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Clinical Protocol CA209548

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

(**CheckMate 548**: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 548)

Protocol Amendment 07

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 07	02-Sep-2021	Updated Appendix 1 Management Algorithms to include the version from Addendum No. 01 to the Nivolumab Investigator Brochure Version 19 (28-Sep-2020) for studies using CTCAE version 4.0. Amended descriptions of DMC activities to clarify that DMC involvement does not continue after study unblinding. Updated COVID-19 vaccine risk/benefit and administration guidance. Updated text regarding contraception for male subjects with female partners.
Protocol Amendment 06	26-Feb-2021	The Data Monitoring Committee (DMC) determined that there was no possibility for the study to have a positive overall survival (OS) result, and recommended to unblind the sites and subjects, which was approved by BMS. The study was officially unblinded on 22-Dec-2020. As a consequence, the timing of the primary OS analysis, originally planned for when 337 and 494 events were to be reached respectively for the population without corticosteroids at baseline and the overall population, has been updated. To prevent any bias due to unblinding of subjects, the primary OS analysis will be conducted using the unblinding date of 22-Dec-2020. Study procedures for subjects remaining on treatment and in safety follow-up have been simplified, and OS follow-up after unblinding has been removed. Protocol language per BMS standards for nivolumab studies and for COVID-19 has been incorporated. Incorporates approved Administrative Letters 10 and 11.
Administrative Letter 14	25-Nov-2020	Study personnel change
Administrative Letter 11	22-Jul-2019	Clarification of the timing of on-study contrast-enhanced magnetic resonance imaging (MRI) scans, clarification of the use of the term ‘indeterminate’ to describe the MGMT status of the tumor in some subjects, corrections to hyperlink labels to Table 4.5.2.1-1 in Table 4.5.2.3-2, and clarification that baseline MRI scan is the last scan prior to randomization that meets the diagnostic quality required in the imaging manual.
Administrative Letter 10	18-Jul-2019	Removal of the interim analysis for Progression Free Survival (PFS).

Approved v8.0 [redacted]

Document	Date of Issue	Summary of Change
Revised Protocol 05	08-Nov-2018	Major Changes • Progression Free Survival is now a primary objective of the study, changed from secondary. • Overall survival (OS) rate at 12 and 24 months and PFS based on investigator assessment by RANO criteria are added as secondary objectives. [redacted] • Blinded Independent Central Review (BICR) of study images has been added to the study. • The statistical section has been revised to support changes in the study objectives. The study will now include 1 formal interim analysis for PFS and 1 formal interim analysis for OS for superiority.
Administrative Letter 06	19-Jul-2017	[redacted]
Revised Protocol 04	17-Jun-2017	Incorporates Amendment 12
Amendment 12	17-Jun-2017	Corrects an error in the Dose Delay Criteria and aligns the Dose Delay Criteria and Dose Discontinuation Criteria with the nivolumab program standards.
Revised Protocol 03	03-Jun-2017	Incorporates Amendment 11
Amendment 11	03-Jun-2017	Changed to a Phase 3 trial with Primary Objective of OS
Administrative Letter 04	08-May-2017	Change in Study Director
Revised Protocol 02	26-Oct-2016	Incorporates Amendment 09
Amendment 09	26-Oct-2016	This amendment updates the nivolumab clinical information in GBM and safety management algorithms as a result of most recent version of the Investigator Brochure (version 15). The amendment also clarifies several items as well as corrects minor errors. [redacted] • Renal, Pulmonary, Hepatic, and Skin safety management algorithms revised based on IBv.15 • Time windows and technical descriptions around assessments and administration schedule have been added or expanded to allow for flexibility at the site level while not affecting the conduct or the analysis of the data.
Revised Protocol 01	22-Apr-2016	Incorporates Amendment 05
Amendment 05	22-Apr-2016	The main purpose of the first global amendment is to provide additional clarification on several items in response to questions arising from investigators and IRB/IEC/HAs:

Document	Date of Issue	Summary of Change
		• Add any ≥ 2 creatinine drug-related abnormality. • Delete provision regarding delay in subjects with baseline Grade 1 ALT, AST or total bilirubin toxicity to be allowed to continue dosing to Grade ≥ 3 toxicity, thus having all subjects delay for ≥ Grade 2 drug-related toxicity. • Modify criteria to specify that subjects with Grade 2 AST/ALT, or total bilirubin elevations may resume dosing when lab values return to baseline and management with corticosteroids is complete. • Modify criteria to specify subjects must discontinue for any Grade 3 non-skin, drug-related adverse event lasting > 7 days or which recurs with some exceptions. • Modify criteria for drug-related liver function test abnormality to discontinue for AST or ALT > 5 x ULN, Total bilirubin > 3 x ULN or concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN. • Add a definition for single blind. Additional modifications are as described below: • Revise resection cutoffs • Clarify time windows and technical descriptions around the infusion, examinations, and administration schedule • Remove exclusion criteria 2d for subjects with interstitial lung disease • Add exclusion criteria 2k to exclude subjects with prior hypersensitivity to dacarbazine (DTIC) • Add a Radiotherapy Guideline Appendix • Move Highly Effective Methods of Contraception to an Appendix • Incorporate other minor changes to correct and/or clarify protocol requirements
Original Protocol	16-Dec-2015	Not applicable

Approved v8.0 [redacted]

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 07:

It was determined following finalization of Protocol Amendment 06 that the Protocol Appendix 1 Management Algorithms were not the current version as included in the Nivolumab Investigator Brochure. Appendix 1 has been updated to include the MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0 from Addendum No. 01 to the Nivolumab Investigator Brochure Version 19 (28-Sep-2020).

Descriptions of Data Monitoring Committee (DMC) activities are amended to clarify that DMC involvement does not continue after study unblinding. Clarification is added regarding COVID-19 vaccine benefit risk and administration. The protocol instructions regarding contraception in male study participants who are sexually active with women of childbearing potential are updated to align with the temozolomide (TMZ) summary of product characteristics (SmPC) or other local regulation. Other minor changes are made for consistency throughout the protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Protocol Summary Study Design; Section 3.1: Study Design and Duration; Section 7: Data Monitoring Committee and Other External Committees	Clarified that subjects may remain on nivolumab and TMZ treatment following study unblinding. Clarified that DMC activities cease following study unblinding.	Subjects may remain on study treatment post-unblinding and will be followed only through the safety follow-up phase. Limited reporting will be completed and subject safety will be monitored by the sponsor.
[redacted]		
Section 3.1.4: Overall Study Duration; [redacted] Section 8.5: Interim Analyses	Text regarding a progression free survival (PFS) interim analysis (IA) was removed.	The PFS IA was previously removed from the protocol, but references to it were inadvertently left in Section 3.1.4 and Section 8.
Section 3.3.1: Inclusion Criteria	Inclusion Criterion 3e was revised.	The requirement is updated to align with the TMZ summary of product characteristics or other local regulatory document.
Section 3.4: Concomitant Treatments; Section 3.4.1: Prohibited and/or Restricted Treatments	Added text regarding COVID-19 vaccines.	Clarified that non-live Covid-19 vaccines are allowed and are to be handled in the same manner as other non-live vaccines.
Section 4.5.1.7: Management Algorithms for Immuno-Oncology Agents; Appendix 1: Management Algorithms	Added myocarditis to the list of adverse event groups for which a management algorithm is included in Appendix 1. Management algorithms updated to current version for studies using CTCAE Version 4.0.	Updated to align with Addendum No. 01 to the nivolumab Investigator Brochure Version 19 (28-Sep-2020) and more-recent version of the management algorithms.
Section 5.1: Flow Chart/Time and Events Schedule; [redacted]	Table 5.1-2 On-treatment Assessments adverse event assessment note updated to include discontinuation from study. [redacted]	Aligned with simplified procedures following study unblinding; subsequent response, survival, [redacted] are no longer needed.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
[redacted]		
Section 6.4: Pregnancy	Instruction that a pregnancy occurring in the female partner of a male subject within 3 months of his last dose of TMZ must be reported to the Sponsor has been updated to 6 months.	The requirement is updated to align with the summary of product characteristics or other local regulatory document.
[redacted]		

PROTOCOL SUMMARY

Clinical Protocol CA209548

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

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab (BMS-936558) 240 mg IV or placebo 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 after 8 doses until progression, unacceptable toxicity (or other reasons), and temozolomide 75 mg/m^2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide 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: Addition of nivolumab to standard radiotherapy (RT) plus temozolomide (TMZ) will increase PFS in subjects with newly-diagnosed GBM of MGMT-methylated or indeterminate subtypes and will increase OS in subjects with newly-diagnosed GBM of MGMT-methylated or indeterminate subtypes without baseline corticosteroids and regardless of baseline corticosteroids.

Objectives:

Primary Objective:

The two primary objectives are:

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

Secondary Objective:

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

[redacted]

[redacted]

Study Design:

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

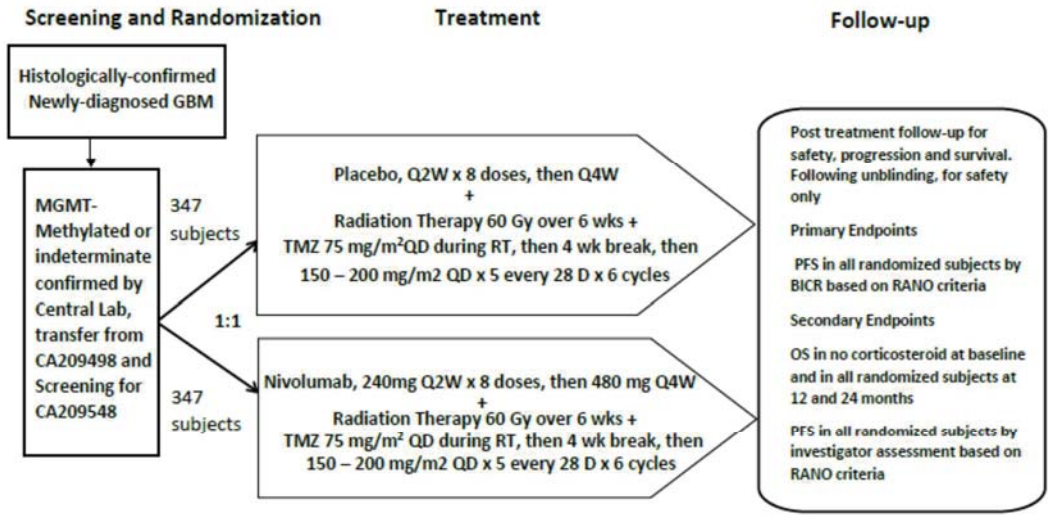
In order to randomize 693 eligible subjects, a total of approximately 780 subjects are expected to be enrolled. After signing consent, eligibility for randomization will be documented. When ready to begin study treatment, subjects will be randomized in a 1:1 ratio to the RT/TMZ/nivolumab or the RT/TMZ/placebo arm, stratified by partial vs. complete resection. 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 approximately 4 weeks (± 7 days) after completing radiation therapy, then every 8 weeks (± 7 days) up to 24 months post randomization, then every 12 weeks until progression regardless of treatment schedule or dose delay. Tumor progression will be assessed using Radiologic Assessment in Neuro-Oncology criteria (RANO). [redacted]

On 09-Dec-2020 the Data Monitoring Committee (DMC) conducted a pre-planned routine safety review of all available safety data, and initially recommended that the study continue unchanged. Subsequently, the DMC noted that it is not possible for the study to demonstrate an OS benefit for the investigational treatment arm, and after further discussion with the DMC, the decision was made to unblind all study subjects, and inform all investigators, ethics committees, and health authorities as required. Following study unblinding, subjects may continue nivolumab and/or TMZ (if applicable) treatment, following protocol procedures. After cessation of nivolumab and/or TMZ treatment for any reason, all randomized subjects will enter a short follow-up phase for reporting of treatment-related adverse events. Subjects in whom disease progression had not been detected at the time study treatment is stopped will no longer be followed for progression. All subjects will no longer be followed for survival.

A DMC will meet regularly during the study until study unblinding to ensure that subject safety is carefully monitored.

Study Schematic:



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

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

Key Inclusion criteria:

- Males and females age ≥ 18 years old
- Newly diagnosed histologically confirmed supratentorial glioblastoma (Grade 4 malignant glioma by World Health Organization including gliosarcoma)
  a) No treatment for GBM other than surgery
  b) 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
  a) No major ongoing safety issues (eg infection requiring IV antibiotics) following surgery
  b) For subjects on corticosteroids at the time of Screening: able to taper steroids (preferably discontinued). Dose at randomization must be ≤ 20 mg prednisone daily or ≤ 3 mg dexamethasone daily (or equivalent)
- As of Amendment 11, this criterion regarding screen fails from CA209498 is not applicable.
- Centrally confirmed (ie, third-party vendor) tumor MGMT-methylated or indeterminate from the CA209498 study
- Karnofsky performance status of ≥ 70
- Clinically appropriate for concomitant temozolomide plus RT, based on investigator judgement

Key Exclusion Criteria:

- Prior treatment for GBM (other than surgical resection)
- Recurrent GBM
- MGMT-unmethylated GBM at central laboratory or tumor not available
- Biopsy-only of GBM at surgery, defined as < 20% resection of enhancing tumor
- Concomitant use of Gliadel® wafer
- 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)

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

Study Drug for CA209548		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Placebo	N/A	IP
Temozolomide	20 mg, 100 mg, 140 mg	IP

Subjects should begin study treatment within 3 days of randomization and chemoradiation within 7 days, but RT should begin within 42 days after definitive resection; 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.

Study Assessments:

Safety Evaluation: Adverse events will be assessed continuously during the study and for 100 days post last treatment. For all treatment discontinuation post unblinding, adverse events will be assessed for 100 days post last nivolumab treatment and for 30 days post last temozolomide treatment, whichever is later. 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 hours 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) up to 24 months post randomization, then every 12 weeks until disease progression. Following study unblinding, tumor assessments will not continue for subjects who have discontinued all study treatment. 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. [redacted] 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); following study unblinding, Follow-up visits 1 and 2 are only required for subjects discontinuing nivolumab and/or temozolomide. Survival status will be assessed every 3 months after follow-up visits are completed and may be completed via telephone or at in person visits; following study unblinding, survival status will not be assessed. Images will be submitted to a central imaging vendor for blinded independent central

review (BICR) at any time during the study until study unblinding. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA209-548 Imaging Manual provided by the central imaging vendor.

Statistical Considerations:

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

One interim analysis will be conducted on OS in the randomized population with no baseline corticosteroid. It will occur with approximately 70% or 236 OS events is reached. The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis, using Lan DeMets alpha spending function with O'Brien-Fleming boundaries. If the planned interim analyses occur exactly at the planned number of events, the projected alpha level will be 0.011 and 0.037. The interim analysis will also be conducted in OS in the overall randomized population. The interim analysis will be conducted at the same time as the interim for the no baseline corticosteroids population in a hierarchy with stopping boundaries at the interim and final analysis based on actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

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

Endpoints:

The two primary endpoints of the trial will be OS in the randomized population with no corticosteroids at baseline as well as in the overall randomized population, and PFS determined by BICR based on RANO criteria.

Secondary endpoints: OS rate at 12 months and 24 months estimated from OS Kaplan-Meier curve. PFS determined by investigator assessment based on RANO criteria.

Analyses:

Primary Endpoints

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

The distribution of OS in the sub-population of subjects with no baseline corticosteroids and in all randomized subjects will be compared in arms RT + TMZ + nivolumab and RT + TMZ at interim and final analyses via two-sided, log-rank tests, stratified by complete resection or partial resection at baseline. The boundaries for declaring superiority at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan DeMets alpha spending function with O'Brien-Fleming boundaries. For example, if the interim and final analyses occur exactly at the planned number of events, superiority of an arm will be declared if $P \leq 0.011$ at the interim analysis or $P \leq 0.037$ at the final analysis. The Kaplan-Meier product limit method will be used to estimate the survival curve in each arm including medians and its 95% CI, OS rates at various time points. The HR and the corresponding two sided (1-adjusted α) % 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).

PFS is defined as the time from randomization to the date of the first documented tumor progression or death by any cause. Subjects who did not have disease progression or die will be censored at the date of the last tumor assessment. Subjects who did not have any on study tumor assessment and did not die will be censored at the last tumor assessment. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the anti-cancer therapy. Subjects who had surgical resection after start of

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study treatment will be censored at the last tumor assessment date prior to initiation of surgical resection. PFS will be determined by BICR based on RANO criteria.

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). PFS will be compared in the first 558 subjects out of the (total) 714 treated subjects. The Kaplan-Meier product limit method will be used to estimate the survival curve in each arm including medians and its 95% CI, PFS rates at various time points. The HR and the corresponding two sided 99% 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).

PFS (based on BICR) will be analyzed in overall randomized subjects and all randomized subjects without baseline corticosteroids.

The CA209548 DMC convened on 09-Dec-2020 to conduct a pre-planned, routine safety review of all data. The OS data clearly show that there is no plausible scenario for this study to have a positive OS result at the final analysis based on either all randomized subjects or on subjects without baseline corticosteroids. This is based on the DMC's review of the OS results to date, with over 80% of the final required number of events reached and related statistical considerations including conditional power of < 1% for a statistically significant final result.

While the group receiving nivolumab has a higher incidence of toxicities, the DMC members believed the increased toxicity was expected and did not warrant stopping the study because of safety, and recommended to unblind the sites and subjects, which was approved by the Sponsor. The study was officially unblinded to investigators on 22-Dec-2020.

As a consequence, the timing of the primary OS analysis, originally planned when 337 and 494 events were to be reached respectively for the population without corticosteroids at baseline and the overall population, has been updated. To prevent any bias due to unblinding of subjects, the primary OS analysis will be conducted using the cut-off date (or last patient last visit [LPLV]) of 22-Dec-2020, which is when the study was unblinded.

Secondary Endpoint

OS rates at 12 and 24 months will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

PFS based on investigator assessment will be analyzed in the first 558 subjects, all randomized subjects and all randomized subjects who did not receive corticosteroids at baseline.

All secondary endpoints will be analyzed at the same time as the OS and PFS primary analyses using the analysis methods already defined in the SAP.

