For Protocol Amendment 3 to NRG-BN007, A Randomized Phase II/III Open-Label Study of Ipilimumab and Nivolumab Versus Temozolomide in Patients With Newly Diagnosed MGMT (Tumor O-6-Methylguanine DNA Methyltransferase) Unmethylated Glioblastoma

NCI/Local Protocol #: NRG-BN007

NCI Protocol Version Date: January 17, 2023

Section	Change
Global	Formatting was corrected and the protocol version date was updated.
Cover pages	Contact information was updated for Dr. Manasawala and Dr. Wolchok.
CTSU Contact Information 8.0 8.1 8.2 8.3 13.1 13.3 13.4	Text was updated per current CTSU, NCTN, and NRG Oncology logistics.
6.3	Reference to the Hepatic AE Management Algorithm was added to the Pancreatitis table for clarity.
9.2	The ipilimumab supply section was updated in response to CTEP's November 3, 2022, Request for Amendment for NCI studies using PMB-supplied ipilimumab.
14.4-14.1	Logistics were clarified.

NRG ONCOLOGY

NRG-BN007
(ClinicalTrials.gov NCT 04396860)

A RANDOMIZED PHASE II/III OPEN-LABEL STUDY OF IPILIMUMAB AND NIVOLUMAB VERSUS TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED MGMT (TUMOR O-6-METHYLGUANINE DNA METHYLTRANSFERASE) UNMETHYLATED GLIOBLASTOMA

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

Coordinating Center:
NRG Oncology
Four Penn Center; 1600 JFK Blvd; Suite 1020; Philadelphia, PA 19103

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Brain Tumor Committee Chair	Minesh Mehta, MD (see protocol cover page/Radiation Oncology Co-Chair role for contact information)

Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Ipilimumab	PMB	732442		DCTD, NCI
Nivolumab	PMB	748726		
Temozolomide	Commercial	362856		

Participating Sites

☒ U.S.
☒ Canada
☐ Approved International Member Sites

Document History

	Version Date
Amendment 3	**January 17, 2023**
Amendment 2	**April 8, 2022**
Amendment 1	February 9, 2021
Initial	July 9, 2020

NRG ONCOLOGY

NRG-BN007

A RANDOMIZED PHASE II/III OPEN-LABEL STUDY OF IPILIMUMAB AND NIVOLUMAB VERSUS TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED MGMT (TUMOR O-6-METHYLGUANINE DNA METHYLTRANSFERASE) UNMETHYLATED GLIOBLASTOMA

CONTACT INFORMATION (17-JAN-2023)		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at http://www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com. .	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. .

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user logging in with a CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users).

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.

For clinical questions (i.e., patient eligibility or treatment-related)
Contact the study data manager listed on the NRG Oncology contact information table on the protocol cover page.

For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)
Contact the CTSU Help Desk by phone or email:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

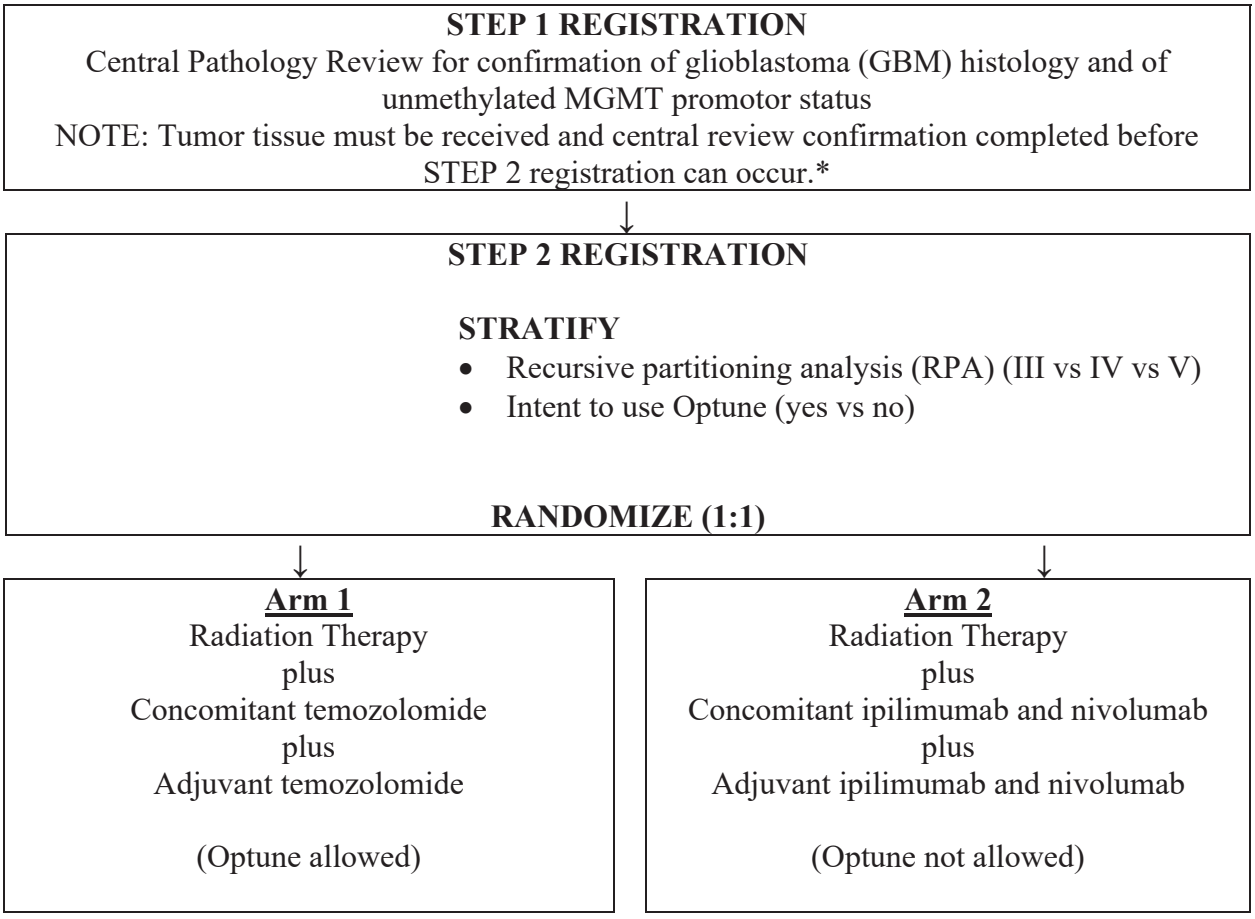
For imaging data submission questions:
IROCimagearchive@acr.org; please include trial number in the email subject line

For TRIAD access and installation support:
TRIAD-Support@acr.org
Triadhelp.acr.org

TRIAD Software Installation:
https://triadinstall.acr.org/triadclient/

TABLE OF CONTENTS

NRG-BN007
SCHEMA (08-APR-2022)



See Section 5.1 for agent treatment details and Section 5.2 for radiation therapy details.
*Patients with methylated MGMT may be considered for enrollment on NRG-BN011. Please see Section 10.2 for additional information.

1. OBJECTIVES

1.1 Primary Objective

1.1.1 Phase II: To determine if adding ipilimumab and nivolumab to radiotherapy significantly prolongs progression-free survival (PFS) versus adding temozolomide to radiotherapy in patients with newly diagnosed glioblastoma (GBM) without MGMT promoter methylation

1.1.2 Phase III: To determine if adding ipilimumab and nivolumab to radiotherapy significantly prolongs overall survival (OS) versus adding temozolomide to radiotherapy in patients with newly diagnosed GBM without MGMT promoter methylation

1.2 Secondary Objectives

1.2.1 To determine if adding ipilimumab and nivolumab to radiotherapy significantly prolongs PFS versus adding temozolomide to radiotherapy in patients with newly diagnosed GBM without MGMT promoter methylation for the phase III part of the study

1.2.2 To determine if adding ipilimumab and nivolumab to radiotherapy significantly increases the 2-year OS rate versus adding temozolomide to radiotherapy in patients with newly diagnosed GBM without MGMT promoter methylation

1.2.3 To evaluate the safety of adding ipilimumab and nivolumab to radiotherapy via comparative frequency between arms of specific adverse events of interest and frequency summaries for all adverse event types

1.2.4 To evaluate the effect of adding ipilimumab and nivolumab to radiotherapy versus adding temozolomide to radiotherapy on patient reported outcomes (PROs), as measured by the MD Anderson Symptom Inventory - Brain Tumor (MDASI-BT) in patients with newly diagnosed GBM without MGMT promoter methylation

1.2.5 To evaluate the effect of adding ipilimumab and nivolumab to radiotherapy versus adding temozolomide to radiotherapy on selected PRO-CTCAE items in patients with newly diagnosed GBM without MGMT promoter methylation

1.2.6 To evaluate the impact of adding ipilimumab and nivolumab to radiotherapy versus adding temozolomide to radiotherapy on neurocognitive function (NCF) in patients with newly diagnosed GBM without MGMT promoter methylation

1.3 Exploratory Objectives

1.3.1 To explore biomarkers in pre-treatment archival tumor tissue that may predict efficacy of ipilimumab and nivolumab as measured by OS, PFS, and 2-year OS rate, such as but not limited to

