complete or partial surgical resection at baseline).

8.4.2.2 Analyses of Secondary Endpoints

The comparison of PFS will be based on a two-sided log-rank test stratified by corresponding stratification factor (complete surgical or partial resection at baseline). The details of the testing procedure will be specified in the SAP. OS[24] will be estimated when all censored subjects have had follow-up of at least 24 months. OS and PFS in the TMB-high population will be estimated using the Kaplan-Meier method. Additional details for the analysis of OS[24] endpoint will be included in SAP.

[redacted]

8.5 Interim Analyses

Not applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority, must be sent to BMS. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS or designee.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), AE tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.2 Records

9.2.1 Records Retention

The investigator (or head of study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator (or head of study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator (or head of study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

Records for IP (whether supplied by BMS, its vendors, or the site) must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If...	Then...
Supplied by BMS (or its vendors):	• Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted)

If...	Then...
	• amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the

Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
AE(s)	adverse event(s)
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine aminotransferase
ALP	Alkaline phosphatase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
BMS	Bristol-Myers Squibb
BOR	Best Overall Response
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
Ca++	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CTA	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTLA 4	Cytotoxic T lymphocyte associated antigen 4
%CV%	geometric mean
DILI	drug-induced liver injury

Term	Definition
dL	deciliter
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTIC	Dacarbazine
EANO	European Association of Neuro-Oncology
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EQ-VAS	EuroQol visual analog scale
EORTC	European Organization for Research and Treatment of Cancer
ESR	expedited safety report
FDA	Food and Drug Administration
FFPE	Formalin-Fixed, Paraffin-Embedded
FLAIR	fast fluid-attenuated inversion recovery
FSH	follicle stimulating hormone
GBM	glioblastoma
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
Gy	gray (radiotherapy dose)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus

Term	Definition
HCV-RNA	hepatitis C virus-ribonucleic acid
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	heart rate
HrQoL	health-related quality of life
HRT	hormone replacement therapy
IB	investigator brochure
ICD	Implantable Cardioverter Defibrillator
ICF	informed consent form
ICH	International Conference on Harmonisation
ICOS	increased activation markers
ie	id est (that is)
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	immunohistochemistry
imAEs	immune-mediated adverse events
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
I-O	immuno-oncology
IP	investigational product
iRANO	Immune Radiologic Assessment in Neuro-Oncology
IRB	Institutional Review Board
IRC	Independent Radiology Review Committee
IU	International Unit
IUDs	Intrauterine devices
IV	intravenous
IVRS	Interactive voice response system
ITIM	Immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
K+	potassium

Term	Definition
kg	kilogram
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test
mAbs	monoclonal antibodies
mg	milligram
Mg/kg	Milligram per kilogram
Mg++	magnesium
MGMT	tumor O-6-methylguanine DNA methyltransferase
mL	milliliter
MRI	Magnetic Resonance Imaging
MST	Medical safety team
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
N	nivolumab (BMS-936558)
Na+	sodium
NANO	Neurologic Assessment in Neuro-Oncology
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NIMP	non-investigational medicinal products
NSCLC	non-small cell lung carcinoma
O_2	Oxygen
OS	overall survival
PBMC	Peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
PD	progressive disease

Term	Definition
PD-1	Programmed cell death protein 1
PD-L 1	Programmed cell death ligand 1
PFS	Progression-free survival
PID	Patient identifier
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PPK	population pharmacokinetics
PR	partial response
PVC	polyvinyl chloride
QD	once a day
QLQ-C30	European Organization for Research and Treatment of Care General Cancer Module
QLQ-BN20	European Organization for Research and Treatment of Cancer - Brain Cancer Module
QOL	Quality of life
QxW	Every x weeks
RANO	Radiologic Assessment in Neuro-Oncology
RCC	Renal cell carcinoma
RNA	ribonucleic acid
RR	respiratory rate
RT	radiation therapy
RT-PCR	reverse transcription polymerase
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SmPC	summary of product characteristics
SNP	single nucleotide polymorphism
SOC	standard of care
SOP	Standard Operating Procedures
T1/2	Geometric elimination half-life
TCR	T cell receptor

Term	Definition
TIL	tumor infiltrating lymphocytes
TMB	tumor mutational burden
TMZ	Temozolomide
TSH	thyroid stimulating hormone
µg	microgram
ULN	upper limit of normal
VAS	visual analogue scale
Vss	volume of distribution at steady state
w	week
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

UNACCEPTABLE METHODS OF CONTRACEPTION

1) Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2) Withdrawal (coitus interruptus)
3) Spermicide only
4) Lactation amenorrhea method (LAM)