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1 INTRODUCTION [redacted]

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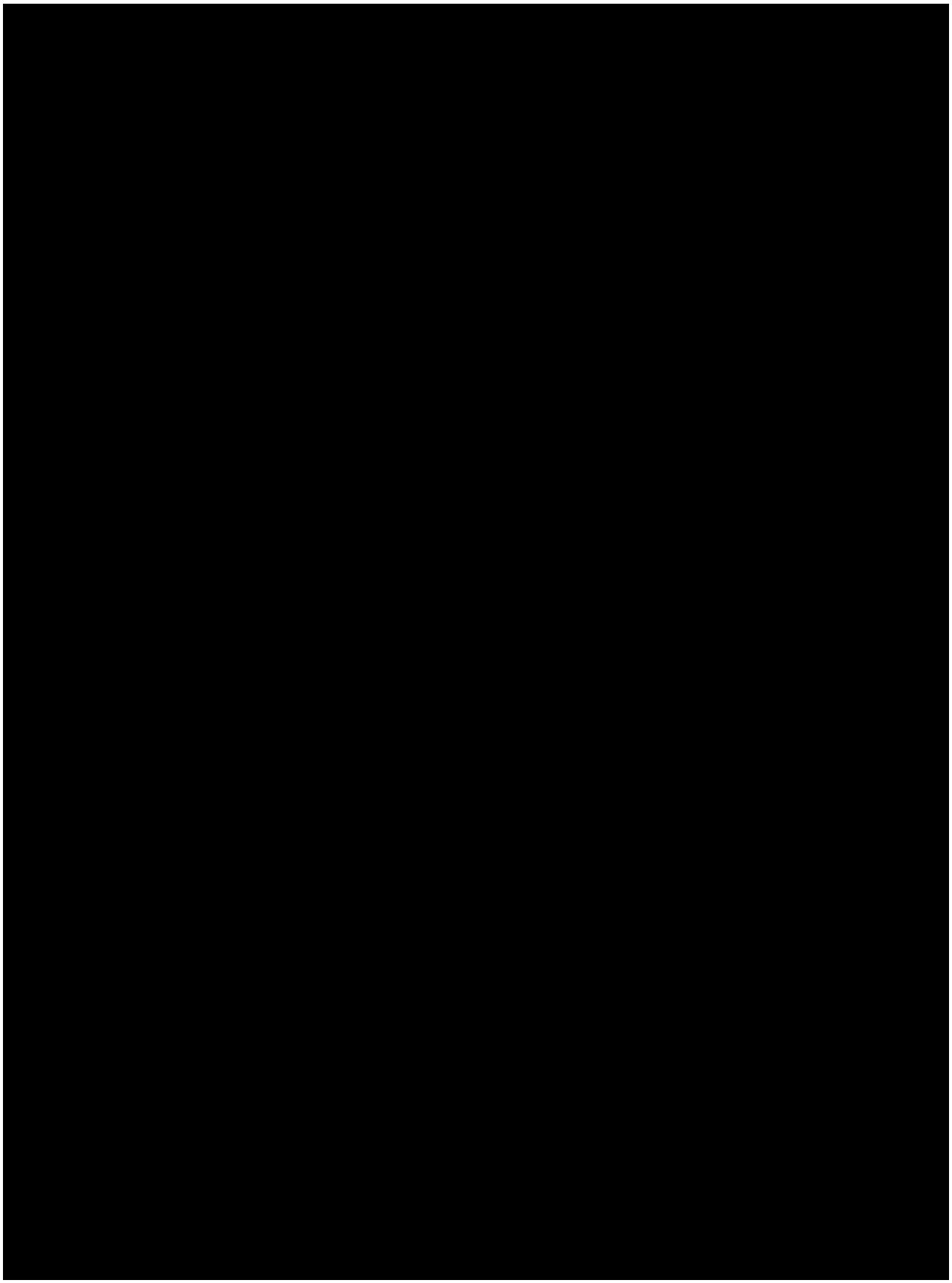