- PDL1 expression
- Mutational burden

1.3.2 To explore (in the two treatment separately) whether the MGMT protein expression correlates with clinical outcomes including OS, PFS, and 2-year OS rate

1.3.3 To evaluate if MGMT protein expression may be predictive of differential treatment effects between the two treatment arms

2. BACKGROUND

GBM remains the most common and aggressive primary brain cancer in adults and is almost

universally fatal. Median survival is approximately 18 months despite multimodality therapy. Temozolomide was demonstrated to prolong survival when added to radiotherapy concurrently and sequentially in 2005. (Stupp, Mason et al. 2005) Since then, most clinical trials for newly diagnosed GBM have incorporated maximal safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide as the standard of care, and experimental agents have been added on to this backbone including recent prior NRG Oncology/RTOG Foundation trials such as RTOG 0525 and 0825, as well as NRG-BN002 and AbbVie M13-913/RTOGF 3508. Immunotherapy with checkpoint inhibitors (ipilimumab targeting CTLA-4, nivolumab targeting PD-1) have revolutionized the treatment of other human cancers, particularly lung and melanoma. However, their efficacy in gliomas is unclear. Ongoing industry-sponsored trials by BMS (NCT02667587, CheckMate-548; NCT02617589, CheckMate-498) are testing the efficacy of nivolumab in newly diagnosed GBM when added to the post-operative radiation setting with or without temozolomide. However, no current ongoing trials are testing the combined effects of ipilimumab and nivolumab in newly diagnosed GBM to our knowledge. Although the combination has been more toxic than either ipilimumab or nivolumab alone in many cancers, extrapolation from other tumor types, particularly melanoma, suggests that combined therapy is also more efficacious than either alone, particularly in those with very low PD-L1 expression in pre-treatment tumor tissue (Wolchok, Chiarion-Sileni et al. 2017) such as most GBMs. In addition, during the last 5 years, medical oncologists and neuro-oncologists have now participated in trials of ipilimumab, nivolumab, and other in-class agents (e.g., pembrolizumab), including NTCN trials such as NRG-BN002 (phase I trial of RT with temozolomide followed by either nivolumab, ipilimumab, or both), gaining comfort with identification and management of associated toxicities. NRG-BN002 in particular, demonstrated no increased toxicity from combined treatment with ipilimumab and nivolumab compared to either drug alone [Sloan AE, Gilbert M et al, 2018 ASCO abstract]. Finally, enthusiasm for immunotherapy approaches remains high among patients seeking trials. Therefore, NRG Oncology, with a long history of rapid accrual to studies for newly diagnosed GBM, will embark on the current study.

While patients on NRG-BN002 received nivolumab and/or ipilimumab only in the adjuvant (post-radiation) setting, other trials in the interim have combined these agents with radiotherapy and/or temozolomide (e.g., NCT02667587, CheckMate-548; NCT02617589, CheckMate-498). In addition, comfort with toxicity management among treatment physicians has improved since accrual to NRG-BN002 began in 2015. Finally, both preclinical and clinical data suggest synergy from auto-vaccination and antigen exposure when radiation is combined with checkpoint blockade.(Vatner, Cooper et al. 2014)

We will mirror the design of NCT02617589 (CheckMate-498: newly diagnosed MGMT unmethylated GBM, randomized to radiation plus temozolomide versus radiation plus nivolumab, open-label) and multiple other studies ongoing or planned for newly diagnosed GBM that omit temozolomide from the experimental arm for patients with GBMs without MGMT promoter methylation. We will omit temozolomide and study the MGMT unmethylated population not because of some proposed benefit restricted to that population; rather, the potential benefit of temozolomide (if any) is limited without MGMT promoter methylation, (Hegi, Diserens et al. 2005), omitting temozolomide will ameliorate its potential immunosuppressive effects (particularly lymphopenia) that could reduce immunotherapy efficacy, and both elements will simplify the study design. Therefore, patients in the

experimental arm will not receive temozolomide in the current trial design. Finally, survival in patients with MGMT unmethylated tumors is unfortunately shorter than those with methylated tumors; therefore, the required time for follow-up, trial completion, and result reporting will be shorter than for a trial that either focuses on the MGMT methylated population or allows MGMT methylated status for eligibility. It is also important to note that in CheckMate-498, omitting temozolomide in the experimental arm and omitting a placebo in the standard arm were not barriers to accrual, and the trial completed accrual rapidly and without difficulty. Should this trial prove positive, then a future study could consider including temozolomide and/or study in patients with MGMT methylated disease.

With regard to ongoing trials, one study of nivolumab in *recurrent* GBM sponsored by BMS (CheckMate-143) failed to show improvement over bevacizumab, both when used as single agents. However, large doses of corticosteroids at the initiation of treatment was not exclusionary. Recent data clearly demonstrate that corticosteroids reduce immune responses to vaccine therapies and prevent maturation and activation of naïve T cells in response to immune checkpoint inhibitor (Giles, Hutchinson et al. 2018, Kes. kin, Anandappa et al. 2019). Therefore, with over 40% of the patients on Checkmate-143 on corticosteroids at initiation of treatment, an efficacy signal for immunotherapy may have been lost. Furthermore, patients with rapidly progressing and bulky tumors were also eligible. This potentially confounded the study as GBM are among the most immunosuppressive tumors known, due to secretion of TGF-B, INO, PGE2, IL-4, IL-10, potentiation of Tregs and sequestration of lymphocytes to bone marrow. In addition to the immunosuppressive effects of tumors, such bulky tumors also likely required steroids making weaning difficult if not impossible. As such sufficient time on drug may not have elapsed for therapeutic effect. Furthermore, the only 2 interventions that received FDA approval after trials demonstrated survival prolongation for newly diagnosed GBM in the last 50 years, temozolomide (Stupp, Mason et al. 2005) and NovoTTF (Optune) (Stupp, Taillibert et al. 2015), both failed to prolong median survival for recurrent GBM (Yung, Albright et al. 2000, Stupp, Wong et al. 2012). The ongoing CheckMate studies for newly diagnosed GBM used nivolumab alone rather than combinations of nivolumab and ipilimumab.

With regard to other available therapies for newly diagnosed GBM, Gliadel will not be allowed, consistent with precedence for other ongoing studies. Gliadel wafers have long been FDA- approved but are exclusionary for nearly all newly diagnosed studies, and its use will be exclusionary in the current trial.

Finally, as described above, corticosteroids can abrogate efficacy of immune checkpoint inhibitors. Therefore, we will require for eligibility only patients on no corticosteroids. This criterion will also serve as a surrogate for disallowing patients with large unresected tumors with surrounding edema without requiring a threshold of post-operative residual tumor volume that would be both arbitrary and difficult to enforce. Extent of resection is captured as part of the recursive portioning analysis (RPA), which will serve as a stratification factor. It remains theoretically possible that imbalance in extent of resection may result because the RPA also accounts for other prognostic factors; however, this approach is compromise that will permit the simplest study design.

Of note, although pseudoprogression from radiation therapy and temozolomide may be exacerbated by immunotherapy, (Okada, Weller et al. 2015, Ranjan, Quezado et al. 2018) we do not believe the existing data from the ongoing NRG phase I trial (NRG-BN002), or other

trials, is sufficiently compelling to support a phase III trial with OS as an endpoint (even with early futility analyses) in the absence of phase II data. Therefore, we will perform a traditional phase II/III study: with PFS as the primary endpoint in phase II and OS in phase III, but will also incorporate an evaluation of OS use if the PFS signal is ambiguous as detailed below. Accruals to phase II will count toward phase III goals. We recognize the use of PFS is an imperfect metric of efficacy for phase II, and the risk of declaring the phase II falsely negative because of pseudoprogression is of concern. However, in RTOG 0525 as well as other trials for newly diagnosed GBM (other than antiangiogenic therapies that can falsely prolong PFS through pseudoresponse), PFS ultimately correlated with OS despite the potential confounding effects of pseudoprogression and the absence of central radiology review. Therefore, we believe this approach, while imperfect, is the best way to balance the leveraging of existing data without exposing a large number of patients to a potentially toxic therapy in phase II without supportive phase II data, taking into account OS as below.

Finally, ipilimumab and nivolumab can induce substantial systemic toxicity as well as encephalopathy. While in many cases based on Common Terminology Criteria for Adverse Events (CTCAE) the adverse events reportedly resolve, dedicated symptom and neurocognitive function (NCF) measures with demonstrated clinical significance have not carefully followed and characterized these side effects. Therefore, we will collect patient reported outcome (PRO) symptom and NCF test data to evaluate the effects of ipilimumab plus nivolumab compared to temozolomide added to radiation therapy to determine the clinical benefit of improved PFS and OS.

There are no competing studies to our knowledge of combined temozolomide, radiation therapy, CTLA-4 inhibition, and PD-1 inhibition in newly diagnosed GBM. Whether the ongoing BMS-sponsored trials of nivolumab (without ipilimumab) are positive or negative, this trial continues to have justification as it uses the dual drug approach which demonstrated superiority to nivolumab alone in some patients with other cancers, such as melanoma. (Wolchok, Chiarion-Sileni et al. 2017). The combination at the doses proposed herein was also reasonably well tolerated as demonstrated in NRG-BN002.(Sloan, Gilbert et al. 2018). ,As in ALLIANCE A071102, we will allow Optune, stratifying by intent to use, to ameliorate concerns about impediments to accrual that could result from drop-out, particularly on the control arm, by disallowing Optune.

Multiple ongoing trials, including NRG-BN002 (Sloan, Gilbert et al. 2018) demonstrated the toxicity profile of immunotherapy agents in GBM is qualitatively similar to that in other tumor types. As reported at ASCO 2018, NRG-BN002 was a phase I study of ipilimumab (3mg/kg), nivolumab (3mg/kg), and the combination (1mg/kg and 3mg/kg, respectively) followed by an expansion cohort for the combined treatment of adults with confirmed unifocal, supratentorial newly diagnosed GBM after gross or near total resection. Treatment with immune-checkpoint inhibitors (ICIs) started after standard chemo-radiotherapy (radiation and temozolomide) along with adjuvant temozolomide; starting dosing of ICIs were at target with dose reduction planned for toxicity. The primary endpoint was the dose limiting toxicity (DLT) from start of ICIs to 8 weeks after for each arm. A standard up-and-down design was used, with 6 evaluable patients enrolled at a given dose level. 32 patients were enrolled at 9 institutions, 6 accrued to each arm and 14 to the expansion cohort. One patient was not treated, yielding 31 analyzable. Median age was 54 years (range: 23-74), 68% were men and 84% were white. Overall, treatment was well tolerated with a 16% rate

of Grade 4 events; the combination did not have an increased toxicity rate over the single agent arms, and there was no reported Grade 5 event. One DLT was seen in each single-agent arm; none was noted in the combination arm. Median follow-up time was 7.1 months (range: 0.5-21.3) for all analyzable patients, at which time 10 of the 31 had progressed (32%) and 8 had died (26%), 7 of which were attributed to disease progression. Median PFS was 16.3 months (95% CI: 8.3-not reached) with a 1-year PFS rate of 53.2% (95% CI: 29.7-76.6%). Median survival was 20.6 months (95% CI: 13.4-23.6). These toxicity and survival results are encouraging, follow-up is ongoing, and the current trial herein is an extension of NRG-BN002 to test efficacy definitively.

As mentioned above, there are two ongoing BMS-sponsored trials for newly diagnosed GBM. However, accrual is complete to both, and both use nivolumab alone as the immunotherapy, and neither incorporate ipilimumab. In more detail, CheckMate-498 is for patients with MGMT unmethylated GBM, comparing nivolumab versus temozolomide (each with radiation therapy); CheckMate-548 is for MGMT methylated cases, comparing nivolumab versus placebo (each with radiation therapy and temozolomide).

Our design extends that of both trials which had no restriction on tumor size or extent of resection, and specifically extends that of CheckMate-498 which also omitted temozolomide in MGMT-unmethylated cases, did not incorporate a placebo, and completed accrual rapidly.

The design of CheckMate-498 further supports our design by omitting temozolomide in MGMT unmethylated cases. Of note, CheckMate-498 accrued rapidly, with approximately 550 patients enrolled over approximately 12 months, despite the lack of placebo control and omission of temozolomide (https://clinicaltrials.gov/ct2/show/NCT02617589).

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Statistics and Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

3.1 Eligibility Criteria (08-APR-2022)
A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to Step 1 Registration

3.1.1 No known IDH mutation. (If tested before step 1 registration, patients known to have IDH mutation in the tumor on local or other testing are ineligible and should not be registered).

3.1.2 Availability of FFPE tumor tissue block and H&E stained slide to be sent for central pathology review for confirmation of histology and MGMT promoter methylation status (See Sections 3.1.1, 3.1.2, and 10). Note that tissue for central pathology review and central MGMT assessment must be received by the NYU Center for Biospecimen Research and Development (CBRD) on or before postoperative calendar day 23. If tissue cannot be received by postoperative calendar day 23, then patients may NOT enroll on this trial as central pathology review will not be complete in time for the patient to start treatment no later than 6 weeks following surgery. Results of central pathology review and central MGMT analysis will generally be conveyed to NRG Oncology within 10 business days of receipt of tissue. Note: In the event of an additional tumor resection(s), tissue must be received within 23 days of the most recent resection and the latest resection must have been performed within 30 days after the initial resection. Surgical resection (partial or complete) is required; a limited biopsy is not allowed because it will not provide sufficient tissue for MGMT analysis.

- Note: The central pathology review and central MGMT results determine eligibility. Therefore, patients may be offered the opportunity to consent REGARDLESS of local pathology and MGMT results, and consent can occur BEFORE local pathology interpretation is finalized and BEFORE local MGMT testing is conducted.

3.1.3 Contrast-enhanced brain MRI within 3 days after surgery.

- MRI with Axial T2 weighted FLAIR{preferred} or T2 TSE/FSE and 3D contrast-enhanced T1 sequences are required.
- 3D pre contrast-enhanced T1 sequences are strongly suggested.

3.1.4 Women of childbearing potential (WOCBP) and men who are sexually active with WOCBP must be willing to use an adequate method of contraception hormonal or barrier method of birth control; or abstinence during and after treatment (see Section 9.0).

3.1.5 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

Prior to Step 2 Registration

3.1.6 Histopathologically proven diagnosis of glioblastoma (or gliosarcoma as a subtype of glioblastoma) confirmed by central pathology review (See Section 10 for details);
Note: diagnoses of "Molecular glioblastoma" per the c-IMPACT-NOW criteria or "CNS grade 4" per the WHO 2021 criteria are NOT relevant;

3.1.7 MGMT promoter without methylation confirmed by central pathology review (See Section 10 for details). Note: Patients with tissue that is insufficient or inadequate for analysis, fails MGMT testing, or has indeterminate or methylated MGMT promoter are excluded.

- Note: *central* pathology review and *central* MGMT results determine eligibility; local pathology or MGMT results cannot be used for eligibility/randomization.
- Note: Patients with methylated MGMT may be considered for enrollment on NRG-BN011. Please see Section 10 for additional information.

3.1.8 IDH mutation testing by at least one method (such as immunohistochemistry for IDH1 R132H) must be performed as part of standard of care and no mutation must be found (i.e IDH wildtype). (If a mutation is identified then the patient will be ineligible and must be registered as ineligible at Step 2.)

- Note: This test is not being performed in real time as part of central review and will not be provided to sites from a centrally performed test.

3.1.9 History/physical examination within 28 days prior to Step 2 registration;

3.1.10 Karnofsky Performance Status (KPS) ≥ 70 within 28 days prior to Step 2 registration;

3.1.11 Neurologic Function assessment within 28 days prior to Step 2 registration;

3.1.12 Age ≥ 18 years;

3.1.13 Adequate hematologic, renal, and hepatic function within 7 days prior to Step 2 registration defined as follows:

– hemoglobin	≥10 g/dl (Note: the use of transfusion or other intervention to achieve Hgb ≥10.0 g/dl is acceptable)
– leukocytes	≥2,000/mm^3
– absolute neutrophil count	≥1,500/mm^3
– platelets	≥100,000/mm^3
– total bilirubin	≤1.5× institutional/lab upper limit of normal (ULN)
– AST(SGOT)	≤2.5 × ULN
– ALT(SGPT)	≤2.5 × ULN
– serum creatinine	≤1.5× ULN
OR	
– creatinine clearance (CrCl) below):	≥50 mL/min (if using the Cockcroft-Gault formula

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg / dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

3.1.14 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.15 For women of childbearing potential (WOCBP), negative serum or urine pregnancy test within 7 days prior to Step 2 registration. Note that it may need to be repeated if not also within 3 days prior to treatment start (see section 4)

- 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) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

3.2 Ineligibility Criteria (08-APR-2022)

Patients with any of the following conditions are NOT eligible for this study.

3.2.1 Prior therapy for tumor except for resection. For example, prior chemotherapy, immunotherapy, or targeted therapy for GBM or lower grade glioma is disallowed (including but not limited to temozolomide, lomustine, bevacizumab, any viral therapy, ipilimumab or other CTLA-4 antibody, PD-1 antibody, CD-137 agonist, CD40 antibody, PDL-1 or 2 antibody, vaccine therapy, polio or similar viral injection as treatment for the tumor, and/or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) as is prior Laser interstitial thermal therapy (LITT), Gliadel wafer, radiotherapy, radiosurgery, gamma knife, cyber knife, vaccine or other immunotherapy, brachytherapy, or convection enhanced delivery;

- Note that 5-aminolevulinic acid (ALA)-mediated fluorescent guided resection (FGR) photodynamic therapy (PDT) or fluorescein administered prior to/during surgery to aid resection is not exclusionary and is not considered a chemotherapy or intracerebral agent

3.2.2 Current or planned treatment with any other investigational agents for the study cancer

3.2.3 Definitive clinical or radiologic evidence of metastatic disease outside the brain

3.2.4 Prior invasive malignancy (except non-melanomatous skin cancer, cervical cancer in situ and melanoma in situ) unless disease free for a minimum of 2 years

3.2.5 Prior radiotherapy to the head or neck that would result in overlap of radiation therapy fields

3.2.6 Pregnancy and nursing females due to the potential teratogenic effects and potential risk for adverse events in nursing infants.