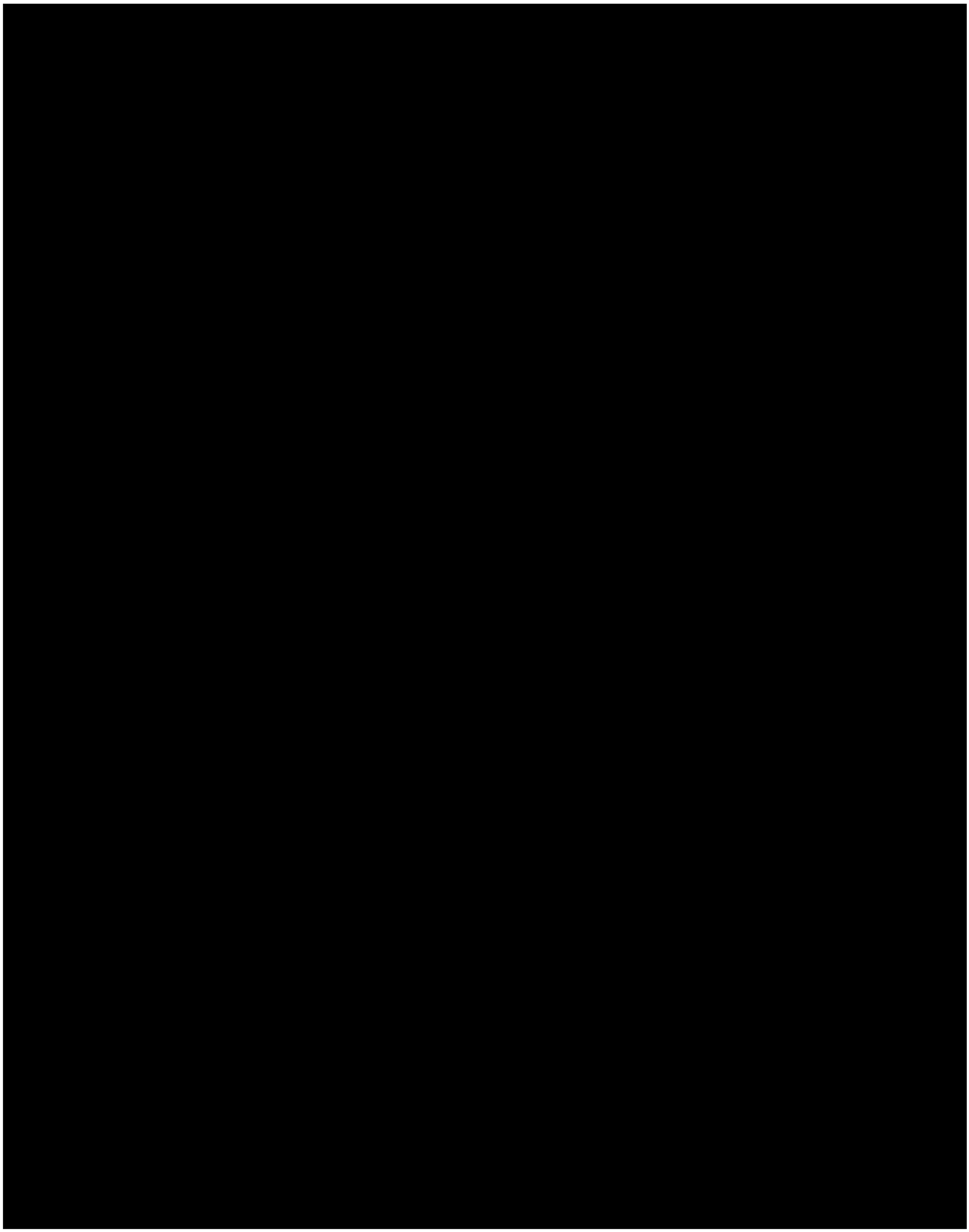

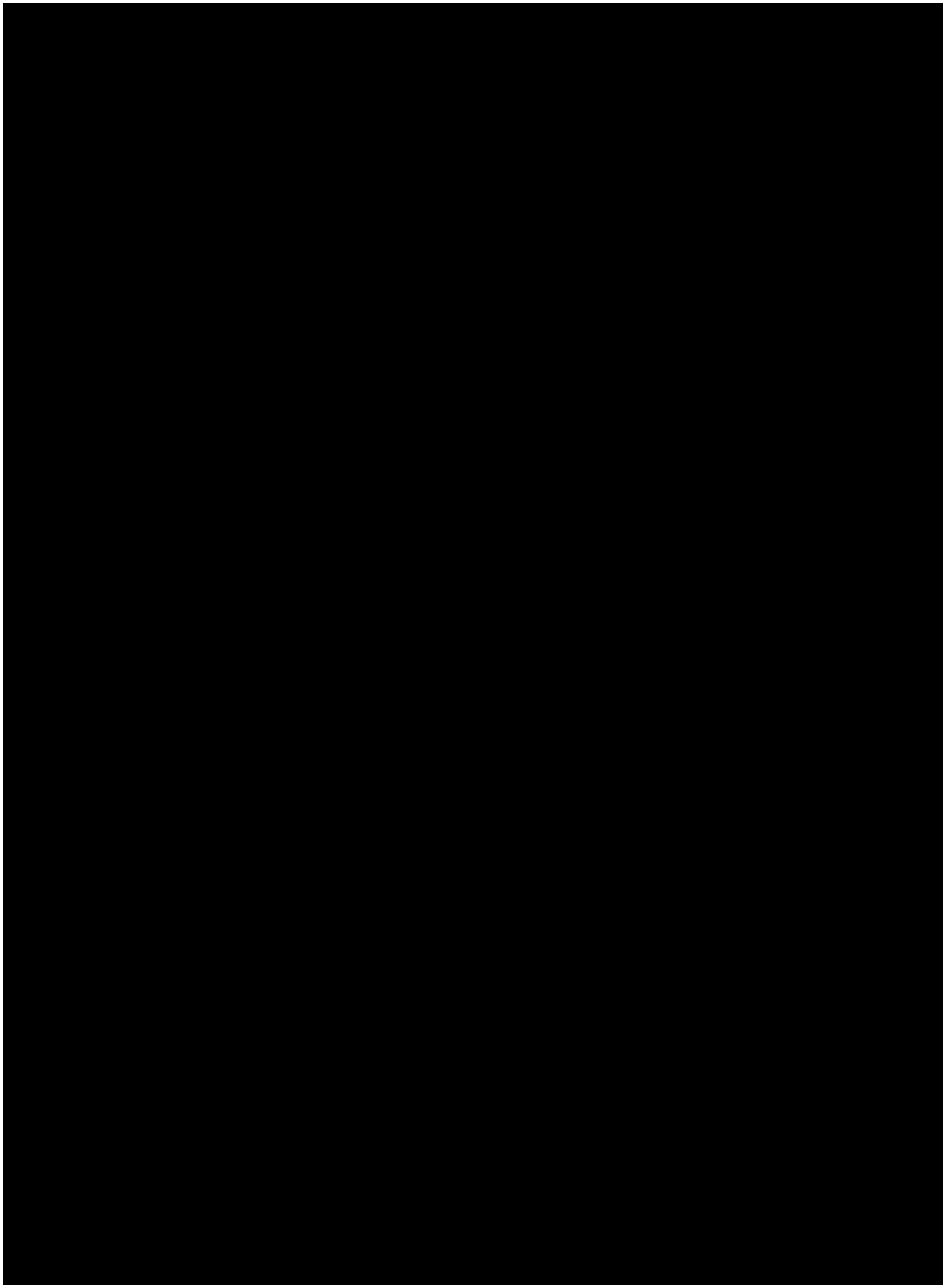

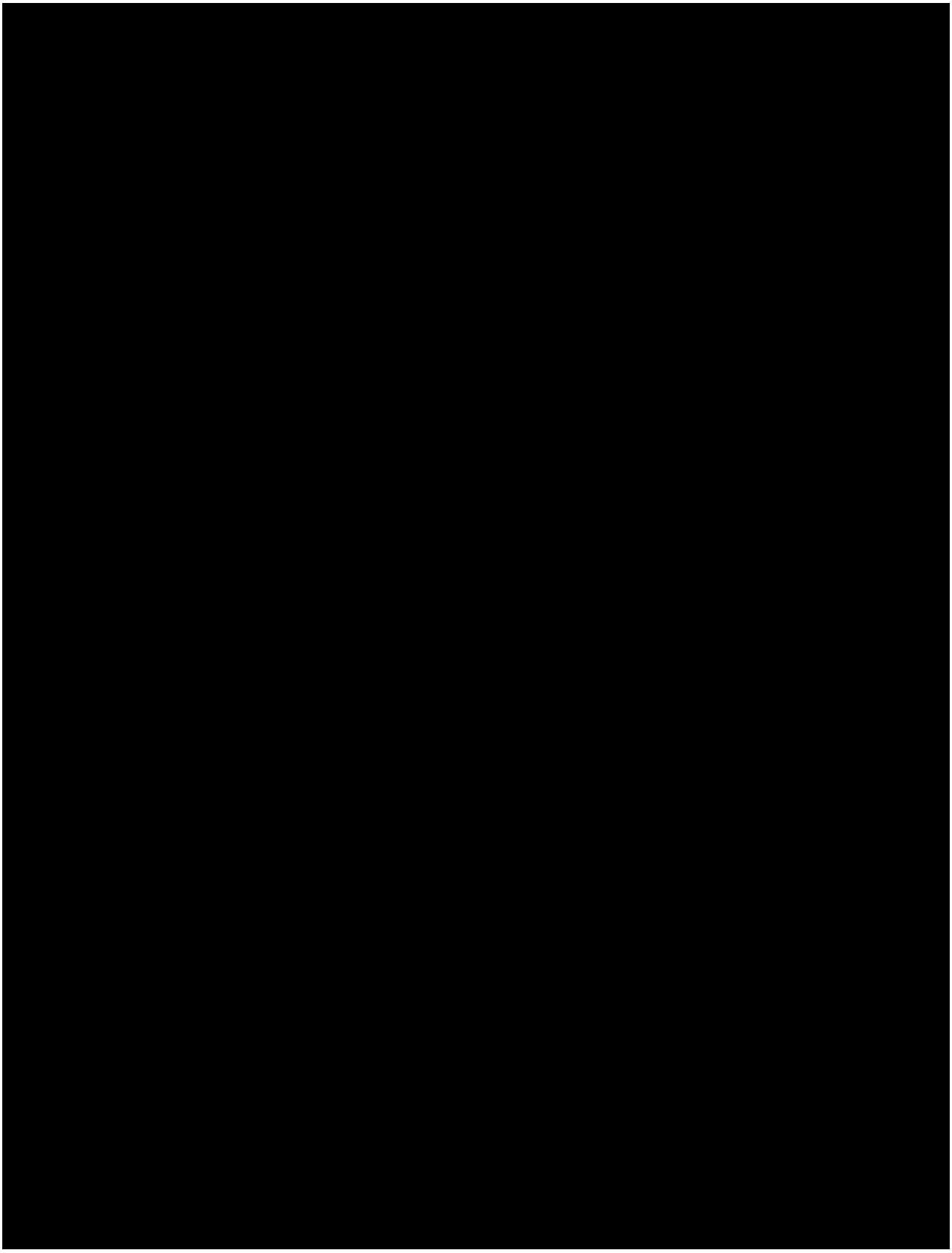

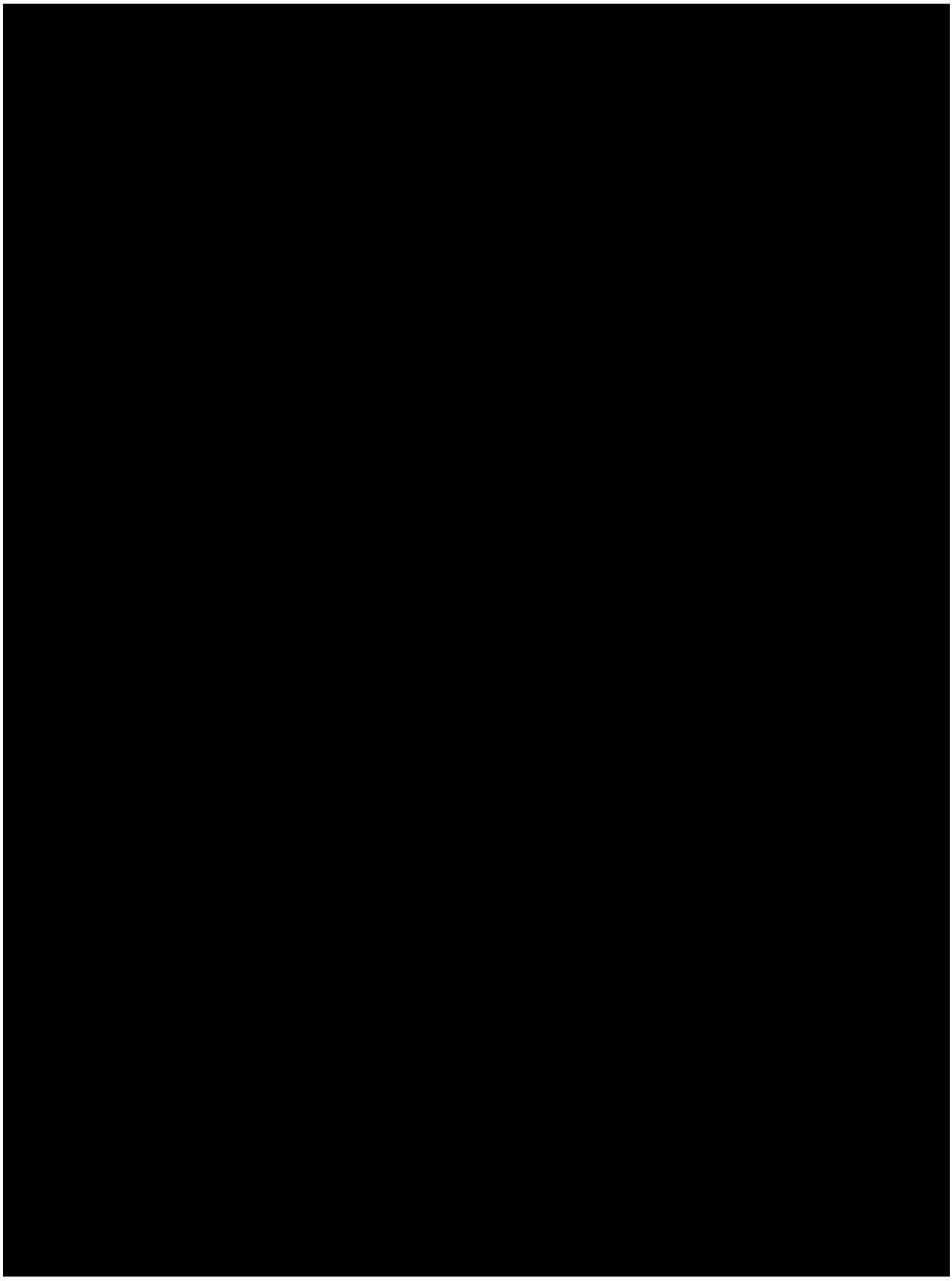

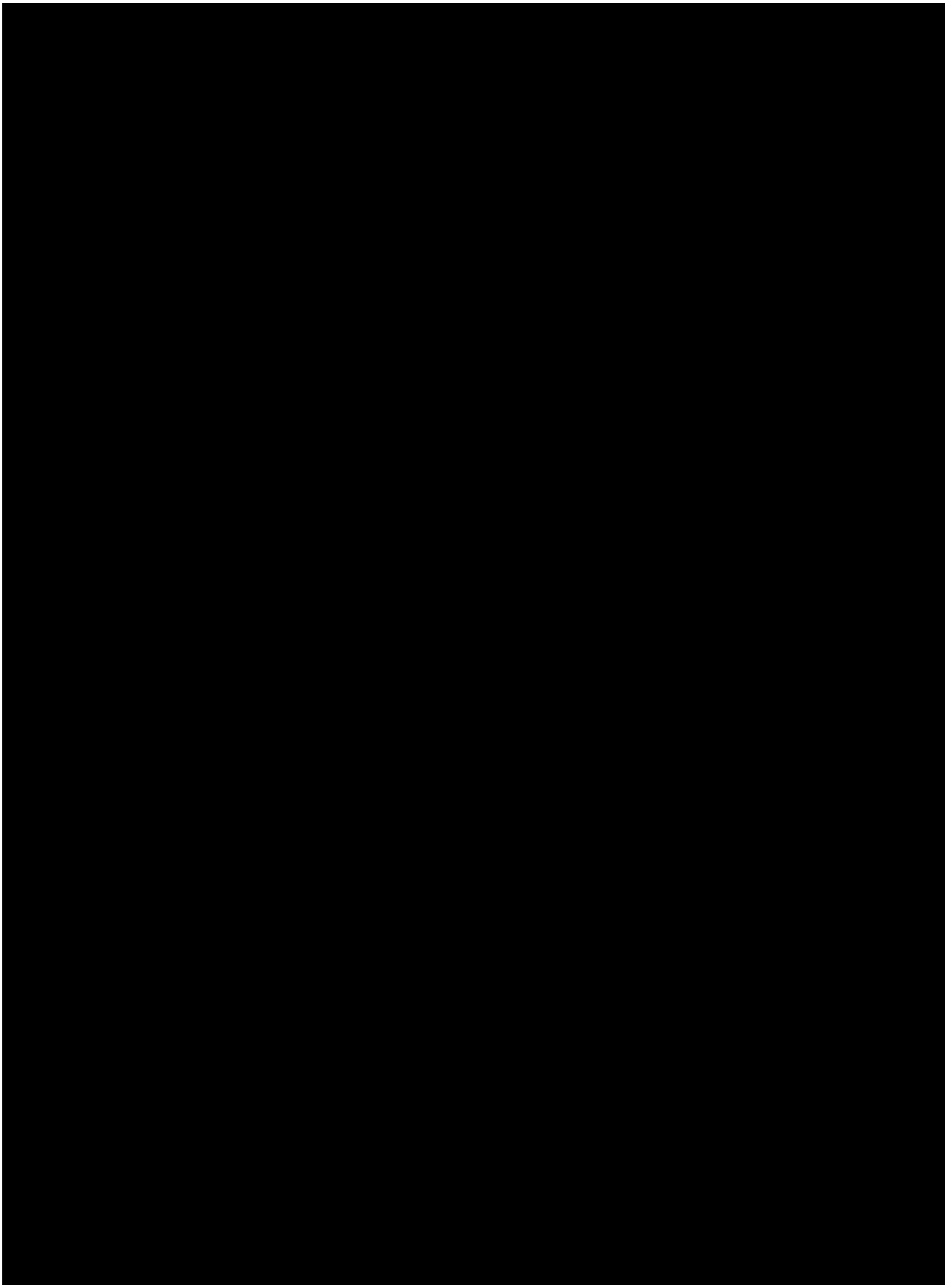

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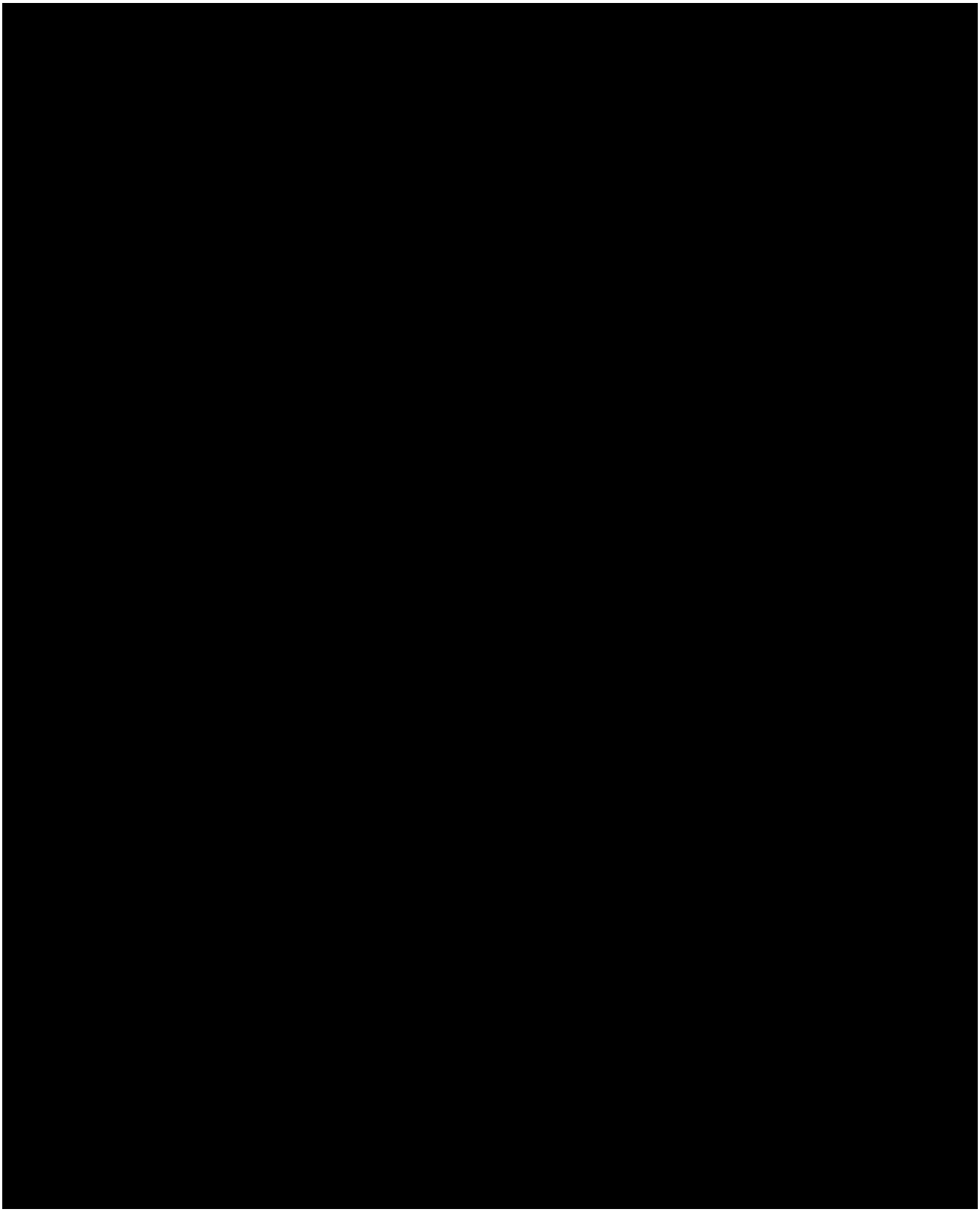

1.2 Research Hypothesis

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

1.3 Objective(s)

1.3.1 Primary Objectives

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

1.3.2 Secondary Objectives

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

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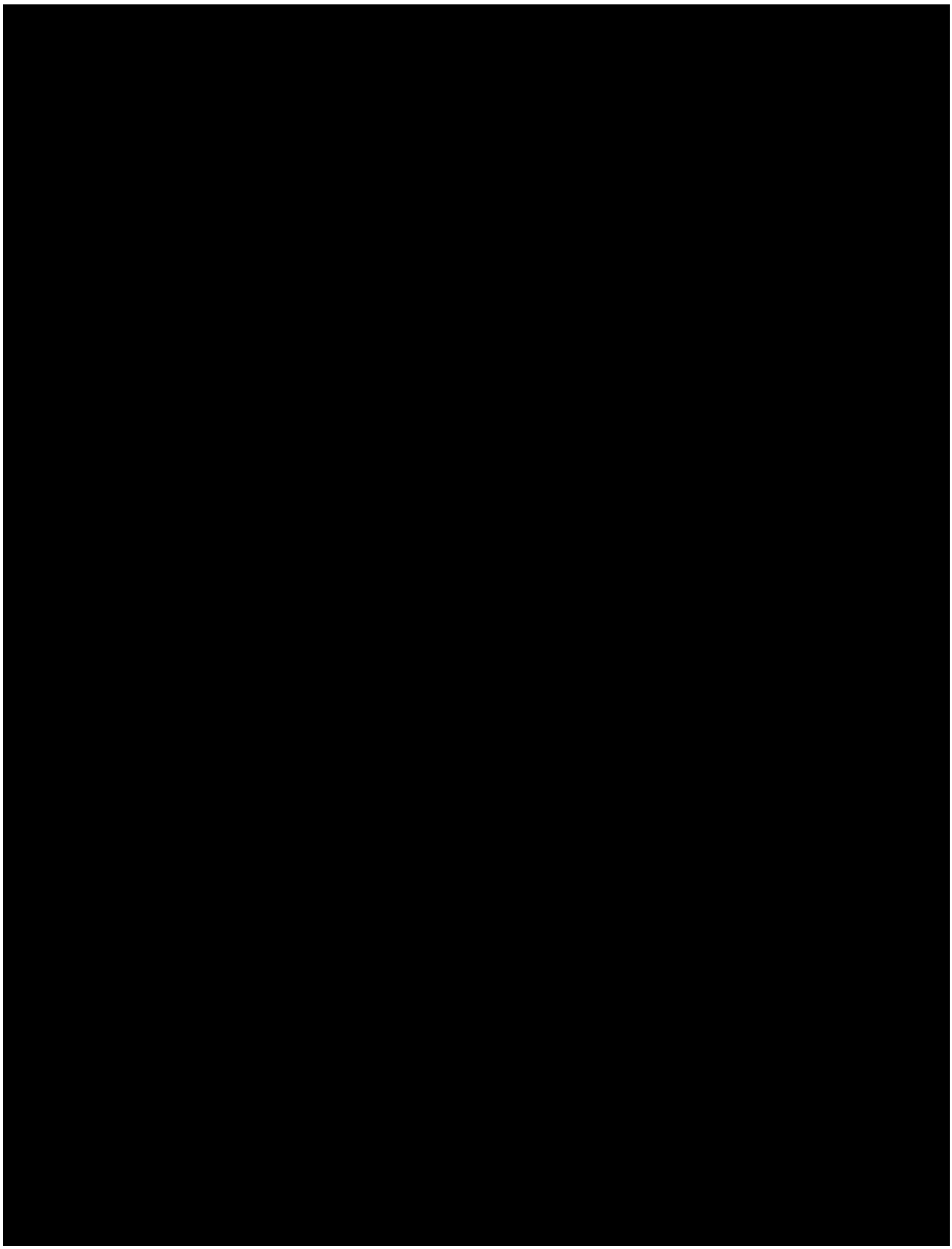

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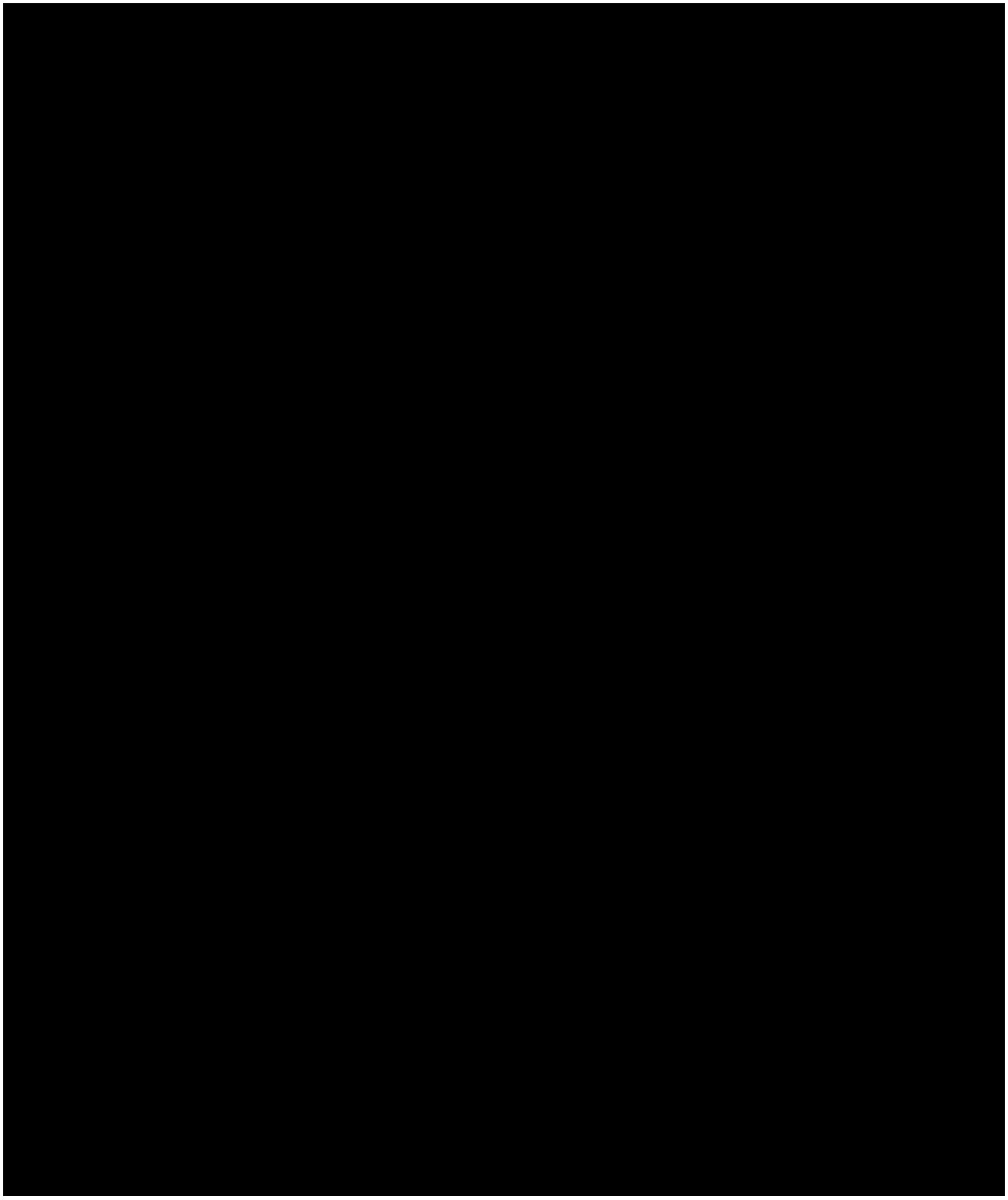

2 ETHICAL CONSIDERATIONS

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), if applicable, also by local health authority 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 and Regulatory Authority(ies), if required by local legislation 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 or local health authority 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 or local health authority 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.

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Investigators must:

- 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.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 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.
- 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.
- 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.
- 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 GBM, following surgical resection of the tumor. Tumor tissue will be evaluated for MGMT methylation by a central laboratory assay

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through the CA209498 study. After enrolling in the CA209498 study, the subjects may enroll in the CA209548 study and begin the screening process while they wait for the MGMT results. The screening number assigned in the CA209498 IVRS will be the same subject number entered by the site to screen the subject into the CA209548 IVRS. Those with a MGMT status of methylated or indeterminate may be eligible to randomize in the CA209548 study. In order to randomize 693 eligible subjects, a total of approximately 780 subjects will be evaluated. For details, see Section 3.1.1.

Subjects with a central laboratory result of MGMT-methylated or indeterminate may continue in the **screening phase,** in which eligibility for randomization will be documented and baseline demographic and disease information submitted; for details, see Section 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. The first on-study contrast-enhanced MRI should be performed 4 weeks (± 7 days) after completing radiation therapy, then subsequent scans should be every 8 weeks (± 7 days) up to 24 months, then every 12 weeks until progression regardless of treatment schedule or dose delays. Tumor progression will be assessed using RANO described in Section 5.4.2. [redacted] For the purposes of this protocol, each cycle duration is 2 weeks until 8 doses of 240 mg of nivolumab/placebo are complete. The remaining subsequent cycles (480 mg or placebo infusion, starting Week 17 in the absence of delays) are 4 weeks in duration. Cycle 9 should start 2 weeks after Cycle 8 begins.

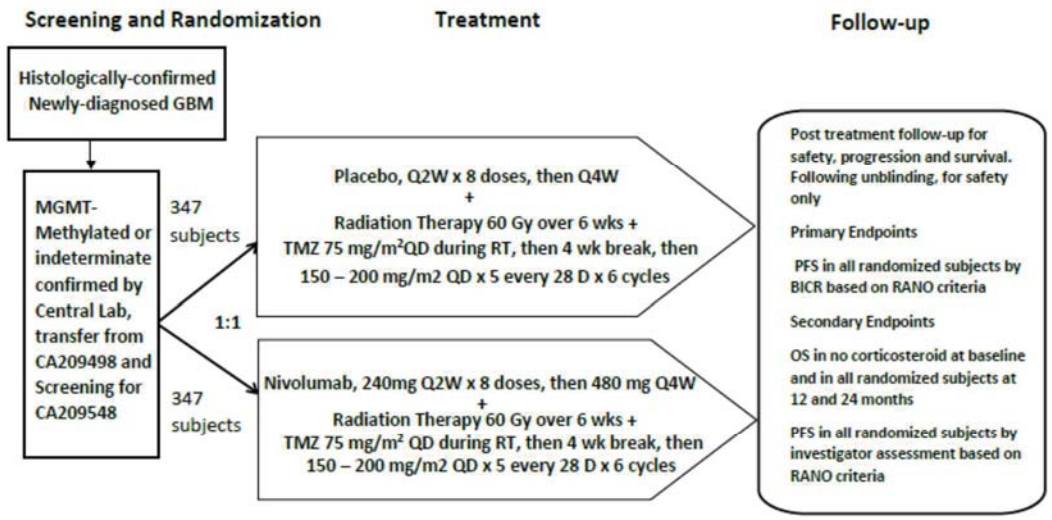
After cessation of all study treatment for any reason, all randomized subjects will enter a **follow-up** phase. In the short-term, visits are defined for reporting of treatment-related adverse events. Following study unblinding, subjects who discontinue all treatment will not be followed for progression per RANO criteria, or for survival. For details on the follow-up phase, see Section 3.1.3.

Baseline and all subsequent scans will be submitted to blinded independent central review (BICR) for review, once the subject is randomized and until study unblinding on 22-Dec-2020.

A Data Monitoring Committee (DMC) will meet regularly during the study until study unblinding 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

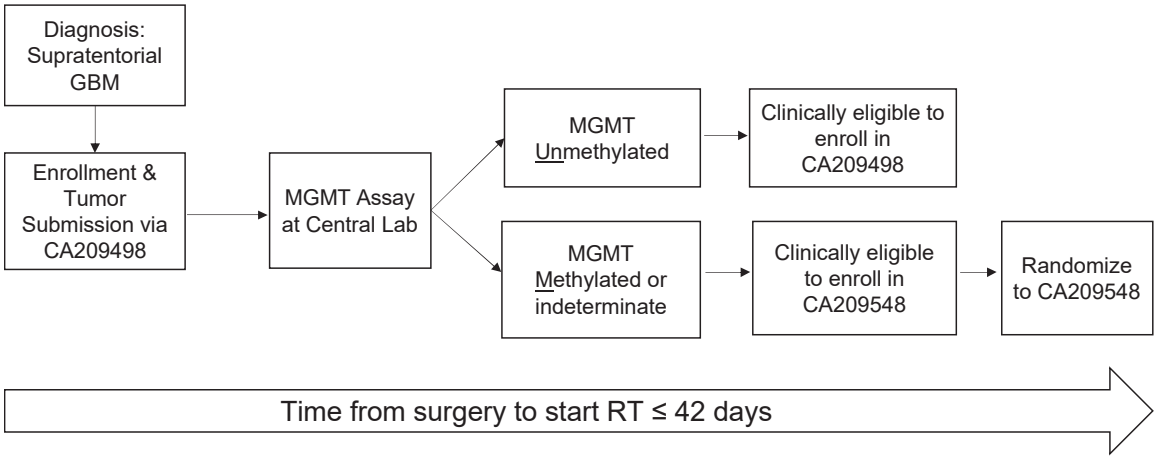


Following unblinding, subjects may continue on nivolumab and/or temozolomide (if applicable) treatment, following all protocol procedures.

3.1.1 Screening Phase

Subjects will provide consent for enrollment and tumor submission in the peri-operative period in the CA209498 study so that MGMT status can be determined. Consent for enrollment in the CA209548 study will occur while waiting for the MGMT results to be obtained and randomization and study treatment will occur once MGMT status of methylated or indeterminate is known and eligibility is established (Figure 3.1.1-1).

Figure 3.1.1-1: Screening and Randomization



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

When possible, subjects should not be on corticosteroids at Screening. 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, temozolomide plus nivolumab or radiotherapy, temozolomide plus placebo.