3.2.7 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ipilimumab, nivolumab, or temozolomide

3.2.9 On any dose of any systemically administered (oral, rectal, intravenous) corticosteroid within 3 days prior to Step 2 registration (see also section 4). Inhaled, topical, and ocular corticosteroids are allowed without limitation but must be recorded. Note that treatment with systemically administered corticosteroid after initiating study treatment is allowed as needed.

3.2.10 Patients with known immune impairment who may be unable to respond to anti-CTLA 4 antibody.

3.2.11 History of interstitial lung disease including but not limited to sarcoidosis or pneumonitis.

3.2.12 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, defined as New York Heart Association Functional Classification III/IV (Note: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.13 Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

3.2.14 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, are excluded, as are patients on active immunosuppressive therapy. These include but are not limited to: patients with a history of immune-related neurologic disease, CNS or motor neuropathy, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as autoimmune vasculitis [*e.g.*, Wegener's Granulomatosis]), systemic lupus erythematosus (SLE), connective tissue diseases (*e.g.*, systemic progressive sclerosis), scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome, Hashimoto's thyroiditis, autoimmune hepatitis are excluded because of the risk of recurrence or exacerbation of disease.

- Exceptions: patients with a history of the following conditions are not excluded, unless receiving active immunosuppressive therapy:
  - vitiligo
  - Type I diabetes
  - rheumatoid arthritis and other arthropathies
  - Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA)
    - anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

3.2.15 Patients who have evidence of active or acute diverticulitis, intra-abdominal abscess, GI obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation are also excluded

3.2.16 Current or planned therapy with warfarin

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

(08-APR-2022)

PRE-TREATMENT ASSESSMENTS

Assessments	Prior to Step 1 Registration	Prior to Step 2 Registration (calendar days)	Prior to Treatment (calendar days)
Hepatitis B virus surface antigen (HBV sAg) and Hepatitis C (HCV RNA) (if applicable)		≤28 days	
IDH testing performed as part of routine care	If positive, patient will not be eligible	If positive, patient will not be eligible	
Submission of tissue for central pathology review and central MGMT analysis*		As soon as possible after surgery. .	
Contrast-enhanced Brain MRI	Within 3 days after surgery		
History/physical examination (to include height/weight and cardiac disease risk assessment and additional cardiac evaluation including lab tests and cardiology consultations as clinically indicated including EKG, CPK, troponin, ECHO cardiogram)		≤28 days	
Karnofsky performance status and neurologic function		≤28 days	
Steroid dose documentation		≤3 days	≤3 days
CMP (inc AST/ALT and serum creatinine or creatinine clearance)		≤7 days	
TSH (with reflex to T4)			≤28 days (Arm 2 only)
CBC with differential (inc ANC, platelets, Hgb, leukocytes)		≤7 days	
Serum or urine pregnancy test (women of childbearing potential; See Section 3.1 for definition)		≤7 days	≤3 days (only required if the test performed prior to step 2 registration is not also within 3 days prior to treatment start)
Patient-reported outcomes: • MDASI-BT • PRO-CTCAE			≤28 days
Neurocognitive function: • HVLT-R • TMT • COWA			≤28 days
Serum, plasma, and whole blood for banking (for patients who consent to biobanking for future research; see Section 10 for details)			Prior to radiation

*Tissue must be received by postoperative calendar day 23 or the case will be ineligible. Local MGMT results are not required to be available prior to consent, enrollment, or tissue submission. Eligibility is based solely on central review.

ASSESSMENTS DURING TREATMENT

Assessments	**Time Point**			
	Concurrent Treatment	**4 weeks post RT completion** (-3 days)	**Arm 1 Adjuvant Phase (28 day cycles)** Day 28 (+/-3 days, unless otherwise specified) of each cycle, prior to starting the next cycle	**Arm 2 Adjuvant Phase (28 day cycles)** Day 28 (+/-3 days, unless otherwise specified) of each cycle, prior to starting the next cycle
Contrast-enhanced Brain MRI*		X	≤14 days prior to odd numbered cycles (starting with cycle 3)	≤14 days prior to odd numbered cycles (starting with cycle 3)
CMP (to include AST/ALT/Total Bilirubin)	Weekly	X	X	X And on Day 15 (+/- 3 days) prior to Nivo dose
TSH with reflex to T4 (Arm 2 only)	≤ 3 days prior to each dose of Ipilimumab	X		≤14 days prior to every other Nivo dose
CBC with differential, ANC, platelets, Hgb, leukocytes	Weekly	X	X And on Day 21 (±2days)	X
History/physical examination		X	X	X
Karnofsky performance status and neurologic function		X	X	X
Adverse event evaluation	Weekly	X	X	X
Steroid dose documentation	Weekly	X	X	At the time of each Nivo dose
Patient-reported outcomes:** • MDASI-BT • PRO-CTCAE			≤14 days prior to cycles 1, 3, and 5	≤14 days prior to cycles 1, 3, and 5
Neurocognitive function:** • HVLT-R • TMT • COWA			≤14 days prior to cycles 1, 3, and 5	≤14 days prior to cycles 1, 3, and 5

Serum and plasma for banking (for patients who consent to biobanking for future research; see Section 10 for details)			≤14 days prior to cycles 1 and 3	≤14 days prior to cycles 1 and 3
Documentation of Optune usage: Arm 1 only			X	

*Note that in a limited number of patients receiving immune checkpoint inhibitor therapy, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. All brain MRI scans must also note the presence or absence of incidental enlargement of the pituitary gland, and if observed must prompt further clinical and/or laboratory endocrine evaluation as required per local investigator discretion.

**Patient-reported outcomes and neurocognitive function assessments should be performed as close to the day of the contrast-enhanced MRI as possible and before the patient receives the results of the MRI. Assessments must be completed regardless of progression or discontinuation of treatment. (If the patient discontinues treatment prior to cycle 1, 3 or 5, the assessment is still required to be completed at the time that cycle would have occurred. Refer to the due date in RAVE).

ASSESSMENTS IN FOLLOW-UP

Assessments	**Time Point** **Note:** Assessments completed post progression, with the exception of Patient Reported Outcomes, Neurocognitive Function, and Adverse Event Evaluation will be left to the discretion of the treating physician. All patients are followed for survival status.		
From end of treatment	**Q 3 months for 1 Year** **3, 6, 9, 12 months** (+/-14 days)	**Q4 months for Year 2** **16, 20, 24 months** (+/-14 days)	**Q6 months until death** **30, 36, 42, months etc** (+/-28 days)
Contrast-enhanced Brain MRI	X	X	X
History and Physical examination	X	X	X
Karnofsky performance status and neurologic function	X	X	X
Adverse event evaluation	X	X	X
Patient-reported outcomes:* • MDASI-BT • PRO-CTCAE	X at 12 month only	X at 24 month only	
Neurocognitive function:* • HVLT-R • TMT • COWA	X at 12 month only	X at 24 month only	
Documentation of Optune usage (Arm 1 only) Required until or unless initiation of other non-protocol disease modifying therapy	X	X	X
Steroid dose documentation	X	X	X

* Patient-reported outcomes and neurocognitive function assessments should be performed as close to the day of the contrast-enhanced MRI as possible and before the patient receives the results of the MRI. If an MRI was not completed, these assessments are still required. Refer to the due dates in RAVE.

Definition of Disease Assessments

Response and progression will be evaluated in this study using an adaptation of the Response Assessment in Neuro-Oncology criteria (Wen et al, J Clin Oncol. 2010 Apr 10;28(11):1963-72. doi: 10.1200/JCO.2009.26.3541. Epub 2010 Mar 15) with modification such that the first MRI performed following completion of radiotherapy is the baseline MRI for determination of radiographic disease.

If PD is confirmed, as stated below, then treatment must be discontinued.

Note that this trial is not collecting response or best response; rather treatment is planned to continue until either 6-12 adjuvant (post-RT) cycles of temozolomide (arm 1) or indefinitely until Progressive Disease (arm 2). Therefore, the only response designation of relevance is Progressive Disease or NOT Progressive Disease (Not-PD).

Response will be assessed by the treating investigator. If there is ambiguity regarding whether the patient has suffered PD, then treatment can continue with reassessment (imaging, clinical) after no more than 2 additional cycles. If PD is confirmed at that time, then the date of PD in the CRF should be changed to the first and earlier time point at which PD was suspected. **If PD is ambiguous, patients should continue protocol therapy**.

PD less than 12 weeks after radiotherapy completion is defined as any of the following:
1. New enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) on diagnostic imaging.
2. Unequivocal evidence of viable tumor on histopathologic sampling (eg, solid tumor areas [i.e., > 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 treatment.

PD greater than or equal to 12 weeks after radiotherapy completion is defined as any of the following:
1. New contrast-enhancing lesion outside of radiation field.
2. Increase by at least 25% in the sum of the products of perpendicular diameters of contrast enhancing disease between the first **post-radiotherapy** scan (**not a pre-radiotherapy** scan), or a subsequent scan with smaller tumor size, and a scan at 12 weeks or later following completion of radiotherapy on stable or increasing doses of corticosteroids.
3. Clinical deterioration not attributable to concurrent medication or comorbid conditions
4. In addition, patients will be declared as having suffered PD (clinically) if they fail to return for evaluation as a result of deteriorating condition.

5. TREATMENT PLAN/REGIMEN DESCRIPTION (09-FEB-2021)

Treatment Overview (Please refer to Section 5.1 and 5.2 for complete information)
Protocol treatment must begin within 6 weeks following surgery.

ARM 1: Participants randomized to Arm 1 will receive radiation therapy (60 Gy/2 Gy fractions) plus concomitant temozolomide (75 mg/m^2/d X 42 days during RT), followed by adjuvant temozolomide150-200 mg/m^2/d on days 1-5 of a 28 day cycle X 6-12 cycles). **If PD is ambiguous, patients should continue protocol therapy**.

ARM 2: Participants randomized to Arm 2 will receive radiation therapy (60 Gy/2 Gy fractions) plus concomitant ipilimumab and nivolumab, followed by adjuvant ipilimumab and nivolumab (ipilimumab 1 mg/kg q 4 weeks X 4 doses; nivolumab 3 mg/kg q 2 weeks until

progressive disease). **If PD is ambiguous, patients should continue protocol therapy**.

Protocol Treatment	Arm 1	Arm 2	Dose
Radiation	**X**	**X**	60 Gy/2 Gy fractions
Temozolomide	**X**		Concomitant: 75 mg/m^2/d X 42 days Adjuvant: 150-200 mg/m^2/d after RT for 6 cycles; up to 12 cycles allowed at the discretion of the treating investigator
Ipilimumab		**X**	1 mg/kg q 4 weeks X4 doses
Nivolumab		**X**	3 mg/kg* q 2 weeks until progressive disease

*After a course of ipilimumab is discontinued or completed, if nivolumab is to be continued as monotherapy, dosing can continue at 3mg/kg weight-based, or change to 240 mg flat dose at the discretion of the treating investigator, every 2 weeks +/- 3 days.

Treatments above continue until/unless one of the criteria in section 5.4 are met (disease progression, intolerable toxicity, withdrawal of consent, etc.)

5.1 Systemic Therapy (08-APR-2022)

Protocol treatment must begin within 6 weeks following surgery.

5.1.1 Arm 1: Temozolomide (standard of care arm)

Temozolomide is to be administered continuously from day 1 of radiation therapy to the last day of radiation (including weekends and holidays) at a daily oral dose of 75 mg/m^2, typically for 42 days but allowing up to a maximum of 49 days in the event of delays or interruptions in radiotherapy. Following completion of radiotherapy, approximately 4 weeks (+/- 3 days) later, "adjuvant" cycles will begin and are defined as 28 days. Patients will receive 6 (to 12) cycles of adjuvant temozolomide at a dose of 150-200 mg/m^2 on days 1-5 of a 28 day cycle. Treatment with 6 adjuvant cycles of temozolomide is required (absent a protocol-specified reason to discontinue early), and up to 12 cycles is permitted at the discretion of the treating investigator if consistent with local practice. More than 12 cycles of adjuvant temozolomide is not allowed.

The dose will be determined using the BSA calculated prior to concurrent treatment. The BSA will be re-calculated prior to every other adjuvant treatment cycle and if a change in more than 10% in weight has occurred, the dose of temozolomide must be adjusted according to the new BSA. The daily dose will be rounded to the nearest 5 mg. More frequent or more stringent dose adjustments for changes in weight are allowed but not required. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. Note: do not open, crush, or chew capsules; capsules must be swallowed whole.

Optune use in the adjuvant phase of treatment is permitted per standard prescribing language and can be started after completion of concurrent treatment. Usage must be documented prior to odd numbered cycles. Optune use is not permitted during concurrent treatment.

5.1.2 Arm 2: Ipilimumab and Nivolumab (investigational treatment arm)

Patients will not receive temozolomide during study treatment.

Optune use is not permitted.

When infusions of ipilimumab and nivolumab are given on the same day, nivolumab is to be administered first, separate infusion bags and filters must be used for each infusion.

Ipilimumab

Starting concurrently with radiotherapy (Day 1), patients will receive ipilimumab 1mg/kg intravenously over 90 minutes every 4 weeks x 4 doses (3 doses during concurrent treatment, and 1 dose during cycle 1 of adjuvant phase Weight will be re-calculated prior to every dose of ipilimumab; if a change in more than 10% in weight has occurred, the dose of must be adjusted according to the new weight. More stringent dose adjustments for changes in weight (such as for changes by less than 10% or with every dose rather than every other dose) are allowed but not required. **Note**: Infusion days are allowed +/- 3 days, except for concurrent day 1, which must occur on the same day as the start of RT.

Nivolumab

Starting concurrently with radiotherapy (Day 1), patients will receive nivolumab 3mg/kg intravenously over 30 minutes every 2 weeks (5 doses during concurrent treatment and then 2 doses during each cycle of adjuvant phase) until either disease progression or another reason to discontinue protocol therapy outlined in section 5.4. Weight will be recalculated prior to every other dose of nivolumab; if a change in more than 10% in weight has occurred, the dose of must be adjusted according to the new weight. To reduce patient burden associated with waiting for re-calculation in situations when weight is unlikely to change by more than 10%, any documented weight collected no more than 2 weeks before the ipilimumab dose may be used, including weight collected at home and collected by phone by the investigator or designee and then documented in the source. Conversely, more frequent or more stringent dose adjustments for changes in weight are allowed but not required.

The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. Follow the same infusion timing detailed above..

Although treatment is intended to be continuous, to align with the schedule of events on the control (temozolomide) arm, a cycle is defined as 28 days, and cycle 1 begins with the first dose of nivolumab administered after radiotherapy to align with sixth nivolumab dose, which is approximately 4 weeks after RT completion (week 11).

Therefore, during 6 weeks of radiotherapy, patients will receive

- Day 1: nivolumab and ipilimumab #1

- Day 15: nivolumab
- Day 29: nivolumab and ipilimumab #2
  After RT ends,
- Day 43 (typically day following completion of radiotherapy): nivolumab
- Day 57 (approximately 2 weeks following completion of radiotherapy): nivolumab and ipilimumab #3
  Adjuvant Phase starts here
- Day 71 (approximately 4 weeks following completion of radiotherapy): nivolumab
- Day 85 (approximately 6 weeks following completion of radiotherapy): nivolumab and ipilimumab #4
- Day 99 (approximately 8 weeks following completion of radiotherapy) and every 14 days thereafter: nivolumab

Notes: All infusion days are allowed +/- 3 days
After a course of ipilimumab is discontinued or completed, if nivolumab is to be continued as monotherapy, dosing can continue at 3mg/kg weight-based, or change to 240 mg flat dose at the discretion of the treating investigator, every 2 weeks +/- 3 days.
Any treatment administered prior to the start of the Adjuvant Phase (Day 71/Week 11) will be considered as concurrent treatment phase.

Treatment Schedule								
	Concurrent Phase of Treatment					Adjuvant Phase		
	Week 1 (Day 1)	Week 3 (Day 15)	Week 5 (Day 29)	Week 7 (Day 43)	Week 9 (Day 57)	Week 11 (Day 71)	Week 13 (Day 85)	Week 15 (Day 99) then every 2 weeks
RT	X							
Ipi	X		X		X		X	
Nivo	X	X	X	X	X	X	X	X

See Section 6 and Appendix II for toxicity management.

5.2 Radiation Therapy (09-FEB-2021)

Concurrent phase of treatment must begin within 6 weeks after resection.

See Section 8.2 for information on installing TRIAD for submission of digital RT data.

Radiation Therapy Schema
60 Gy will be given in 30 fractions over 6 weeks (5 days per week). However, for purposes of nomenclature, the "concurrent phase of treatment" continues until the beginning of week 11 (day 71) as in the table above (Section 5.1.2).

5.2.1 Treatment Technology

This protocol requires photon treatment. 3D-CRT, fixed gantry-IMRT, helical tomotherapy, and volumetric modulated arc therapy (VMAT) are allowed, subject to protocol localization and dosimetry constraints. Although very limited in availability, if a center chooses to, and has a credentialed MR-Linac, photon therapy delivery using this technology is permissible as long as the dosimetric guidelines are met. Proton therapy is not permissible on this protocol, because of an ongoing protocol specifically addressing its role (NRG-BN001).

Treatment shall be delivered with megavoltage (MV) machines of a minimum energy of 6 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Electron, particle, or implant boost is not permissible. IMRT delivery will require megavoltage radiation therapy machines of energy ≥ 6 MV.

Treatment is performed using a **sequential boost** to the contrast-enhancing region of the target. Patient-specific quality assurance is highly recommended prior to start of treatment and is described in Section 5.2.10.

5.2.2 Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices. A 3-point or 5-point thermoplastic mask, with a headrest, is strongly recommended, but other options (for example BOS frame, etc.) are also allowed. Patients will be treated in a supine position. Additional immobilization devices such as a bite block and/or knee-wedge are permitted. Not using an immobilization device is NOT permitted.