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 in any diameter 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 > 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 definitive surgery to initiation of RT should not exceed 42 days but may be delayed if clinically required. Typically, a delay from randomization to initiation of chemoradiation may be up to 7 days, or longer if clinically required. Subjects should begin nivolumab or placebo within 3 days after randomization and may be given at any time prior to chemoradiation start.

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. 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 adverse events related to RT, see Section 6.

Note: Suspected progression occurring during or within 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 adverse events, for maximum clinical benefit (investigator decision), for subject request, disease progression, or another reason.

Following study unblinding, subjects who discontinue the experimental arm will be evaluated for adverse events 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. Subjects on placebo arm who discontinue study temozolomide treatment will be evaluated for adverse events with a visit at 35 days (± 7 days) after last dose. All adverse events must be documented for a minimum of 100 days after discontinuation of nivolumab and for 30 days following discontinuation of temozolomide treatment, but drug-related toxicities should continue to be followed until they resolve, return to baseline, or are deemed irreversible. Subjects will not be followed for progression per RANO criteria, or for survival.

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3.1.4 Overall Study Duration

Enrollment and randomization of 693 subjects is expected to require approximately 25 months. One interim analysis and a final analysis on OS in the no baseline corticosteroid population were planned after approximately 236 and 337 deaths have been reported, respectively. Depending on assumptions, these analyses were anticipated to occur at approximately 45 and 69 months after first subject is randomized, respectively. Following study unblinding, the final analysis on OS will use the unblinding date for the data cut-off. One final analysis on PFS in the first 558 randomized subjects in all comers is planned after approximately 404 events have been reported. Depending on assumptions, this analysis is anticipated to occur at approximately 35 months after first subject is randomized. See Statistical Considerations, Section 8 for details.

Data will be collected after the pivotal OS final analysis has occurred, for subjects remaining on treatment. The study will be closed when safety follow-up has completed for the last subjects to discontinue study treatment.

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) [47]

i) No treatment for GBM other than surgery

ii) Post-operative baseline MRI following consensus recommendations[51] 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.

b) Substantial recovery from surgical resection

i) No major ongoing safety issues (eg, infection requiring IV antibiotics) following surgery

ii) For subjects on corticosteroids at the time of Screening: able to taper steroids (preferably discontinued). Dose at randomization must be ≤ 20 mg prednisone or ≤ 3 mg dexamethasone daily (or equivalent). Subjects who do not need corticosteroids or able to taper down to ≤ 20 mg prednisone.

c) As of Amendment 11, this criterion regarding screen fails from CA209498 is no longer applicable.

d) Centrally confirmed (ie, third-party vendor) tumor MGMT-methylated or indeterminate from the CA209498 study

e) Karnofsky Performance Status of ≥ 70 (Appendix 3)

f) Clinically appropriate for concomitant temozolomide plus RT, based on investigator judgment

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) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of the study treatment with nivolumab/placebo 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) As of Amendment 11, this criterion has been merged into 3.d.

e) As of Protocol Amendment 06, this criterion refers to TMZ treatment. 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 TMZ and for 6 months after the last dose of study treatment, or as noted in the locally applicable package insert, summary of product characteristics (SmPC), or similar document.

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 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 Exclusions

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

b) Recurrent GBM

c) MGMT-unmethylated GBM at central laboratory or tumor not available

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

e) Concomitant use of Gliadel® wafer

f) 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)

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) 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

c) Subjects with a 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

d) Not applicable per Protocol Amendment 05.

e) Subjects with severe renal insufficiency, ie, glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 (who should not receive contrast materials)

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 (no restriction for vascular access device)

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

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

k) Subjects with a hypersensitivity to Dacarbazine (DTIC)

l) Subjects who have received a live/attenuated vaccine within 30 days of first treatment.

3) Physical and Laboratory Test Findings

a) Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or history of active chronic hepatitis B

b) Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative), or history of active chronic hepatitis C

c) 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

b) 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.

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 the screening phase, and systemic corticosteroids will be discontinued if possible prior to randomization.

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

COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during the administration of the BMS study treatment and after the last administration of the BMS study treatment.

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 adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.3)
- Any live/attenuated vaccine (eg, live COVID-19, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

3.4.2 Other Restrictions and Precautions

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

3.4.2.1 Imaging Restriction and Precautions

Study-related MRI imaging of the brain will be performed using contrast materials. It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the image acquisition manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and standards 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 both TMZ and nivolumab/placebo, see Sections 4.5.1.5 and 4.5.2.3
- Maximum clinical benefit, as determined by investigator
- Subject's request to stop study treatment (other than for an AE)
- Any clinical adverse event (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
- Termination of the study by Bristol-Myers Squibb
- 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 other antineoplastic treatment

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 pregnancy and if allowed by local regulations, a discussion between the investigator and the BMS Medical Monitor/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 page.

3.6 Post Study Drug Follow up

In this study, o*verall survival is the primary endpoint of the study*. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Following study unblinding, however, subjects who discontinue study drug will only be followed for safety as required and in line with Table 5.1-3. BMS may request that survival data be collected on all treated/randomized subjects outside of the 3 month 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 contacts or is lost to follow-up.

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,

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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.

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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 CA209548

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
Placebo[a]	N/A	IP	N/A	Not provided by BMS	Per institution
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] The term "open-label" refers to the medication as it is upon receipt at the pharmacy. The trial will be conducted in a single-blinded fashion, ie, nivolumab/placebo blinded to site staff and patients. 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.

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.

In this protocol, investigational products are nivolumab (BMS-936558), nivolumab placebo (0.9% sodium chloride for injection or 5% dextrose for injection), and temozolomide. Although not a medicinal product, Radiation Therapy is also considered part of study treatment.

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 nivolumab (BMS-936558).[46]

4.3.1 Nivolumab (BMS-936558)

For details regarding drug storage, preparation, administration, and use time please refer to the nivolumab (BMS-936558) Investigator Brochure[46] 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 from both the CA209498 and CA209548 studies, the subject must first be enrolled into the CA209498 study by calling an interactive voice response system (IVRS) to obtain the subject number. The subject identification number in the CA209498 study will become the study number for the CA209548 study. Every subject that signs the informed consent form must be assigned a subject number in IVRS. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth of subject
- Gender (at birth) of subject
- Patient ID from the CA209498 study

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

- Subject number
- Date of birth of subject
- Extent of tumor resection: Complete or Partial

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to receive radiotherapy plus temozolomide combined with nivolumab or placebo. MGMT-methylation status will be transferred from the testing laboratory to the IVRS database.

The exact procedures for using the IVRS 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 Section 3.1. The first dose of nivolumab is to be administered within 3 days of randomization. Treatment details are described below.

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Table 4.5-1: Selection and Timing of Dose

Drug	Dose	Frequency of administration	Route of administration	Duration
Nivolumab/ Placebo (BMS-936558)	240 mg 480 mg, after 8 doses	Every 2 weeks, for 8 doses Every 4 weeks after 8 doses	30 minute intravenous (IV)	Until progression, unacceptable toxicity, or discontinuation from treatment
Temozolomide (TMZ)	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 as well as others with written permission of Sponsor

Treatment modifications (eg, dose delay, reduction, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in Sections 4.5.1 and 4.5.2. If the toxicity is considered related to either TMZ or nivolumab/placebo, both may be delayed, based on investigator judgment. However, if the toxicity is related to one or the other, then that one should be delayed or discontinued as appropriate. If the subject continues on either study drug, the visit schedule and assessments will continue as described in Table 5.1-2.

4.5.1 Nivolumab/Placebo Dosing

To reduce bias, this study is blinded for the investigational agent. Therefore, all provisions for dosing and dose modification apply equally to the 2 treatment arms until study unblinding.

The pharmacist will be unblinded to randomized arm; matched infusions (0.9% sodium chloride for injection or 5% dextrose for injection) will be provided to subjects on the control arm.

Nivolumab (BMS-936558) is to be administered as an IV infusion over 30 minutes. At the end of the infusion, flush the line with a sufficient quantity of 5% dextrose solution or normal saline.

4.5.1.1 Nivolumab/Placebo Dose and Schedule

Subjects should begin study treatment within 3 days of randomization, but RT should begin within 42 days after definitive resection. Subjects will continue on study treatment until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever comes first.

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.

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 date will be considered a delay. For Q4W dosing cycles, subjects may be dosed within a ± 3 day window. Subsequent dosing should be based on the actual date of administration of the previous dose of drug. Note: The 480 mg dosing starts at Cycle 9, which begins 2 weeks after the start of Cycle 8 (Week 17 in the absence of delays).

There are no premedications recommended for nivolumab on the first cycle.

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. Nivolumab/placebo should be delayed (see Section 4.5.1.3) for toxicities considered at least possibly-related to nivolumab. If toxicity is related to TMZ only, then only that agent should be interrupted; see Section 4.5.2.3. If the toxicity is considered related to either TMZ or nivolumab/placebo, both may be delayed, based on investigator judgment.

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.

4.5.1.2 Dose Modifications for Nivolumab/Placebo

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

4.5.1.3 Dose Delay Criteria for Nivolumab/Placebo

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 adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- 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 AST/ALT or total bilirubin will require dose discontinuation (See Section 4.5.1.5).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.
- Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection, either confirmed or suspected

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/Placebo

Subjects may resume treatment with study drug when the drug-related AE(s) resolve(s) 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
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
- Subjects with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after all of the following:
  - 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (e.g. RT-PCR or viral antigen), 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation by the Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

4.5.1.5 Treatment Discontinuation Criteria for Nivolumab/Placebo

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 adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, 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 adverse event 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 adverse events, 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.
- 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 adverse events 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.

Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor 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.

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- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.
- Following study treatment unblinding, a decision by the treating physician and the subject to discontinue treatment.

4.5.1.6 Continuing Nivolumab/Placebo 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). At the discretion of the investigator, subjects may 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 is a component of RANO criteria.] 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 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.[48]

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
- Myocarditis

The above algorithms are found in Appendix 1 and in the nivolumab Investigator Brochure.[49]

4.5.1.8 Treatment of Nivolumab/Placebo-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/placebo 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/placebo 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 nivolumab/placebo 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/placebo 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/placebo. 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/placebo 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 will be administered temozolomide (TMZ, Temodar®) daily during RT and as maintenance therapy for 6 cycles. **TMZ dosing will be performed according to investigator judgment;** the following guidance is drawn from published literature.

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. The timing of maintenance TMZ cycles may be adjusted for clinical convenience, eg, to coincide with nivolumab/placebo dosing.

Table 4.5.2.1-1: Dose Levels for Maintenance TMZ 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 first maintenance cycle
1	200 mg/m^2/day	Dose during subsequent maintenance TMZ 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 109/L and ANC ≥ 1.5 x109/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 adverse events (see Table 4.5.2.3-2). If there was a prior dose reduction or discontinuation 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 maintenance.

As noted in Section 4.5.1.1, if toxicity is related to TMZ only, then only that agent should be interrupted. If the toxicity is considered related to either TMZ or nivolumab/placebo; however, both may be delayed, based on investigator judgment.

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 109/L, platelet count ≥ 100 x 109/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

TMZ dosing will be performed according to investigator judgment; the following guidance is drawn from published literature.

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
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 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 to 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

The blinding strategy selected for the protocol is the single-blinding design, also called "site-subject blinded."[50] The subjects, investigator, and site staff will be blinded to the study therapy administered. Each investigative site must assign an unblinded pharmacist/designee. Designated staff of BMS Research & Development will be unblinded to facilitate drug supply and safety monitoring. [redacted]

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if the treatment assignment should be unblinded.

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

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

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

[redacted]

On 09-Dec-2020, the DMC conducted a pre-planned routine safety review of all available safety data and initially recommended that the study continue unchanged. Subsequently, the DMC noted that it is not possible for the study to demonstrate an OS benefit for the investigational treatment

arm, and after further discussion with the DMC, the decision was made to unblind all study subjects, and inform all investigators, ethics committees, and health authorities as required.

4.7 Treatment Compliance

Assessment of study medications will be performed at each study visit. Subjects 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. Drug accountability will be reviewed at each visit to confirm treatment compliance. Sites should discuss discrepancies with the patient at each visit.

4.8 Destruction or Return of Investigational Product

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.

Approved v8.0 [redacted]

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.

Approved v8.0 [redacted]

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedures (CA209548)

Procedure	Screening Visit	Notes: Windows refer to calendar days
Informed Consent for enrollment	X	Call IVRS to obtain subject number
Inclusion/Exclusion Criteria	X	Centrally-confirmed MGMT-methylated or indeterminate GBM
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
Post-operative 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, Glucose, within 14 days prior to randomization. TSH, T3 and T4 (Free or Total), Hep B/C (HBsAG, HCV antibody or HCV RNA), within 28 days prior to randomization
Pregnancy Test [WOCBP]	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]		

[a] 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. 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 (CA209548)[a]

Procedure	Concomitant RT + TMZ + Nivo/ placebo	TMZ Break/ Nivo/ placebo	Maintenance	Notes: Cycle duration is 2 weeks until 8 doses of nivo/placebo are complete. Remaining subsequent cycles are 4 weeks in duration. Procedures must be done within 72 hours prior to dosing unless otherwise specified.
IVRS Randomization call	X			Confirm eligibility criteria prior to randomization
Targeted Physical Examination, Vital Signs, Performance Status	X	X	X	Weight, Karnofsky Performance Status, BP, HR, RR, temperature
Adverse Events Assessment	Continuously			Record at each visit
Concomitant Medications	Continuously			Record at each visit, including steroid dose
Radiation Therapy	X			Total dose 60 Gy over 6-7 weeks, see Section 3.1.2.2
CBC with Differential	X	X	X	Weekly during RT, then Day 1 and 22 of maintenance TMZ (repeat weekly if TMZ delayed), then prior to each nivo/placebo dose, and as clinically indicated.
Chemistry Panel[a]	X	X	X	Chemistry panel every 4 weeks prior to nivolumab/placebo dose: AST, ALT, ALP, T.Bili, albumin, BUN or serum urea, creatinine, Ca, Na, K, Cl, Glucose, and as clinically indicated.
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]	X	X	X	Serum or urine pregnancy test every 4 weeks (± 3 days; minimum sensitivity 25 IU/L or equivalent units of HCG)
[redacted]				
Tumor Assessment			X	Contrast-enhanced MRI 4 weeks (± 7 days) after completing RT, then every 8 weeks (± 7 days)[b] up to 24 months, then every 12 weeks until progression, see Imaging Manual and Section 5.4. Following study unblinding, tumor assessments will not continue for subjects who have discontinued all study treatment.

Table 5.1-2: On-Treatment Assessments (CA209548)[a]

Procedure	Concomitant RT + TMZ + Nivo/ placebo	TMZ Break/ Nivo/ placebo	Maintenance	Notes: Cycle duration is 2 weeks until 8 doses of nivo/placebo are complete. Remaining subsequent cycles are 4 weeks in duration. Procedures must be done within 72 hours prior to dosing unless otherwise specified.
[redacted]				
Dispense Nivolumab/Placebo	X			Day 1 within 3 days of randomization up to 7 days prior to RT start, then every 2 weeks for 8 doses, then every 4 weeks, see Section 4.5.1
Dispense Temozolomide	X		X	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 Submission 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

[a] If a subject discontinues nivolumab or placebo but continues TMZ, on-treatment assessments should continue. Chemistry panel will be collected every 4 weeks prior to TMZ dosing.

[b] 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 (CA209548)

Procedure	Treatment Follow-up[a]	Survival Follow-up[b]	Notes
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 nivolumab-related adverse events until resolved, return to baseline or deemed irreversible or until lost to follow-up, withdrawal of study consent, or discontinuation from the study.
Laboratory Tests	X		CBC w/differential, LFTs, BUN, creatinine and TSH at 35 days, repeat labs at 115 days 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		Every 8 weeks (± 7 days) for 24 months and then every 12 weeks until progression, required only for subjects who did not progress on study treatment (eg, discontinued for AEs). Following study unblinding, tumor assessments will not continue for subjects who have discontinued study treatment. See Section 5.4.
[redacted]			
Tumor Sample Submission at time of progression or suspected progression	At time of PD or suspected PD		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; following study unblinding, this is optional.
[redacted]			

Table 5.1-3: Treatment Follow-up and Survival Follow-up (CA209548)			
Procedure	**Treatment Follow-up[a]**	**Survival Follow-up[b]**	**Notes**
[redacted]			
Survival Status	X	X	Every 3 months (clinic visit or telephone contact), during Survival phase, include documentation of subsequent chemotherapy. Following study unblinding, survival status will not be collected.

[a] Subjects must be followed for at least 100 days after last dose of study drug (whichever was administered the latest). 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 last dose. Following study unblinding, Follow-up Visit #1 and Follow-up Visit #2 will occur for subjects who were treated with nivolumab, and Follow-up Visit #1 will occur for subjects who were treated with placebo and were receiving temozolomide at time of unblinding.

[b] Survival Follow-up visits to occur every 3 months from Follow-up Visit 2 until study unblinding. 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 period will be permitted (in addition to any parameters that require a confirmatory value). Screening procedures that were performed do not need to be repeated if they meet the timing criteria in Table 5.1-1 (eg, within 14 days of randomization, 28 days of randomization). 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 BMS 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
- Laboratory Manuals for collection and handling of blood samples [redacted] and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms

[redacted]

- Imaging Manual includes specifications for Radiology scan submission

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include height, weight, BSA, Karnofsky Performance Status, BP, HR, RR, and temperature and should be performed as noted in Table 5.1-1. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose of study drug. Concomitant medications including steroid dose within 14 days prior to first dose of study drug through the study treatment period will be collected (see Section 5.1).

Baseline local laboratory assessments should be done within 14 days prior to first dose to include: CBC w/differential to include ANC, Chemistry panel including AST, ALT, alkaline phosphatase, total bilirubin, BUN or serum urea level, albumin, creatinine, phosphorus, Ca, Na, K, Cl, and glucose. TSH, T3 and T4 (Free or Total), and Hep B and C testing (HBVs Ag, HCV Ab, or HCV

RNA) to be collected within 28 days prior to randomization (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) to be done at screening, within 24 hours prior to first dose, and then every 4 weeks regardless of dosing schedule, and at each safety follow up visit. Where required by local regulations, an HIV test must also be performed. Cycle 1 pre-dose laboratory assessments do not need to be collected if the screening assessments were collected within the specified timeframe, ie, 14 days or 28 days prior to treatment start.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Table 5.1-3), toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in person or documented telephone calls to assess the subject's status are acceptable.

On-treatment laboratory assessments include CBC w/differential to include ANC, done weekly during RT, then Day 1 and 22 during maintenance TMZ, then prior to each nivolumab/placebo cycle. Chemistry panel including AST, ALT, alkaline phosphatase, total bilirubin, albumin, BUN or serum urea, creatinine, Ca, Na, K, Cl, glucose will be performed every 4 weeks prior to nivolumab/placebo dosing or prior to TMZ dosing if the subject has been determined to be in the placebo arm. TSH, T3 and T4 (Free or Total, only if TSH abnormal) will be performed every 8 weeks for all subjects, or as clinically indicated. Pregnancy test will be performed every 4 weeks. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.03.

On-study weight, Karnofsky performance status, and vital signs should be assessed every 2 weeks during RT followed by every 4 weeks in maintenance and at each on-study visit prior to dosing for nivolumab/placebo. Vital signs should also be taken as per institutional standard of care for subjects during and after dosing. The start and stop times of the infusions should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse events page.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations). Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.4 Efficacy Assessments

All subjects will undergo brain Magnetic Resonance Imaging (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 are not required; in this case the last scan prior to randomization that meets the diagnostic quality required in the imaging manual provided by the central imaging vendor will be considered the baseline MRI.