5.2.3 Simulation Imaging

A planning CT scan of the cranial contents with 3.0 mm slice thickness or less will be required. Intravenous contrast is recommended as per institutional guidelines, but not mandated. For photon planning, the institution must have an established relationship between CT number and electron density. The planning CT will be fused with the pre- and post-operative MRI scans. Rigid registration is permitted, but deformable fusion is not permitted, given the multitude of different deformational algorithms, several of which have not been centrally validated. Image fusion must be performed by a qualified medical physicist or by a dosimetrist under the supervision of a qualified medical physicist, and reviewed by the attending physician. We strongly recommend that the following MR sequences be fused with the planning CT:

1. Preoperative T1 + contrast axial series
2. Preoperative F T2 weighted LAIR (or equivalent), or alternatively T2 axial series.
3. Postoperative T1 + contrast axial series (must be obtained within ≤3 days of surgery).
4. Postoperative T2 weighted FLAIR (or equivalent), or alternatively T2 axial series.

The postoperative MRI scan must be obtained ≤3 days after surgical resection. If >3 week have

elapsed between surgical resection and radiotherapy planning, a repeat postoperative MRI with T2 weighted/FLAIR and contrast enhanced T1 sequences is highly recommended for radiotherapy planning purposes. **Target volume delineation will be based upon the postoperative contrast-enhanced and T2 weighted FLAIR (preferred over conventional T2) MRI**, although the preoperative image should also be evaluated, commensurate with standard practice. Preoperative MRI is therefore encouraged to be used as an assistive tool for contouring.

5.2.4 Definition of Target Volumes and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	Description	Validation **Required/Required when applicable/Optional**
GTV_4600	GTV to receive 46 Gy	**Required**
CTV_4600	CTV to receive 46 Gy	**Required**
PTV_4600	PTV to receive 46 Gy	**Required**
GTV_6000	GTV to receive 60 Gy	**Required**
CTV_6000	CTV to receive 60 Gy	**Required**
PTV_6000	PTV to receive 60 Gy	**Required**

Detailed Specifications

GTV_4600: Either the T2 weighted FLAIR (or the conventional T2) on the post-operative MRI scan, inclusive of all contrast-enhancing T1 abnormality on the post-operative MRI and the surgical cavity. Areas of vascular infarction or compromise of normal brain should be excluded if they are deemed to not be part of the original pre-operative T2 weighted FLAIR or conventional T2 abnormality, and a comparison of the pre- and post-operative scans will assist in this process. As a guide, we recommend the following sequential and step-wise process:

a. Contour the GTV_4600 using the T2 weighted FLAIR (or conventional T2) abnormality on the post-op MRI scan, and include the surgical cavity on the T1 post contrast scan.
b. Contour the GTV_4600 T2 weighted FLAIR (or conventional T2) abnormality on the preop scan and include the T1 enhancing tumor.
    i. Do not switch between T2 weighted FLAIR and conventional T2 for the pre and post op scans. Use only the T2 weighted FLAIR or only the conventional T2 on both sequences.
c. Compare the GTV_4600 on the postop scan vs. the preop scan.

i. In general, the volume of GTV_4600 on the preop scan should be larger than on the postop scan, and none of the postop volume should expand outside the preop volume.
ii. If the postop GTV_4600 expands outside the preop GTV_4600, review with neurosurgery/diagnostic radiology to exclude any possible areas of infarction, vascular compromise, etc., especially if the post-op scan is ≤3 days after surgery.
iii. In some instances, the postop GTV_4600 will be larger than the preop volume because of disease progression, especially if several weeks have elapsed between the 2 scans; in this case, once you have confirmed that the volumetric discrepancy is not because of a vascular event, use the larger postop GTV_4600 for planning purposes.
iv. In some instances the postop GTV_4600 will be larger than the preop GTV_4600 because the surgical cavity and resection path extend beyond the preop T2 weighted FLAIR (not common) abnormality; in this case, once you have confirmed that the volumetric discrepancy is not because of a vascular event, use the larger postop GTV_4600 for planning purposes.

CTV_4600: Is defined as the GTV_4600 plus a margin of 2 cm, which may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc. to as low as 0 mm to "fixed" barriers, i.e., bone, and falx and as low as 3 – 5 mm to "non-rigid" barriers such as brain stem, ventricles, etc. In the uncommon situation that there is no surrounding T2 weighted FLAIR and/or conventional T2 abnormality, the CTV 4600 in those instances should include the post-operative MRI enhancement and the surgical resection cavity plus a 2 cm margin, with reduction permitted as described above. In those uncommon situations where an extensive polar lobectomy has been achieved, and no true residual disease or surgical cavity is present, GTV_4600 will be defined only by the residual postop T2 weighted FLAIR abnormality, and the CTV will reflect a 2 cm margin expansion, using the same guidelines as above.

GTV_6000: Contrast enhancing T1 abnormality and the surgical cavity on the post-operative MRI scan. Areas of vascular infarction or compromise of normal brain should be excluded if they are deemed to not be part of the original pre-operative tumor volume, and a comparison of the pre- and post-operative scans will assist in this process. The exception to this is the polar tumor, e.g., temporal lobe, frontal lobe, or occipital lobe tip, where a gross total resection is achieved, and no post-operative "cavity" remains, consequential to the partial or total lobectomy. For these uncommon patients, GTV_6000 will be defined as either the conventional T2 or the T2 weighted FLAIR abnormality on the post-operative MRI scan, i.e., in these cases, GTV_4600 = GTV_6000.

CTV_6000: Is defined as the GTV_6000 plus a margin of 2 cm. The CTV_6000 margin may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc. to as low as 0 mm to "fixed" barriers, i.e., bone, and falx and as low as 3 – 5 mm to "non-rigid" barriers such as brain stem, ventricles, etc..

PTV_4600 and PTV_6000: In general the PTV is the CTV plus a geometric 5 mm expansion in all dimensions. This can be reduced to 4 mm if daily volumetric (3D) or non-volumetric (2d) IGRT is utilized. The PTV may extend beyond bony margins and the skin surface.

5.2.5 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	Description	Validation **(Required/Required when applicable/Optional)**
Brain	Whole brain parenchyma	Required
BrainStem	Brainstem	Required
Cochlea_L	Left cochlea	Optional
Cochlea_R	Right cochlea	Optional
OpticChiasm	Chiasm	Required
OpticChiasm_PRV	Chiasm planning risk volume	Required
OpticNrv_L	Left optic nerve	Required
OpticNrv_R	Right optic nerve	Required
OpticNrv_PRV_L	Left optic nerve planning risk volume	Required
OpticNrv_PRV_R	Right optic nerve planning risk volume	Required
Lens_L	Left lens	Required
Lens_R	Right lens	Required
Retina_L	Left retina	Required
Retina_R	Right retina	Required
Glnd_Lacrimal_L	Left lacrimal gland	Required
Glnd_Lacrimal_R	Right lacrimal gland	Required
SpinalCord	Spinal Cord	Required

Detailed Specifications

All structures must be contoured on the planning CT, using the postoperative MRI for guidance. All structures should be reviewed on both CT and registered MRI images.

Lens_L, Lens_R, Retina_L, Retina_R, OpticNrv_L, OpticNrv_R: Due to variance in eye position between the CT and MRI, if possible, the structures should be contoured using the CT dataset only. At times, for contouring the optic nerves, as they exit through the bony canal, switching the CT sequence between soft-tissue and bone windows is useful. The retina is defined

as the innermost of the three layers that form the wall of the eyeball. Please contour the 5 mm posterior wall of the eye.

OptNrv_PRV_L: Left optic nerve should be expanded by a volumetric expansion of 3 mm.

OptNrv_PRV_R: Right optic nerve should be expanded by a volumetric expansion of 3 mm.

OpticChiasm: Located above the pituitary fossa, the optic chiasm includes both anterior and posterior limbs. Frequently, the fused T2 weighted/FLAIR MRI is useful for identify and validating the chiasm contour, especially the coronal MRI; therefore, in some cases it may be necessary to fuse a coronal MR sequence clearly demarcating the chiasm, or reformatting thin slice MR axial images into coronal views. Please note that the MR position of the chiasm is only for guidance for contouring on the CT dataset, due to potential variation in CT/MRI fusion.

OpticChiasm_PRV: Optic chiasm should be expanded by a volumetric expansion of 3 mm.

BrainStem: Brainstem contour should include all three components: midbrain, pons, and medulla. The brainstem is bordered superiorly by the tentorial incisures and inferiorly by the foramen magnum. It can be visualized on post-operative MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.

SpinalCord: Spinal cord should be contoured, wherever possible, on the CT dataset only.

Brain: Whole brain parenchyma includes all intracranial contents, inclusive of target volumes. Because some volumetric change could have occurred in the whole brain parenchyma due to evolving post-operative changes, it is recommended, whenever possible to contour the whole brain parenchyma using the CT dataset only.

Cochlea_L, Cochlea_R: It is strongly recommended that the left and right cochlea be contoured using the CT dataset on bone window.

Glnd_Lacrimal_L, Glnd_Lacrimal_R: The lacrimal gland is located supero-laterally to the extraconal portion of the orbit, medial to the zygomatic process of the frontal bone and is superior to the lateral rectus muscle and lateral to the superior rectus muscle.

5.2.6 Dose Prescription

The initial target volume will be treated to 46 Gy in 23 fractions. After 46 Gy, the conedown or boost volume will be treated to a total of 60 Gy, with seven additional fractions of 2 Gy each (14 Gy boost dose). Isodose distributions for the initial target volume (PTV_4600) and the conedown target volume (PTV_6000) are required on all patients. A composite plan is required showing the respective target volumes.

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here.

Cases will be scored using the Compliance Criteria table.

Target Standard Name	**Dose [Gy]**	**Fraction Size [Gy]**	**# of fractions**	**Dose specification technique**
PTV_4600	46	2.0	23	At least 95% of PTV receives 46 Gy
PTV_6000	60	2.0	30	≥95% of PTV should receive ≥ 60 Gy

5.2.7 Compliance criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Normalization of Dose: The plan is normalized such that at least 95% of the PTV_6000 volume receives the prescription dose of 60 Gy.

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met

Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable
PTV_4600	D95% [Gy]	>=46	>=43.7
PTV_6000	D95% [Gy]	59.25-60.75	57.0-63.0
	D10% [Gy]	<=63	<=65.12
	D0.03cc [Gy]	<=64.0	<=66.0

Per Protocol range is excluded from Variation Acceptable range.

Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
BrainStem	D0.03cc [Gy]	<=55	<=60
OpticNrv_PRV_L or OpticNrv_PRV_R	D0.03cc [Gy]	<=55	<=60

OpticChiasm_PRV	D0.03cc [Gy]	<=55	<=60
Brain	D5% [Gy]	<=65	<=67
Retina_L or Retina_R	D0.03cc [Gy]	<=45	<=50
Lens_L or Lens_R	D0.03cc [Gy]	<=7	<=10
Glnd_Lacrimal_L or Glnd_Lacrimal R	D0.03cc [Gy]	<=40	<=45
Cochlea_L or Cochlea_R	Mean dose	<=45	<=50
SpinalCord	D0.03cc [Gy]	<=50	

Per Protocol range is excluded from Variation Acceptable range.

Exceptions:

1. SpinalCord does not have a Variation Acceptable; Deviation Unacceptable occurs when SpinalCord dose limit for Per Protocol is not met.
2. Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met for both OptNrv_PRV_L and OptNrv_PRV_R; or OptNrv_PRV_L if the subject does not have a serviceable vision in the right eye; or OptNrv_PRV_R if the subject does not have a serviceable vision in the left eye. **The optic nerve or chiasm dose will not be scored as unacceptable if the patient has no serviceable vision in the concerned eye (or both eyes in the case of chiasmal dose); it is therefore imperative that this information be clearly provided.**
3. Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met for both Retina_L and Retina_R; or Retina_L if the subject does not have serviceable vision in the right eye; or Retina_R if the subject does not have serviceable vision in the left eye. **The retinal dose will not be scored as unacceptable if the patient has no serviceable vision in that eye (or both eyes if that is the case); it is therefore imperative that this information be clearly provided.**
4. Exceeding the dose limits for Variation Acceptable for Lens_L or Lens_R will not be scored as Deviation Unacceptable.
5. Exceeding the dose limits for Variation Acceptable for Cochlea_L or Cochlea_R will not be scored as Deviation Unacceptable.
6. Exceeding the dose limits for Variation Acceptable for Lacrimal Gland_L or Lacrimal Gland_R will not be scored as Deviation Unacceptable.

Delivery Compliance criteria

	Per Protocol	Variation Acceptable
Start date	≤ 6 weeks after surgery	None
Overall Treatment time	≤ 46 days	47 – 49 days
Interruptions	≤ 4 days	5 – 7 days

5.2.8 Treatment Planning Priorities and Instructions

- Treatment planning priorities

1. SpinalCord
2. BrainStem
3. OpticChiasm_PRV
3. OpticNrv_PRV_L and OpticNrv_PRV_R
4. PTV_4600
5. PTV_6000
6. Brain
7. Retina_L and Retina_R
8. Gland_Lacrimal_L and Glnd_Lacrimal_R
9. Lens_L and Lens_R

- Required algorithms

For photon treatment planning, acceptable choices of algorithm are listed at http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf. An algorithm that is not included in this list must be credentialed by IROC Houston. For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported. These principles hold for Pencil Beam type algorithms and for homogeneous dose calculations when allowed for a clinical trial.

- Primary dataset for dose calculation

Planning CT image is the primary dataset for dose calculation.

-Dose matrix resolution

Dose grid size should be <= 3 mm in all directions.

5.2.9 Patient specific QA

For photon IMRT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. The recommended patient specific QA criteria is for 90% of the comparison points to pass a ±3%/3mm Gamma Index analysis.

5.2.10 Daily Treatment Localization/IGRT

Image-guided radiation therapy (IGRT) is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment. IGRT should be credentialed by IROC when IGRT is used for patient setup.

Imaging should be performed at least once per week. Daily IGRT is highly recommended for

IMRT and image-guidance is per individual institutional standards and the margins stated in Section 5.2.4. Acceptable IGRT methods include orthogonal kV imaging, cone beam or in room diagnostic CT with referenced geometry to treatment machine (ex. CT on rails) or tomotherapy based fan beam imaging.

Use of 4 mm PTV margin expansion is based on the requirement that IGRT will be used for daily setup and localization.

Image registration may be performed based on bony structures and/or existing implanted fiducial markers. It is important to include as much of the anatomy of this structure as possible to ensure correct alignment of the head. **Caution should be taken to avoid excess repeat imaging on a given treatment day to minimize subject dose outside the treatment region, and steps to control subject position to less than 3 mm should not be taken.**

Setup errors identified on IGRT images of > 1 mm or > 1 degree should be corrected.

Management of Radiation Dose to the Patient from IGRT
NRG Oncology is concerned about the estimated doses given from IGRT, and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by avoiding the use of this technology to make small changes in patient positioning that are within the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g. requiring frequent corrections that are larger than the PTV margins). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

5.2.11 Case Review
See section 12.1 for details.

5.3 General Concomitant Medication and Supportive Care Guidelines (08-APR-2022)

5.3.1 Permitted Supportive/Ancillary Care and Concomitant Medications
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication. Specific permitted supportive/ancillary care and concomitant medications include but are not limited to the following:

- Anticonvulsants
- Antiemetics
- Anticoagulants other than warfarin
    - Pulmonary embolism and deep venous thrombosis are known complications of glioblastoma. They can be treated per investigator discretion other than with warfarin.
- Antidiarrheals
- Analgesics
- Hematopoietic Growth Factors
- Highly active antiretroviral therapy (HAART)

- Note that systemic (oral, rectal, intravenous) corticosteroids are disallowed within 3 days prior to step 2 registration and within 3 days prior to the first administration of study treatment, but are allowed as needed after that although doses must be submitted as part of the data submission process. Inhaled, topical, and ocular corticosteroids are permitted without limitation.

Herbal and Nutritional Supplements

The concomitant use of herbal therapies is not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However the use of general nutritional foundation supplements will be allowed including: calcium with vitamin D and/or minerals, Omega3s (fish oil), Vitamin B6, Vitamin B12, a basic multivitamin , L-glutamine, or probiotics oral supplements will be permitted at long as at or below the FDA approved recommended dose allowance (RDA) by a healthcare provider. Herbal-based multivitamins are not allowed. Any additional supplements will need prior review and approval by the Principal Investigator/Neuro-Oncology Chair, Co-Chair, or NRG Oncology approved designee.

Pneumocystis carinii prophylaxis

Prophylaxis against P. carinii pneumonia is strongly recommended for all patients receiving temozolomide during radiotherapy, such as (but not limited to): trimethoprim-sulfamethoxazole (Bactrim forte, Bactrim DS) 1 tablet 3 times per week or monthly pentamidine inhalations (300 mg via aerosol monthly) or dapsone 100 mg po each day (except in patients with G6-PD deficiency) or atovoquone (1500 mg of suspension po qd with food). Prophylaxis is strongly recommended to continue for the duration of radiotherapy, regardless of the lymphocyte count.

5.3.2 Prohibited and Restricted Therapies

All Patients

Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study (with the exception of Optune, which is allowed in Arm 1 only), before progression, including but not limited to:

- Any non-study anti-cancer directed agent (investigational or non-investigational)
- Any other investigational agents
- Any other CTLA-4 inhibitors or agonists
- CD137 or other immunologic activation agonists
- Immunosuppressive agents
- Bevacizumab
- Lomustine
- Radiotherapy except as outlined
- Radiosurgery (including stereotactic radiosurgery, gamma knife, cyber knife)
- Diet changes or other medications with a goal of treating the tumor (such as ketogenic diet or metformin in the absence of diabetes mellitus)
- Laser interstitial thermal therapy (LITT).

- Laser interstitial thermal therapy (LITT) that completely ablates the tissue does not exclude active recurrence; patients who undergo LITT after enrollment should be considered to have pursued alternate therapy, protocol therapy must be discontinued, and the patient should be considered unevaluable for progression as of the date of the first MRI concerning for progression.

In addition, treatment with warfarin is not permitted.