On treatment and follow-up assessments may be performed at designated time points in Table 5.1-2 and Table 5.1-3 (± 7 days). 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. Investigators may obtain more frequent follow-up MRI scans as medically indicated. [redacted] Local radiologic assessment of tumor measurements will be used for clinical management and investigator-assessed disease progression (see Section 4.5.1.6 and Section 5.4.2).

Subjects who are unable (due to coexisting medical condition, eg, 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 overall survival as long as there is no safety issue which would require monitoring by MRI.

Images will be submitted to a central imaging vendor for blinded independent central review (BICR) at any time during the study until study unblinding. Prior to scanning first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA209-548 Imaging Manual provided by the central imaging vendor. 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 adverse events 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.

Sites will be trained in image acquisition parameters, image submission process, application of RANO criteria[34] (as outlined in Section 5.4.2) prior to scanning the first study subject. These guidelines will be outlined in a separate Site Imaging Manual, following recent consensus recommendations.[51] All radiologic imaging from this study (including scans performed prior to Screening) until study unblinding will be transmitted to a centralized imaging core lab for BICR.

Any incidental 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.

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.[33] 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.

5.4.2 Assessment of Response

Response will be assessed using RANO[34] criteria. Subjects who have undergone visible-total or near-total resection and have no lesion measuring ≥ 1 cm on 2 perpendicular diameters on baseline MRI cannot have a complete or partial response and will be followed only for recurrence. These subjects will be considered non-evaluable for BOR analysis, but their disease status will be assessed (SD or PD) at each tumor assessment, and they will be included in analysis of PFS and OS. If no signs of progression are observed, according to MRI, the radiologic assessment will be categorized as SD. The appearance of any index or non-index lesion consistent with tumor will be categorized as PD.

The assessments that will contribute to evaluation of PD include response assessments recorded between the date of randomization and the first to occur of the following:

- The date of objectively documented progression per RANO criteria
- The date of subsequent therapy, or
- The date of pathology results from diagnostic surgical resection

The criteria in Table 5.4.2-1 will be used for assessing progression.

Table 5.4.2-1: Criteria for Determining First Progression Depending on Time From Initial Chemoradiotherapy	
Response	**Criteria[a]**
Progressive disease < 12 weeks after completion of chemoradiotherapy	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 (eg, solid tumor areas [ie, > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.
Progressive disease ≥ 12 weeks after chemoradiotherapy completion	1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids. 2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first postradiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence. 4. For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR nonenhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (eg, effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

NOTE: Radiologic interpretation guidelines, definitions and tumor measurement instructions will be provided separately in a separate imaging manual. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.

Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery

* Stable doses of corticosteroids include subjects not on corticosteroids

[redacted]

Table 5.4.2-2: Assessment of Best Overall Response

Best Overall Response	Criteria
Complete Response (CR)	CR observed in consecutive assessments ≥ 4 weeks apart per RANO
Partial Response (PR)	PR observed in consecutive assessments ≥ 4 weeks apart per RANO
Stable Disease (SD)[a]	SD observed and does not qualify for CR or PR **or** Suspected PD followed with histologic results not confirming PD, and no CR, PR or SD observed

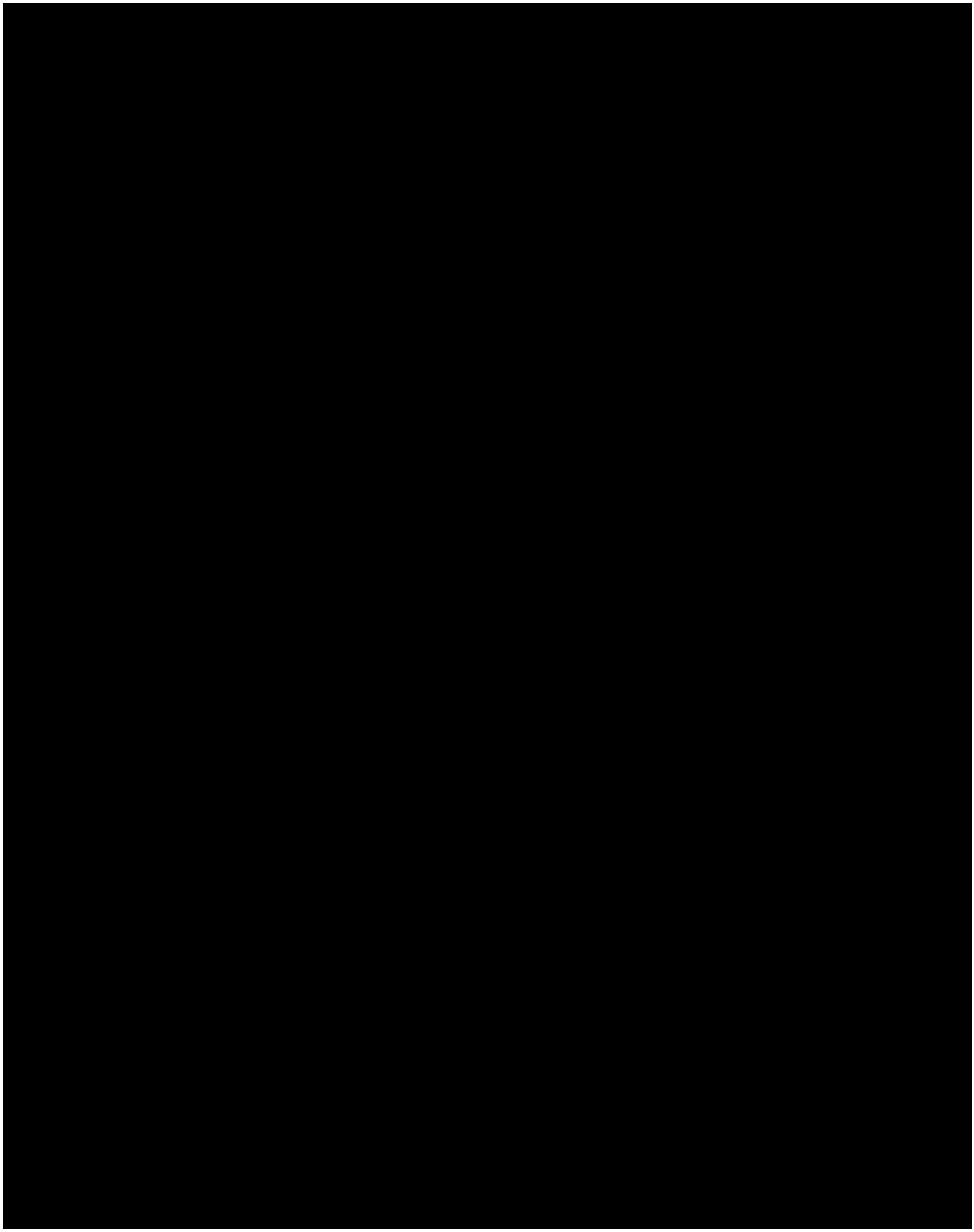
Table 5.4.2-2: Assessment of Best Overall Response

Best Overall Response	Criteria
Not Evaluable (NE)	Insufficient data to determine disease progression or response
Progressive Disease (PD)	No CR, PR, or SD prior to PD

a To qualify for SD there must be a minimum on-treatment period of 10 weeks.

The minimum duration between baseline post-operative scan and first on-study scan in order to determine BOR of SD is 4 weeks after completion of RT. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response will depend on the subsequent assessments. For example, a subject who has SD at a time point < 4 weeks post-RT and PD at a second assessment will have a best response of PD.

[redacted]



[redacted]

5.6.1 Tumor Samples

[redacted] Tumor tissue (block or slides) must be available for submission prior to randomization. If a block is not available, a minimum of 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. Additional biopsies obtained at any time, eg, if progression is suspected, should also be submitted.

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.

[redacted] 2 paraffin blocks are requested (1 minimum). If only slides are available, they should be unstained, have a recommended tissue section thickness of 4 microns and be positively charged. Slides must be shipped refrigerated at 2-8° C.

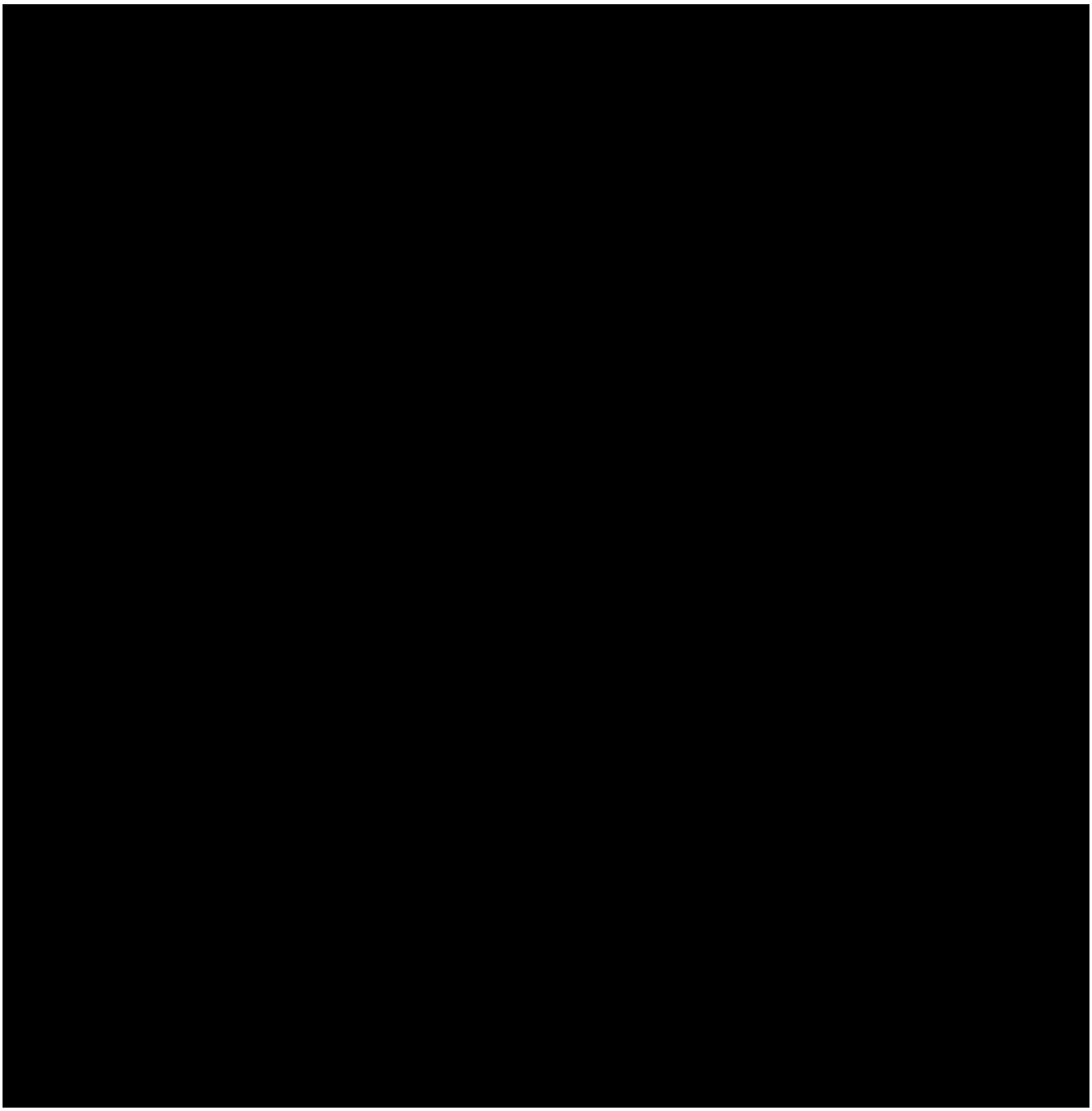
An assessment of tissue quality by a pathologist is strongly encouraged at the time of the procedure.

Sample shipments should include a completed requisition form containing collection date, collection method, primary/met, site, fixation conditions, and a copy of the 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 MGMT-methylated or indeterminate status. Testing will be performed using a centralized RT-PCR assay through study CA209498.



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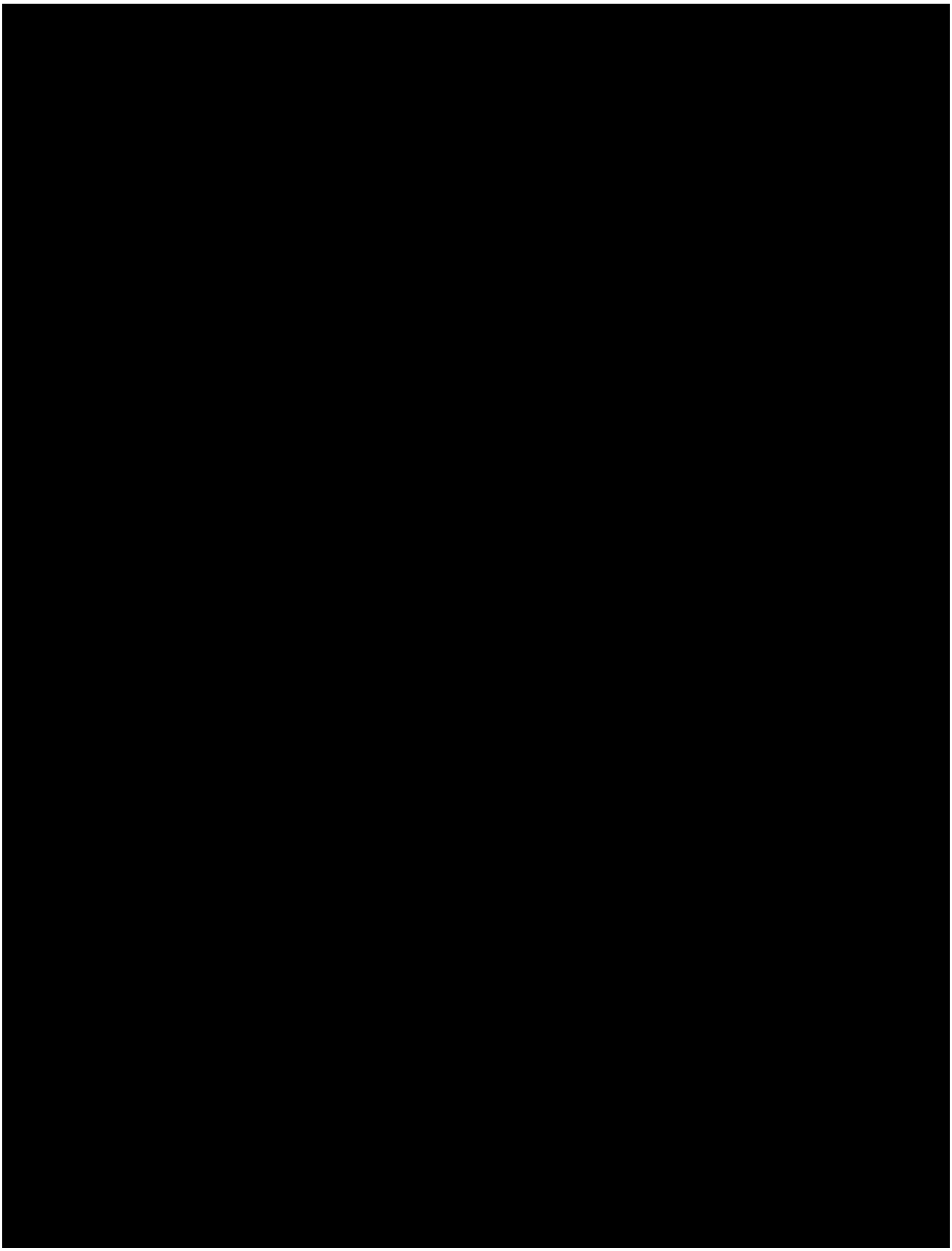

[redacted]

[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 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 until study unblinding for storage and for analysis by blinded independent central review. The site will be informed of quality issues or need for repeat scanning via queries from the core lab.

[redacted]

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease

temporally associated with the use of study drug, whether or not considered related to the study drug.

The definition of immune-mediated AEs can be found in Section 0.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

> Related: There is a reasonable causal relationship between study treatment administration (including SOC) and the AE.
>
> Not related: There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship. In this study the relationship may be assessed to any component of the study treatment: radiation therapy, TMZ, and/or nivolumab/placebo.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI)

Approved v8.0 [redacted]

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE. (See Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anticancer therapy in the absence of any other SAEs

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection, must be collected that occur during the screening period and within 100 days following the last dose of nivolumab and for 30 days following the last dose of temozolomide. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). For subjects randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of nivolumab treatment, and for 30 days following discontinuation of temozolomide treatment.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the subject's case report form.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (electronic) as appropriate: Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the Sponsor or designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call Sponsor or designee within 24 hours of awareness of the pregnancy.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours

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of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant within 6 months (or as noted in the locally applicable package insert, summary of product characteristics [SmPC] or similar document) of the last dose of TMZ should be reported to Sponsor or designee. In order for BMS to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

- AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

"Treatment effect," collected in CNS studies only, is a neurologic AE related to nivolumab attributable to the immune-reaction at or around the tumor site. Most commonly, these are 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. Following study unblinding, the DMC will be discontinued, and the sponsor will monitor safety for the subjects remaining on treatment.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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

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

The primary objectives of the study are:

- to compare progression-free survival (PFS) in an all-comers group of subjects with newly diagnosed MGMT-methylated or indeterminate GBM subtypes treated with RT plus TMZ combined with nivolumab or placebo.
- to compare overall survival (OS) of subjects with newly diagnosed MGMT methylated or indeterminate GBM subtypes without baseline corticosteroids and regardless of baseline

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corticosteroids (ie, all-comers) treated with RT plus TMZ combined with nivolumab or placebo.

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

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

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

- PFS and OS follows exponential distribution
- Median PFS in RT+TMZ arm is 10.0 months
- Hazard ratio (HR) of arm RT + TMZ + nivolumab vs RT + TMZ for PFS is 0.68, translated to median PFS improvement of 4.7 months (10.0 months vs 14.7 months for arm RT + TMZ and arm RT + TMZ + nivolumab, respectively)
- Median OS in RT+TMZ arm is 26.0 months[54]
- Hazard ratio (HR) of arm RT + TMZ + nivolumab vs RT + TMZ is 0.7 for the randomized population with no baseline corticosteroid, translated to median OS improvement of 11.1 months (26.0 months vs 37.1 months for arm RT + TMZ and arm RT + TMZ + nivolumab, respectively)
- Hazard ratio (HR) of arm RT + TMZ + nivolumab vs RT + TMZ is 0.75 for the overall randomized population, translated to median OS improvement of 8.7 months (26.0 months vs 34.7 months for arm RT + TMZ and arm RT + TMZ + nivolumab, respectively)
- Proportion of no baseline corticosteroid population within the entire newly-diagnosed MGMT-methylated or indeterminate GBM subtypes is 0.70

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

One interim analysis will be conducted on OS in the randomized population with no baseline corticosteroid. It will occur approximately 20 months after accrual is finished or when 70% or 236 OS events is reached which is estimated to occur at 45 months after study start, providing a 58% probability of stopping under H1. The stopping boundaries at the interim and final analyses will

be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the planned interim analyses occur exactly at the planned number of events, the projected alpha level will be 0.011 and 0.037. See Table 8.1-1. The interim analysis will also be conducted on OS in the overall randomized population. The interim analysis will be conducted at the same time as the interim for the no baseline corticosteroids population in a hierarchy with stopping boundaries at the interim and final analysis based on actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

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

The technique of alpha-recycling will be used to adjust for multiplicity with details provided in the SAP.

Power calculations were done using East v 6.3 and R.

Table 8.1-1: Key Parameters of Sample Size Calculation of PFS and OS

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

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.

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8.3 Endpoints

8.3.1 Primary Endpoint(s)

The two primary endpoints of the trial will be OS in the randomized population with no corticosteroids at baseline as well as in the overall randomized population, and PFS determined by BICR, based on RANO criteria (see Section 5.4.2).

8.3.2 Secondary Endpoint(s)

OS rate at 12 months and 24 months estimated from OS Kaplan-Meier curve.

PFS determined by investigator assessment based on RANO criteria.

[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

OS is defined as time from the date of randomization to the date of death. Subjects who have not died by the end of the study will be censored to last known date alive. The analysis of the OS endpoint will be based on all randomized subjects in the respective populations of no baseline corticosteroids and the overall randomized population. A group sequential testing procedure will be applied to OS to control the overall type I error from interim and final analyses. Each analysis will be conducted in a hierarchy first testing OS in the population of no baseline corticosteroids and then if positive in the overall randomized population. The α spending function is described in Section 8.1.

PFS is defined as the time from randomization to the date of the first documented tumor progression or death by any cause. Subjects who did not have disease progression or die will be censored at the date of the last tumor assessment. Subjects who did not have any on study tumor assessment and did not die will be censored at the last tumor assessment. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the anti-cancer therapy. Subjects who had surgical resection after start of study treatment will be censored at the last tumor assessment date prior to initiation of surgical resection. PFS will be determined by BICR based on RANO criteria.

8.4.2.1 Analyses of Primary Endpoint

The distribution of OS in the sub-population of subjects with no baseline corticosteroids and in all randomized subjects will be compared in arms RT + TMZ + nivolumab and RT + TMZ at interim and final analyses via two-sided, log-rank tests, stratified by complete resection or partial resection at baseline. The boundaries for declaring superiority at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. For example, if the interim and final analyses occur exactly at the planned number of events, superiority of an arm will be declared if $P \leq 0.011$ at the interim analysis or $P \leq 0.037$ at the final analysis. The Kaplan-Meier product limit method will be used to estimate the survival curve in each arm including medians and its 95% CI, OS rates at various time points. The HR and the corresponding two-sided (1-adjusted α) % 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).

The comparison of PFS (by BICR) will be based on a two-sided log-rank test stratified by corresponding stratification factor (complete surgical or partial resection at baseline). PFS will be compared in the first 558 subjects out of the (total) 714 treated subjects. The Kaplan-Meier product limit method will be used to estimate the survival curve in each arm including medians and its 95% CI, PFS rates at various time points. The HR and the corresponding two-sided 99% 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).

PFS (based on BICR) will be analyzed in overall randomized subjects and all randomized subjects without baseline corticosteroids.

The CA209548 DMC convened on 09-Dec-2020 to conduct a pre-planned, routine safety review of all data. Although the initial recommendation was that the study should continue unchanged and this was communicated to study investigators, subsequently the DMC notified BMS that they had deliberated further and unanimously agreed on the following:

- The OS data clearly shows that there is no plausible scenario for this study to have a positive OS result at the final analysis based on either all randomized patients or on patients without baseline corticosteroids. This statement is based on the DMC's review of the OS results to date, with over 80% of the final required number of events reached and related statistical considerations including conditional power of < 1% for a statistically significant final result.
- While the group receiving nivolumab has a higher incidence of toxicities, the DMC members believed the increased toxicity was expected and did not warrant stopping the study because of safety.

The DMC recommended to unblind the sites and subjects, which was approved by BMS. The study was unblinded to investigators on 22-Dec-2020. As a consequence, the timing of the primary OS analysis, originally planned for when 337 and 494 events were to be reached respectively for the population without corticosteroids at baseline and the overall population, has been updated. To prevent any bias due to unblinding of subjects, the primary OS analysis will be conducted using the cut-off date (or LPLV) of 22-Dec-2020, which is when the study was unblinded.

The primary OS analysis in all randomized subjects without baseline corticosteroids and the primary PFS analysis in all randomized subjects will report a p-value as planned in the alpha recycling plan. Overall survival in all randomized subjects will be tabulated descriptively, as described in the current SAP. Potential subsets analyses will be presented descriptively. The primary analysis of PFS per BICR will be conducted using the cut-off date of 14-Jun-2019 with a database lock date of 09-Aug-2019 (the primary PFS analysis assessed by the DMC in 2019). The same analysis will also be conducted using the cut-off date of 22-Dec-2020.

Based on CP calculation (< 1%) for OS, there is no plausible scenario for this study to have a positive OS result. Therefore, only selected analyses will be included in the primary Clinical Study Report, as described in the current SAP.

8.4.2.2 Analyses of Secondary Endpoints

Overall survival rates at 12 and 24 months will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

PFS based on investigator assessment will be analyzed in the first 558 subjects, all randomized subjects and all randomized subjects who did not receive corticosteroids at baseline.

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All secondary endpoints will be analyzed at the same time as the OS and PFS primary analyses using the analysis methods already defined in the SAP.

[redacted]

8.5 Interim Analyses

This study will include 1 formal interim analysis on OS for superiority.

A formal interim analysis for superiority of OS will be performed when approximately 236 (70% of planned events or 236/337) events is reached in the population of no baseline corticosteroids. Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary will be used. The stopping boundary will depend on the actual number of OS events at the time of the interim analysis. At the time of the interim analyses, the DMC will review OS and other efficacy endpoints as defined in the DMC charter.

In addition to the formal planned interim analysis for OS, the DMC will have access to periodic interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

8.6 End of Study Analyses at Study Closure

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

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

Data to be reported:

- Subject disposition
- Duration of treatment (nivolumab, temozolomide)
- Death

- Adverse events
- Serious adverse events

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) 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), adverse event 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 or designee, whichever is longer. The investigator (or head of study site in Japan) must contact BMS or designee prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the 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, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

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

If...	Then...
	• amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • 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. [redacted] 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 Sponsor or designee 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 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 Sponsor of designee.

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 Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. 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 or designee. 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 or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

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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.

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11 LIST OF ABBREVIATIONS

Term	Definition
ACTH	adrenocorticotropic hormone
[redacted]	
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
BICR	Blinded Independent Central Review
BMS	Bristol-Myers Squibb Company
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
[redacted]	
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
[redacted]	
%CV%	geometric mean

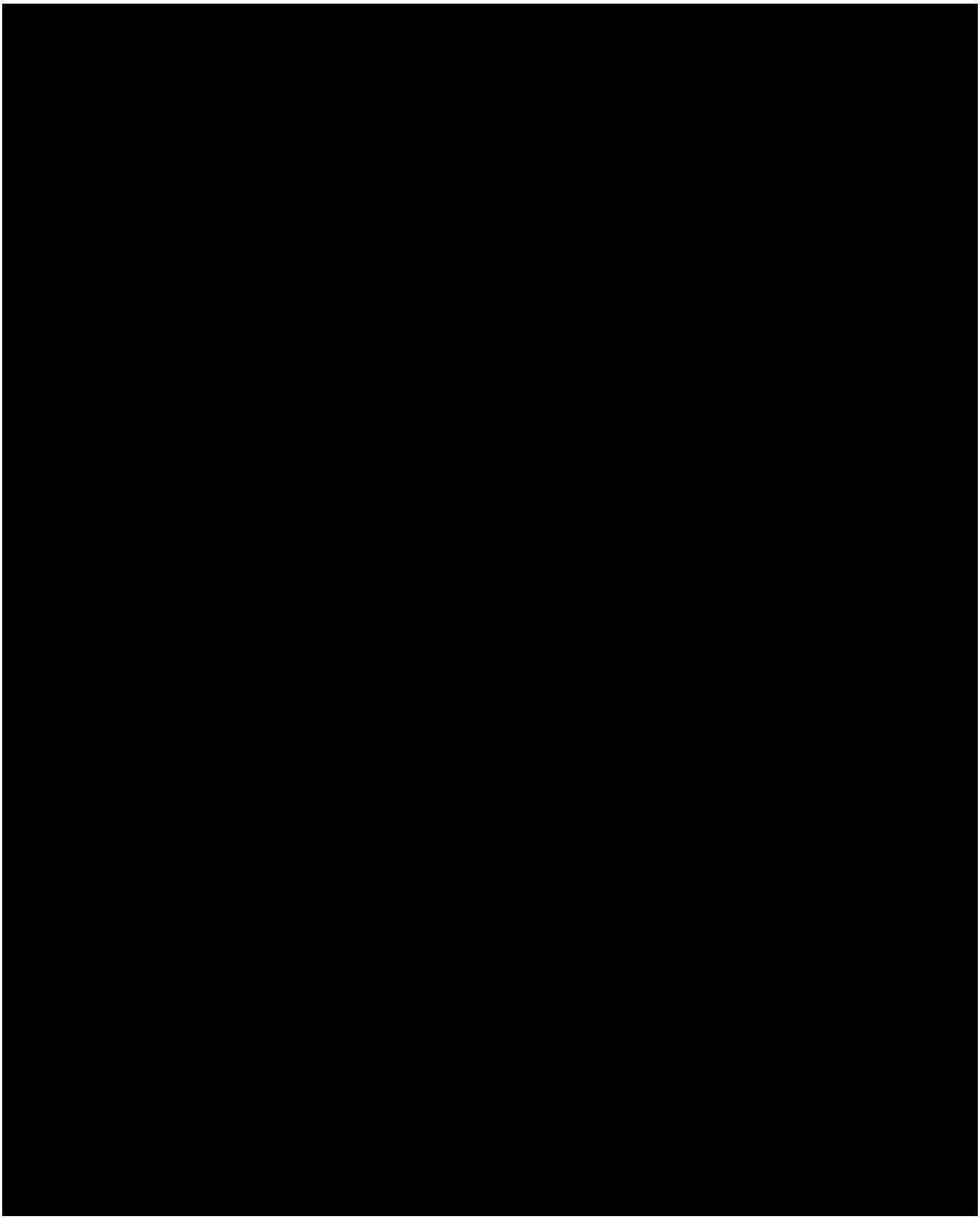
Term	Definition
DILI	drug-induced liver injury
dL	deciliter
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTIC	Dacarbazine
[redacted]	
EC	ethics committee
ECG	electrocardiogram
[redacted]	
eCRF	electronic case report form
EDC	electronic data capture
Eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
[redacted]	
ESR	expedited safety report
FDA	Food and Drug Administration
[redacted]	
FLAIR	fast fluid-attenuated inversion recovery
FSH	follicle stimulating hormone
GBM	glioblastoma
GCP	Good Clinical Practice
[redacted]	
Gy	Gray (radiotherapy dose)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

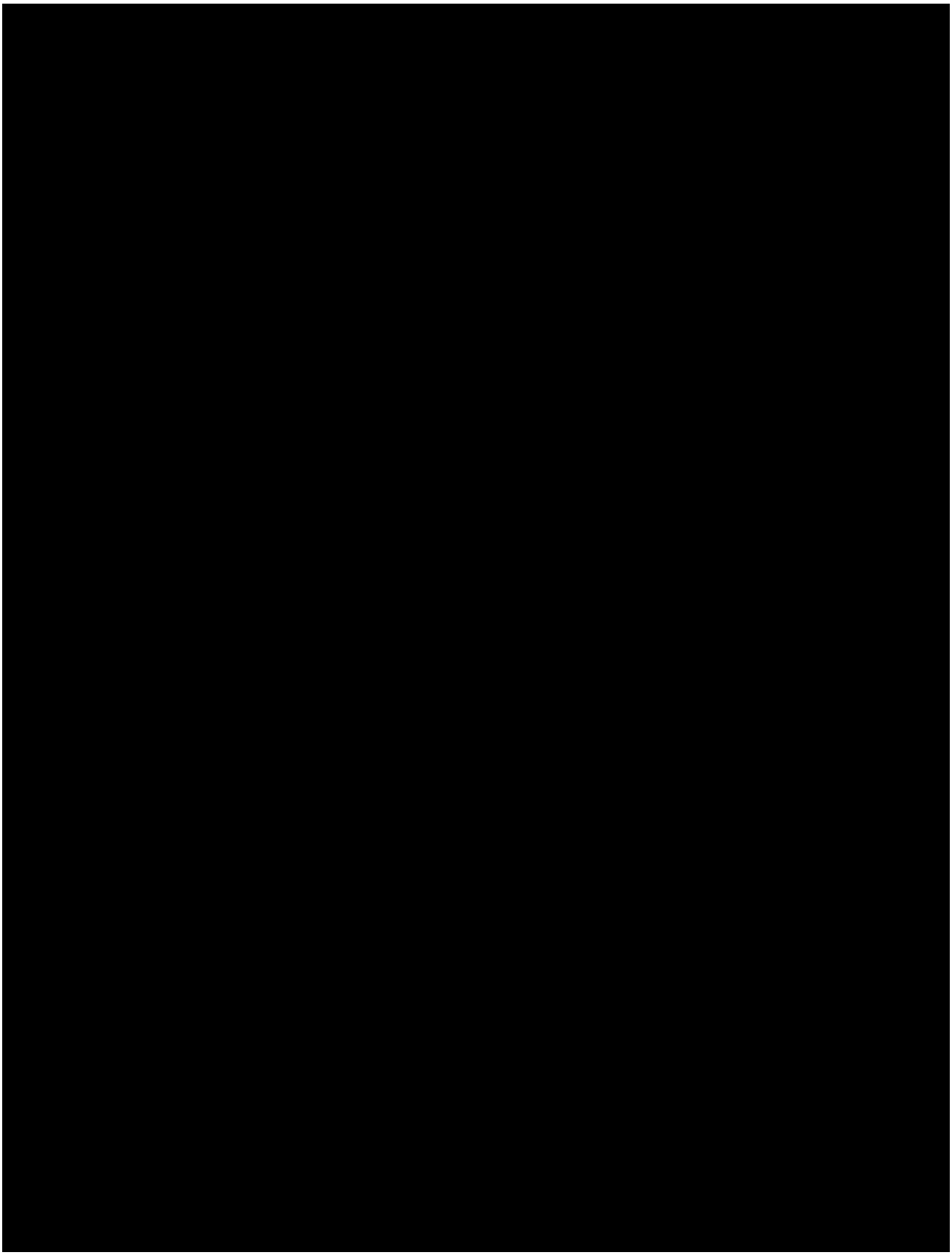
Term	Definition
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCV-RNA	hepatitis C virus-ribonucleic acid
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
[redacted]	
HR	heart rate
HRT	hormone replacement therapy
[redacted]	
IB	investigator brochure
ICD	implantable cardioverter defibrillator
ICF	informed consent form
ICH	International Conference on Harmonisation
[redacted]	
Ie	id est (that is)
IEC	Independent Ethics Committee
[redacted]	
IMP	investigational medicinal products
imAEs	immune-mediated adverse events
IND	Investigational New Drug Exemption
I-O	immuno-oncology
IP	investigational product
[redacted]	
IRB	Institutional Review Board
IRC	Independent Radiology Review Committee
IU	international unit
IUDs	intrauterine devices
IV	intravenous
IVRS	interactive voice response system

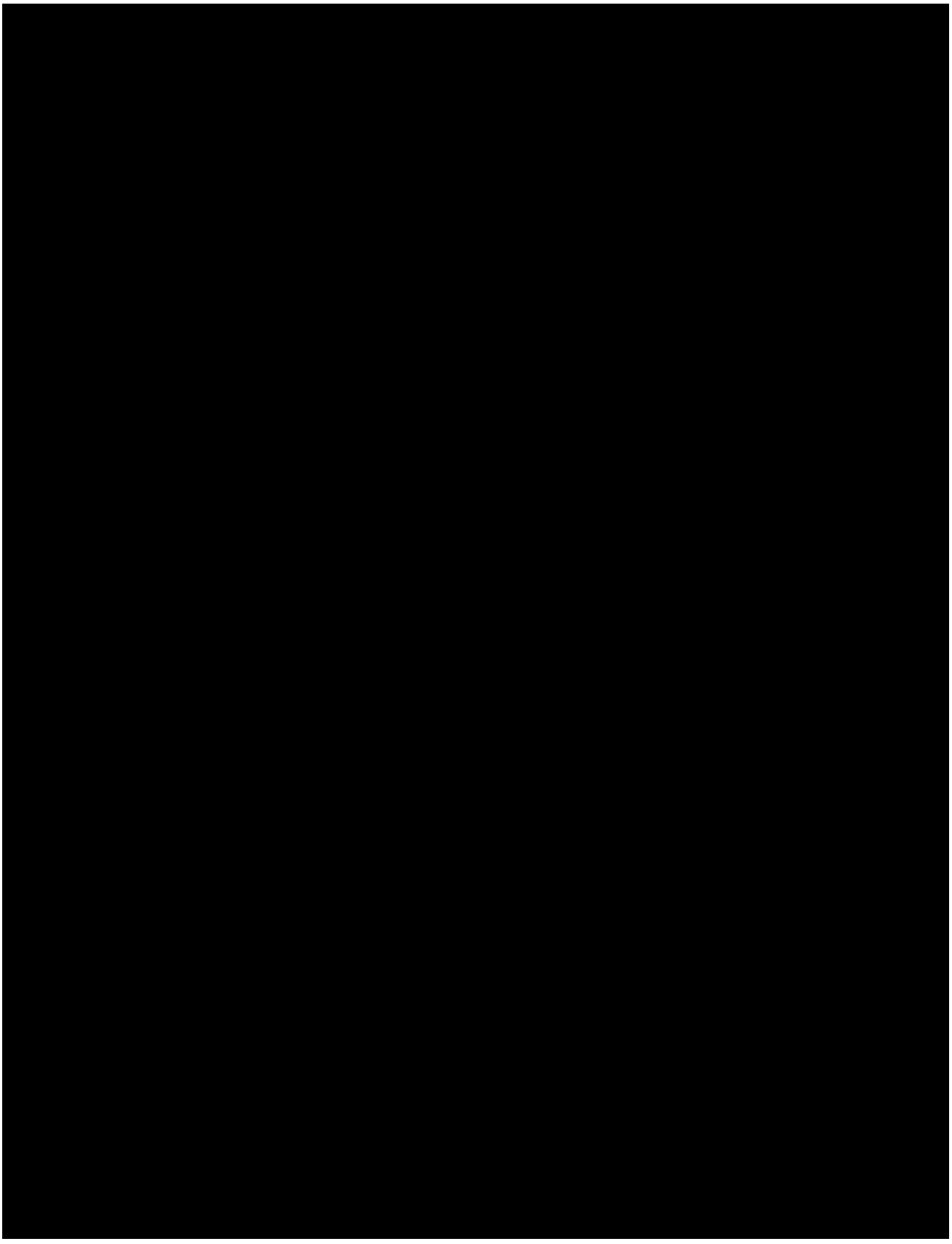
Term	Definition
[redacted]	
K+	potassium
Kg	kilogram
[redacted]	
LPLV	Last patient last visit
[redacted]	
mg	milligram
Mg/kg	milligram per kilogram
Mg++	magnesium
MGMT	tumor O-6-methylguanine DNA methyltransferase
mL	milliliter
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
[redacted]	
µg	microgram
N	number of subjects or observations
N	nivolumab (BMS-936558)
Na+	sodium
[redacted]	
N/A	not applicable
[redacted]	
NCI	National Cancer Institute
NE	not evaluable
NIMP	non-investigational medicinal products
[redacted]	
O_2	oxygen
OS	overall survival

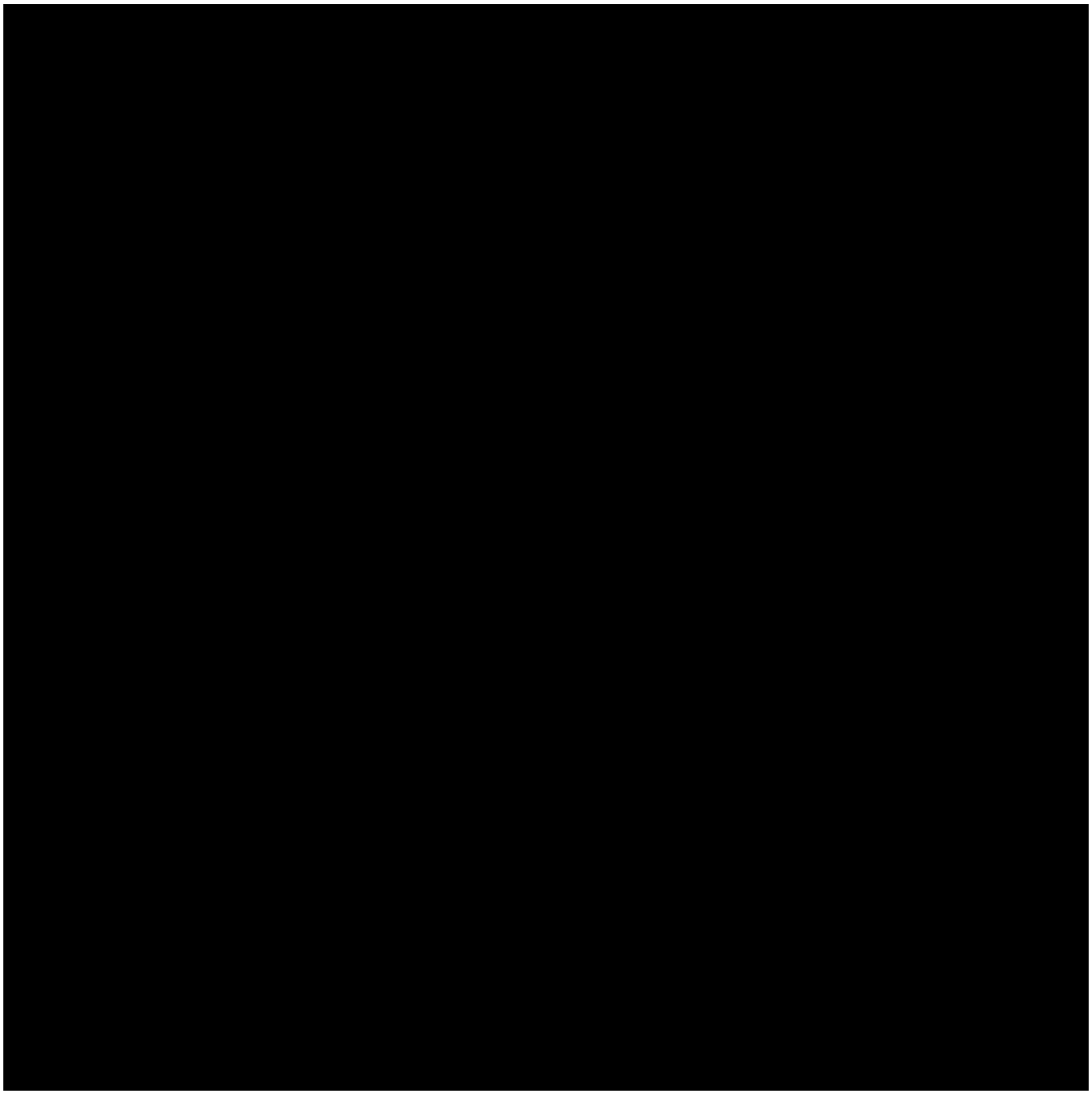
Term	Definition
[redacted]	
PCR	polymerase chain reaction
[redacted]	
PD	progressive disease
[redacted]	
PFS	progression-free survival
PID	patient identifier
[redacted]	
PO	per os (by mouth route of administration)
[redacted]	
PR	partial response
PVC	polyvinyl chloride
QD	once a day
[redacted]	
QOL	quality of life
RANO	Radiologic Assessment in Neuro-Oncology
[redacted]	
RR	respiratory rate
RT	radiation therapy
[redacted]	
RT-PCR	reverse transcription polymerase
SAE(s)	serious adverse event(s)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	statistical analysis plan
SD	stable disease
SmPC	summary of product characteristics

Term	Definition
[redacted]	
SOC	standard of care
SOP	standard operating procedures
T1/2	geometric elimination half-life
[redacted]	
TIL	tumor infiltrating lymphocytes
[redacted]	
TMZ	Temozolomide
TSH	thyroid stimulating hormone
µg	microgram
ULN	upper limit of normal
[redacted]	
w	week
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential









APPENDIX 1 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 4.0

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

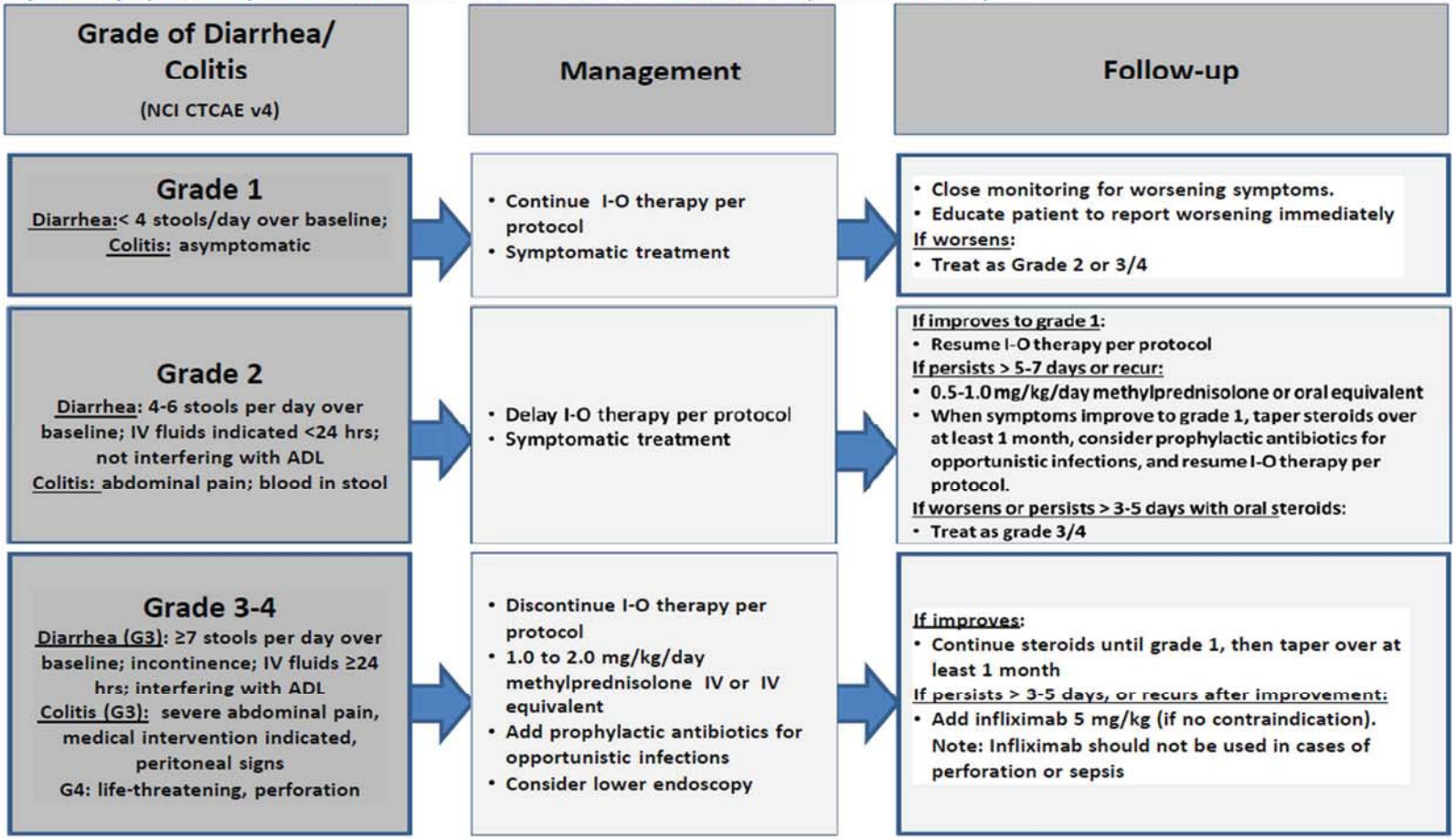
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Approved v8.0 [redacted]

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

28-Sep-2020

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

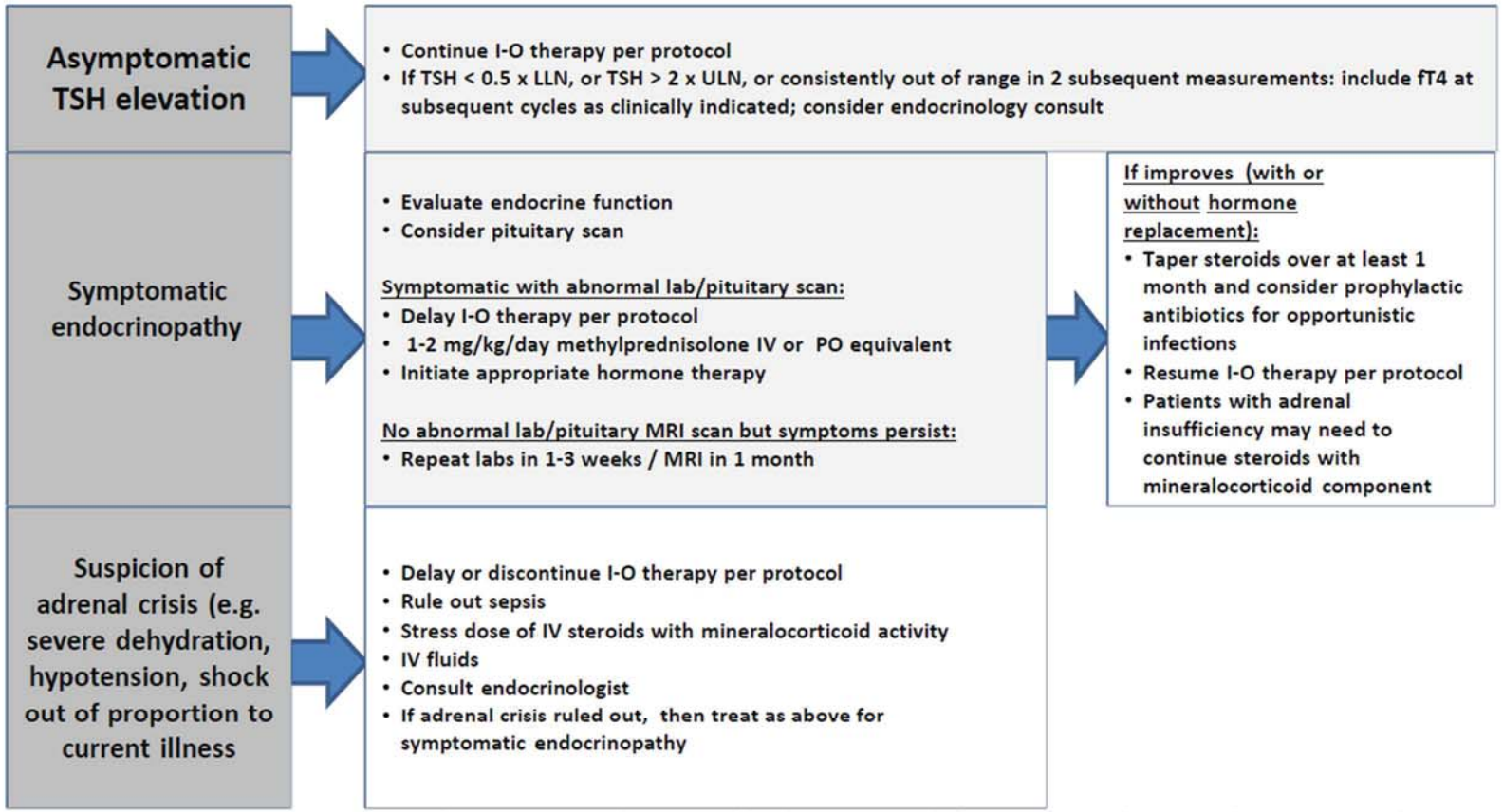
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



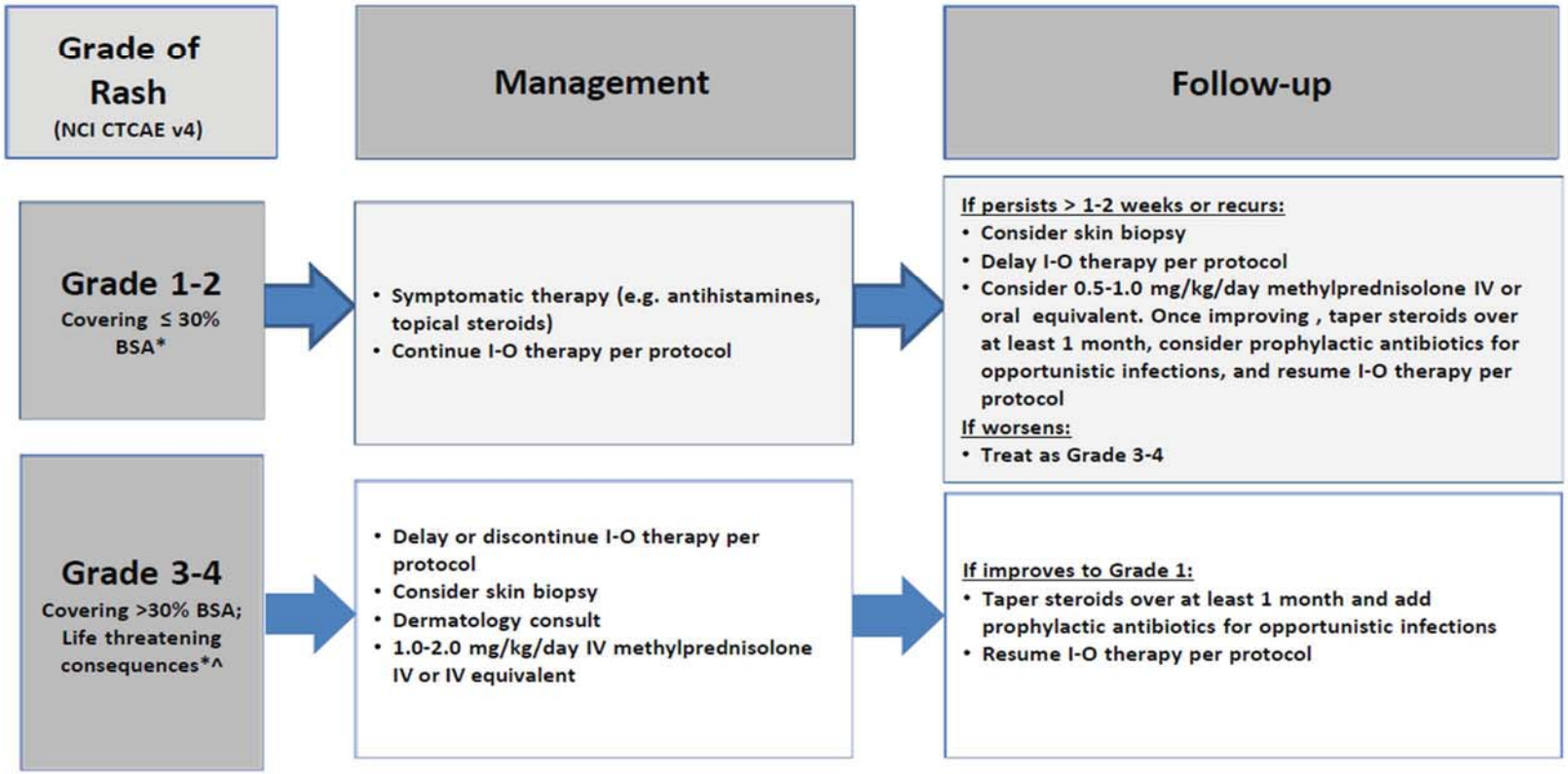
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Approved v8.0 [redacted]

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

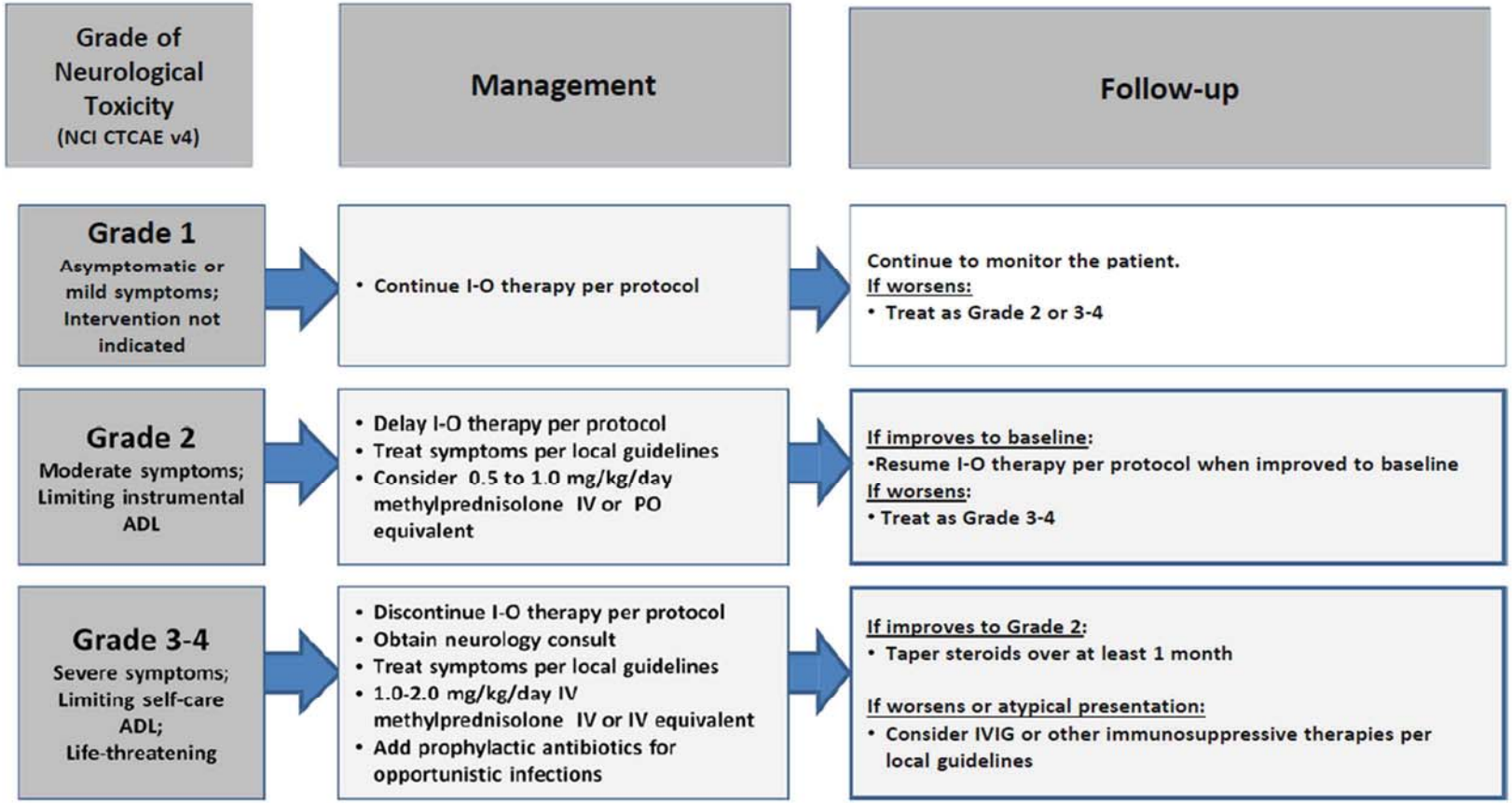
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

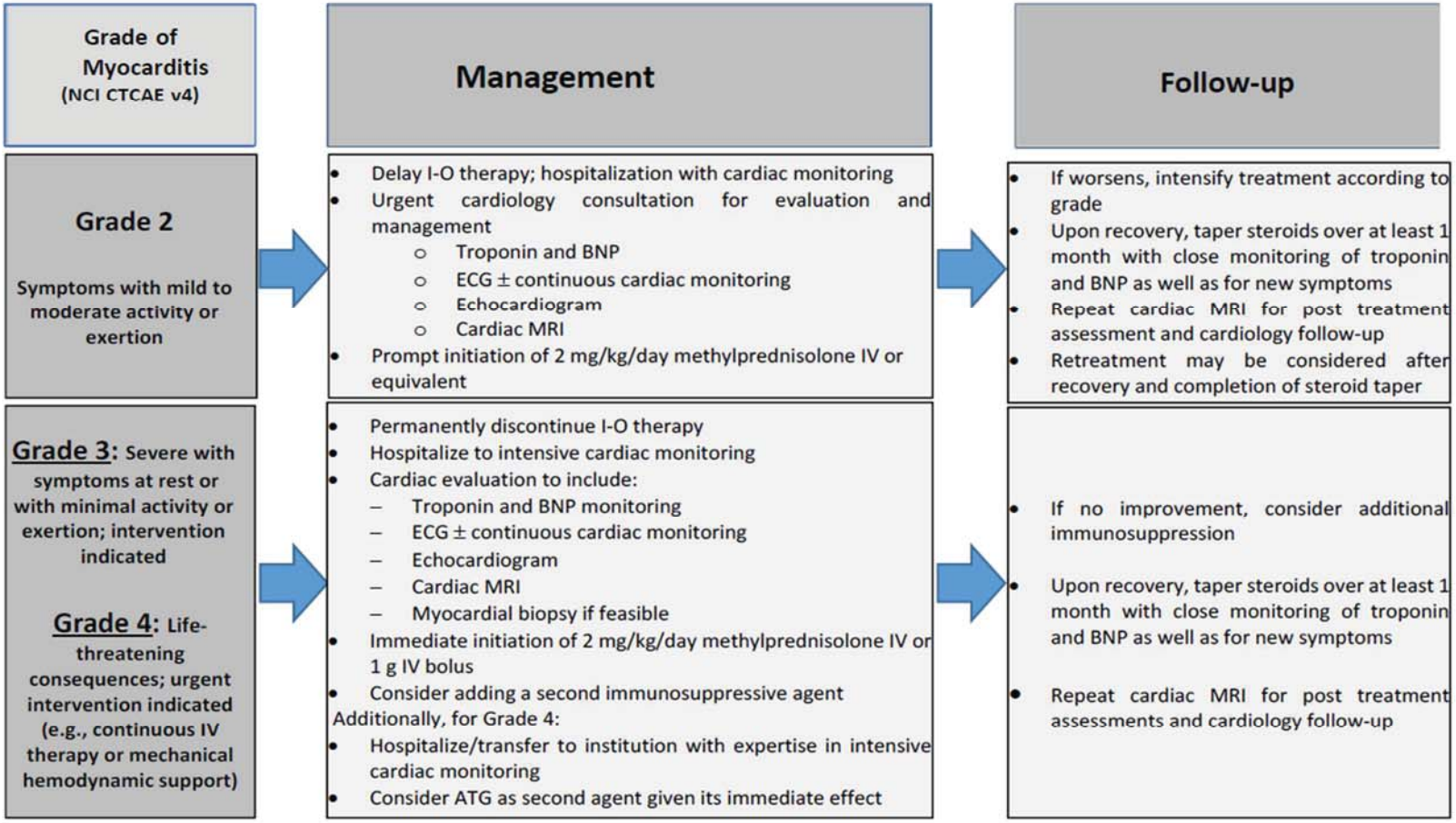


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Approved v8.0 [redacted]

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

28-Sep-2020

Approved v8.0 [redacted]

APPENDIX 2 RADIATION THERAPY GUIDELINES

Radiation therapy for GBM contributes importantly to both efficacy and toxicity. Modern radiotherapeutic management of GBM was recently summarized: Niyazi M, et al. (2016) ESTRO-ACROP guideline "target delineation of glioblastomas". Radiother Oncol 118:35-42.

A high level of experience is assumed in participating centers. Guidelines are provided in order to support appropriate homogeneity in a trial environment without imposing excessive constraints on expert practice. Therefore, the following guidelines should be interpreted as expectations rather than protocol requirements.

Dose Specification

A total dose of 60 Gy, in 2 Gy daily fractions on 5 days/week, will be administered in 6 weeks (30 fractions). Radiation treatment duration may be extended due to delays or holidays up to 7 weeks (49 calendar days).

Radiation treatment will be delivered with a megavoltage machine with photon energy ≥ 6 MV utilizing either 3-D Conformal or Intensity-Modulated (IMRT or VMAT) approaches. Electron, particle, or implant boost is not permitted.

An initial target volume (see below definitions) will be irradiated to 46 Gy in 23 fractions with an additional 14 Gy in 7 fractions to the boost volume for a total of 60 Gy. Alternatively, based on institutional practice, a one-phase approach to a dose of 60 Gy, is acceptable.

Simulation and Treatment Planning

Simulation using treatment planning CT (supine position with immobilization, eg, thermoplastic mask) is standard. Fusion with MR images for target and OAR delineation is mandatory.

Target volumes will be based upon post-operative contrast-enhanced MRI, although pre-operative imaging should be used for correlation, and may be modified based on subsequent scans if anatomic shift is evident. The method of dose volume planning and documentation should be not be investigational.

The initial gross tumor volume (GTV1) is defined by either the T2 or the FLAIR abnormality, including enhancing tumor volume and surgical cavity. The boost volume (GTV2) will be based on the T1-enhancing tumor volume plus the surgical cavity. Derived clinical target volumes (CTV1-2) are the corresponding GTV plus a margin of approximately 2 cm; smaller margins are permitted, based on clinical judgment and anatomic constraints. Planning target volume (PTV1-2) margins, typically approximately 0.5 cm, will be determined by institutional practice based on technical considerations and reproducibility. Weekly verification is expected.

Doses will be specified such that at least 95% of the planned CTV shall receive 100% of the prescribed dose, with acceptable variance of 90% PTV coverage for clinical or technical reasons. Isodose distributions must be recorded. Details of field modification will be determined by the radiation oncologist using currently-accepted practice based on primary tumor extension, natural structures and organs at risk (eg, optic chiasm or brainstem), as well as on reproducibility considerations, potential overlap regions and the like.

Approved v8.0 [redacted]

APPENDIX 3 KARNOFSKY PERFORMANCE SCALES

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort, some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death nor imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX 4 HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

At a minimum, subjects must agree to use one highly effective method of contraception as listed below. Local laws and regulations may require use of alternative and/or additional contraception methods.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1) Progestogen only hormonal contraception associated with inhibition of ovulation.
2) Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3) Nonhormonal IUDs, such as ParaGard®
4) Bilateral tubal occlusion
5) Vasectomised partner with documented azoospermia 90 days after procedure
   - Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
6) Intrauterine hormone-releasing system (IUS).
7) Complete abstinence
   - Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
   - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).
   - It is not necessary to use any other method of contraception when complete abstinence is elected.
   - Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5.
   - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
   - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Approved v8.0 [redacted]

UNACCEPTABLE METHODS OF CONTRACEPTION

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

Approved v8.0 [redacted]

APPENDIX 5 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 06, 26-Feb-2021

The CA209548 Data Monitoring Committee (DMC) convened on 09-Dec-2020 to conduct a pre-planned, routine safety review of all data. Although the initial recommendation was that the study should continue unchanged and this was communicated to study investigators, subsequently the DMC notified BMS that they had deliberated further and unanimously agreed on the following:

- The overall survival (OS) data clearly shows that there is no plausible scenario for this study to have a positive OS result at the final analysis based on either all randomized patients or on patients without baseline corticosteroids. This statement is based on the DMC's review of the OS results to date, with over 80% of the final required number of events reached and related statistical considerations including conditional power of < 1% for a statistically significant final result.
- While the group receiving nivolumab has a higher incidence of toxicities, the DMC members believed the increased toxicity was expected and did not warrant stopping the study because of safety.

The DMC recommended to unblind the sites and patients, which was approved by BMS. The study was unblinded to investigators on 22-Dec-2020. As a consequence, the timing of the primary OS analysis, originally planned for when 337 and 494 events were to be reached respectively for the population without corticosteroids at baseline and the overall population, has been updated. To prevent any bias due to unblinding of patients, the primary OS analysis will be conducted using the cut-off date (or last patient last visit [LPLV]) of 22-Dec-2020, which is when the study was unblinded.

Following unblinding, study subjects who were currently on nivolumab therapy, tolerating the treatment, and were considered by the treating physician to derive benefit were permitted to continue if they choose. However, study procedures in the treatment and follow-up phases are now simplified, since additional post-unblinding data are no longer needed for analyses.

Protocol languages per BMS standards for nivolumab studies and for COVID-19 have also been incorporated.

This protocol amendment incorporates the changes from the approved Administrative Letters 10 and 11 which are not detailed in the summary of key changes below.

Summary of key changes of Protocol Amendment 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	The study contacts and naming conventions have been updated. The name, address, and confidentiality statement of the Sponsor have been updated.	Changes in BMS personnel and team assignments. Changes in the BMS protocol model document.

Approved v8.0 [redacted]

Summary of key changes of Protocol Amendment 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Summary: Study Design	Unblinding information has been added. Follow-up for progression and survival after study treatment discontinuation has been deleted.	The study was unblinded following DMC recommendation, necessitating this amendment to update the timing of the primary OS analysis and to simplify study procedures following unblinding.
[redacted]		
3.1: Study Design and Duration	Post-treatment follow-up instructions revised to remove contrast MRI. BICR submission will stop with unblinding, clarification added.	Following study unblinding, the collection of imaging data for analysis purposes is not relevant; BICR and post-treatment imaging data is no longer needed.
Summary: Study Schematic Figure 3.1-1: Study Design Schematic	Schematic figure updated to: safety only following unblinding Clarification added below figure indicating that following unblinding, subjects may continue on treatment.	Aligned with changes concerning study unblinding.
Summary: Study Assessments 3.1.3: Follow-up Phases	Follow up procedures have been further clarified. Instructions for assessments after treatment discontinuation for reasons other than disease progression have been removed.	Aligned with simplified procedures following study unblinding; [redacted]
3.1.4: Overall Study Duration	Updates due to unblinding, including the timing of study closure, have been made.	The study was unblinded following DMC recommendation; the OS primary analysis will include data through the date of study unblinding. Additional OS data are not required, so the study will close following all subjects' treatment discontinuation and safety follow-up.
3.3.1: Inclusion Criteria	Male contraception requirements revised for Inclusion Criterion 3e.	Updated per BMS standard for all studies with nivolumab.
3.5: Discontinuation of Subjects following any Treatment with Study Drug	Post-treatment follow-up for progression and survival has been removed.	Aligned with changes concerning study unblinding.

Summary of key changes of Protocol Amendment 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
3.6: Post Study Drug Follow-up	Post-treatment follow-up for survival has been removed.	Aligned with changes concerning study unblinding.
4.5.1: Nivolumab/Placebo Dosing	Unblinding clarification added.	Due to study unblinding, the provisions for dosing and dose modification no longer apply for the placebo treatment arm.
4.5.1.3: Dose Delay Criteria for Nivolumab/Placebo 4.5.1.4: Criteria to Resume Dosing for Nivolumab/Placebo	Added SARS-CoV-2 infection criteria	Updated per BMS standard for COVID-19 protocol language.
4.5.1.5: Treatment Discontinuation Criteria for Nivolumab/Placebo	Decision by treating physician and subject to discontinue treatment following unblinding has been added to criteria for discontinuation.	Aligned with changes concerning study unblinding.
4.6: Blinding/Unblinding	Statement regarding unblinding has been added.	The study was unblinded following DMC recommendation, necessitating this amendment to update the timing of the primary OS analysis and to simplify study procedures following unblinding.
Table 5.1-2: On-treatment Assessments Table 5.1-3: Treatment Follow-up and Survival Follow-up	Footnote ‘a’ added to chemistry panel row. Footnote ‘a’ updated to clarify chemistry panel collection in relation to TMZ dosing. [redacted] notes clarified to include instructions following unblinding. Footnote ‘a’ updated to add instructions following unblinding. Footnote ‘b’ updated to clarify that survival follow-up visits do not occur following unblinding.	Aligned with simplified procedures following study unblinding; subsequent response, survival, [redacted] are no longer needed.
5.3: Safety Assessments	Clarification for subjects on TMZ treatment following placebo discontinuation has been added. Instruction to evaluate for cardiac or pulmonary toxicity has been added.	Aligned with changes concerning study unblinding. Updated per BMS standard for all studies with nivolumab.

Summary of key changes of Protocol Amendment 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
5.4: Efficacy Assessments [redacted] 5.8.3: Results of Central Radiology Assessments [redacted]	Clarification has been added to discontinue BICR submission, [redacted] following unblinding.	Aligned with simplified procedures following study unblinding; subsequent response data [redacted] are no longer needed.
[redacted]		
6.1.1: Serious Adverse Event Collection and Reporting 6.2.1: Nonserious Adverse Event Collection and Reporting 6.4: Pregnancy	Clarification has been added concerning SAEs and non-serious AEs related to SARS-CoV-2. Clarification for collection of nonserious AEs for a minimum of 100 days following discontinuation of nivolumab and 30 days following discontinuation of TMZ has been added. Clarification that a pregnancy occurring in the female partner of a male subject within 3 months of his last dose of TMZ must be reported to the Sponsor has been added.	Updated per BMS standard for COVID-19 protocol language. Aligned with simplified procedures following study unblinding; continued AE collection is not needed for subjects discontinuing the placebo treatment arm. Subjects in the placebo treatment arm who discontinue TMZ treatment require 30 days of adverse event collection following the last TMZ dose. Updated pregnancy reporting per BMS standard for all nivolumab studies.

Summary of key changes of Protocol Amendment 06		
Section Number & Title	**Description of Change**	**Brief Rationale**
Summary: Primary Endpoints 8.1: Sample Size Determination 8.4.2.1: Analyses of Primary Endpoint 8.5: Interim Analyses	Statement describing the impact of DMC unblinding decision has been added. Statistical description of the primary OS analysis has been updated. PFS interim analysis updated per Administrative Letter 10.	The study was unblinded following DMC recommendation; the OS primary analysis will include data through the date of study unblinding, and is no longer event driven. The PFS interim analysis was removed.
Summary: Secondary Endpoints 8.4.2.2: Analyses of Secondary Endpoints	Clarification for the timing of secondary endpoint analysis added.	Aligned with updated timing for the OS primary analysis.
8.6: End of Study Analyses at Study Closure	Section added to describe what analyses will occur at study closure once all post unblinding data have been collected.	Subjects may remain on study treatment post unblinding and will be followed through the safety follow-up phase. Limited reporting will be completed as described in the analysis plan.

Overall Rationale for Revised Protocol 05, 08-Nov-2018

Per Revised Protocol 05, progression free survival (PFS) has been changed from a secondary to a primary objective of the study. In support of this change, blinded independent central review (BICR) has been added and may occur at any time during the study. Overall survival (OS) rate at 12 and 24 months and PFS based on investigator assessment by RANO criteria have been added as secondary objectives. The statistical section has been revised to support changes in the study objectives. The study will now include 1 formal interim analysis for PFS and 1 formal interim analysis for OS for superiority.

[redacted]

Updates per BMS standards for nivolumab studies and changes per Administrative Letter 06, as described in the document history on the preceding page, have also been incorporated.

Summary of key changes of Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Synopsis, Objectives, Research Hypothesis, and Study Schema [redacted] • Sections 1.3.1 and 1.3.2 Primary and Secondary Objectives	Change of PFS to a primary rather than a secondary objective. Addition of OS rate at 12 and 24 month as a secondary objective.	PFS has been changed to a primary objective of the study and is supported by the addition of BICR. PFS as surrogate survival marker enables an earlier assessment of treatment effects. Survival rates at 12 and 24 months are widely used endpoints in

Summary of key changes of Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted] • Section 3.1 Study Design and Duration and Figure 3.1-1 Study Design Schematic		neuro-oncology to better describe long-term survival or a "plateau".
• Synopsis Objectives • Section 1.3.2 and 1.3.3 Secondary [redacted] Objectives	PFS based on investigator assessment by RANO criteria added as a secondary objective. [redacted]	As a secondary endpoint, PFS will also be estimated by investigator assessment based on RANO criteria to compare it with PFS determined by BICR. [redacted]
• Synopsis, Study Assessments • 5.4 Efficacy Assessments	Language added to specify that study images will be submitted to a central imaging vendor for blinded independent central review (BICR) at any time during the study.	The addition of BICR supports the change of PFS to a primary objective of the study. BICR performed by blinded radiologists at a central facility provides the most objective evaluation of the PFS endpoint.
• Synopsis, Statistical Considerations • Section 8: Statistical Considerations	The statistical section has been revised to support changes in the study objectives. Of note, the study will now include 1 formal interim analysis for PFS and 1 formal interim analyses for OS for superiority.	Aligned with changes in study objectives.
• Section 3.1.4 Overall Study Duration	Text changes that reflect changes in the study objectives and interim analyses.	Aligned with changes in study objectives and updated statistical considerations.
• Section 3.3.1, Inclusion Criteria, 4. Physical and Laboratory Test Findings e)	Updated to: Serum creatinine ≤ 1.5 x ULN unless (*changed from or*) creatinine clearance (CrCl) ≥ 50 mL/min) (measured or calculated [*added*] using the Cockcroft-Gault formula)	Aligned with BMS standard for studies of nivolumab in subjects with glioblastoma.
• Section 3.3.2 Exclusion Criteria 2) Medical History • Section 3.4.1 Prohibited and/or Restricted Treatments	Treatment with any live/attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) has been added as an exclusion criterion and is prohibited during treatment and until 100 days post last dose.	Updated to BMS standard for all studies with nivolumab.

Summary of key changes of Revised Protocol 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
• Section 3.4.2.1 Imaging Restriction and Precautions	Standard language for imaging added to this section	Updates per BMS standard.
• Section 4.5.1.5 Treatment Discontinuation Criteria for Nivolumab/Placebo	Updated to: Grade 3 drug-related uveitis, pneumonitis, bronchospasm, *neurologic toxicity*, [added], *myocarditis* [added], hypersensitivity reaction, or infusion reaction of any duration requires discontinuation	Updated to BMS standard for all studies with nivolumab.
• Section 5.6.1. Tumors Samples	Subsections revised to align with standard BMS practice.	Update per BMS technology standard.
[redacted]		
• Appendix 1: Hepatic Adverse Event Management Algorithm	Deletion of footnote stating I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN	Updated per BMS standard for all studies with nivolumab.
Throughout the protocol	Minor editorial corrections and clarifications with no impact on protocol content.	