Patients Randomized to Arm 1
No additional Arm-specific restrictions

Patients Randomized to Arm 2
Patients may use standard vaccines. Where possible, routine vaccination for influenza, pneumococcal pneumonia, and COVID-19 should be given prior to the start of therapy but may be administered during treatment when clinically indicated. Vaccination should be given when there is enough separation to distinguish any vaccine reactions from drug toxicity. There is no experience using live attenuated vaccination during ipilimumab therapy, so that live vaccine should be used cautiously during treatment.

5.3.3 Participation in Other Trials
Patients are not allowed to participate in other therapeutic trials of interventions with anticancer therapy as a goal (drug, device, diet, or other) before progression. However, trials that do not add experimental agents are allowed (e.g. imaging trials, quality of life, seizure, prevention/treatment, etc). In addition, adjuncts that were already administered at the time of surgery designed to guide or enhance surgical resection (e.g., 5-ALA, fluorescein) are not exclusionary.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression
  - Patients who undergo tumor-directed surgery during protocol therapy for suspected recurrence or to distinguish treatment effect (i.e., pseudoprogression) from tumor recurrence who are found to have active tumor on local pathologic analysis must be discontinued. The date of progressive disease must be backdated to the date of first suspected progression. Patients without active tumor may continue on protocol therapy.
- Intercurrent illness that prevents further administration of treatment
- Adverse event(s) which require(s) permanently going off study treatment (see also Section 6 and specific algorithms in Appendices II and III)
- Any dosing interruption lasting >6 weeks, with the following exceptions: Dosing interruptions >6 weeks that occur for non-drug-related reasons may be allowed if approved by the Medical Neuro-Oncology Study Chair/designee. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the

Medical Neuro-Oncology Study Chair/designee must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Patient decides to withdraw consent for participation in the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Arm 1: completion of 6 cycles of adjuvant cycles of therapy, with up to 12 total adjuvant cycles permissible at the discretion of the treating investigator
- Note that Optune may continue indefinitely at the discretion of the treating investigator (Arm 1).

6. TREATMENT MODIFICATIONS/MANAGEMENT

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

6.1 Temozolomide (08-APR-2022)

Temozolomide During Concomitant Radiation Therapy

No dose reduction will be made, but delay or discontinuation of temozolomide administration will be decided weekly according to hematologic and non-hematologic adverse events (AEs), as specified below.

If one or more of the following are observed:

- ANC < 1.5 x 10^9/ L
- Platelet count < 100 x 10^9/ L
- Grade 3 treatment-related non-hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy, and fatigue)

then treatment with concomitant temozolomide will be withheld until all of the following conditions are met:

- ANC ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Grade ≤ 1 non-hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy, and fatigue)

In case of hematologic AE as defined above, a complete blood count (CBC) should be performed at least twice weekly. In case of non-hematologic AE, the patient must be assessed at least weekly with relevant laboratory test(s). As soon as all of the above conditions are met, the administration of temozolomide must resume at the same dose as used initially.

If one or more of the following are observed:

- ANC < 0.5 x 10^9/L (Grade 4)

- Platelet count < 25 x 10^9/L (Grade 4)
- Grade 4 treatment-related non-hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy)

then treatment with concomitant temozolomide must be **stopped**.

Adjuvant temozolomide treatment (below) can be initiated if hematologic adverse events resolve (platelet > 100 x 10^9/L and ANC > 1.5 x 10^9/L). A delay of up to 6 weeks is permitted to allow for resolution of adverse events.

If the administration of temozolomide has to be interrupted, the radiotherapy will proceed normally. Missed doses of temozolomide during the concurrent phase of treatment with radiotherapy will not be made up at the end of radiotherapy. The total number of days and total dose of temozolomide will be recorded on the temozolomide CRF.

If the duration of radiotherapy exceeds 7 weeks, then concomitant treatment with temozolomide must be stopped after 49 days of temozolomide treatment.

Cases of hepatic injury, including fatal hepatic failure, have been observed in patients enrolled in clinical studies utilizing the agent temozolomide. In addition, it was noted that liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. For patients with significant liver function abnormalities, the risks and benefits of treatment continuation should be carefully considered.

Summary of Temozolomide Delay or Discontinuation During Concomitant Radiation Therapy

AE	Value	Grade	Action
ANC	≥ 0.5 and < 1.5 x 10^9/L		**Delay** temozolomide until: ---ANC ≥ 1.5 x 10^9/L ---Platelet ≥ 100 x 10^9/L ---Non-hem AE ≤ 1
Platelet count	≥ 25 and < 100 x 10^9/L		
Non-hematologic (except nausea/vomiting unless the patient has failed maximal antiemetic therapy and fatigue)	NA	3	
ANC	< 0.5 x 10^9/L	4	**Stop** concomitant temozolomide
Platelet count	< 25 x 10^9/L	4	
Non-hematologic (except nausea/vomiting unless the patient has failed maximal antiemetic therapy)	NA	4	

Concomitant temozolomide, if radiotherapy is interrupted

If radiotherapy has to be interrupted for technical or medical reasons unrelated to the temozolomide administration, then treatment with daily temozolomide may continue at the discretion of the treating investigator. If radiotherapy has to be permanently interrupted then treatment with daily temozolomide can stop or be continued at the discretion of the treating investigator; if stopped, temozolomide can resume with the initiation of the adjuvant phase of treatment.

Post-Radiation (Adjuvant) Temozolomide

Dosing is based on adverse events (AEs) during the prior treatment cycle. If multiple AEs are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.

Dose Level	Temozolomide Dose, mg/m^2/day	Remarks
-2	100	Reduction if prior AE
-1	125	Reduction if prior AE
0	150	Starting dose cycle 1 (adjuvant)
+1	200	Escalated dose at cycle 2, for cycles 2-12 (see dose escalation description)

Delay

On day 1 of each cycle (up to 9 days prior, coinciding with day 21 +/- 2 days of the prior cycle), ANC $\geq$ 1.5 x 10^9/L, platelet count $\geq$ 100 x 10^9/L and all treatment-related grade 3 or 4 non-hematologic AEs (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) must have resolved (to grade $\leq$ 1).

If these re-treatment parameters are not met, the treatment will be delayed to a maximum of 6 consecutive weeks with parameters rechecked at least weekly. If, after 6 weeks of delay, re-treatment parameters are not met: then any further adjuvant treatment with temozolomide must be stopped.

Dose escalation

If, during the first cycle, all treatment-related non-hematologic AEs observed were grade $\leq$ 2 (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) and with platelets $\geq$ 100 x 10^9/L and ANC $\geq$ 1.5 x10^9/L: then the temozolomide dose should be escalated to dose level +1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade $\geq$ 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose cannot be escalated in further cycles (3-12).

Dose reductions

If any treatment-related non-hematologic AE observed was grade > 2 (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) and/or if platelets < 50 x 10^9/L and/or ANC < 1 x 10^9/L, then the dose should be reduced by one dose level. For patients who would require dose reductions to a dose level < 100 mg/m^2/day, temozolomide will be stopped. Also, if any of the same non-hematologic grade 3 AE recurs (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) after reduction for that AE, then temozolomide will be stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) then adjuvant temozolomide

treatment should be stopped.

- *Subsequent cycles (3-6 and up to 12 allowed):* Any dose reductions of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the nadir (lowest/worst) ANC and platelet counts observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied.

- *Important:* If the dose was reduced or delayed for adverse events, there will be no dose escalation.

The reason(s) for dose reduction and/or delay must be documented in the CRF.

Summary of Dose Modification or Discontinuation During Post-Radiation Temozolomide

Worst Non-Hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue**)** **During the Previous Cycles**	
Grade	**Dose Modification**
0-2	No dose modifications for non-hematologic AEs. Dose escalations (only for cycle 2) or reductions based on ANC and platelet counts are applicable.
3	Reduce by one dose level (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable. No further escalation is possible. If the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then stop.
4	Stop (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable.

Nadir Values		**Platelets**		
		≥100 x 10^9/L	**50 – 99 x 10^9/L**	**< 50 x 10^9/L**
ANC	**≥ 1.5 x 10^9/L**	Escalation to DL 1 (cycle 2 only)	Dose unchanged	Reduce by 1 dose level
	≥1 & <1.5 x 10^9/L	Dose unchanged	Dose unchanged	Reduce by 1 dose level
	< 1 x 10^9/L	Reduce by 1 dose level	Reduce by 1 dose level	Reduce by 1 dose level

Note: A complete blood count must be performed 21 days (± 48 hours) after the first daily dose of each adjuvant treatment cycle.

Hematologic AE on Day 1 of Each Cycle (≤ 3 days before)	
AE	**Delay**

ANC< 1.5 x 10^9/L and/or Platelet count < 100 x 10^9/L	Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

Non-Hematological AE (except for alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue**) on Day 1 of Each Cycle (≤ 3 days before)**	
Grade	**Delay**
2-3	Delay up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks, then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

6.2 Nivolumab and Ipilimumab: General Guidelines (08-APR-2022)

If treatment is delayed >6 weeks for an adverse event the ipilimumab and nivolumab must be permanently discontinued.

Any patients who require additional immune suppressive treatment beyond steroids must discontinue nivolumab and ipilimumab.

Patients requiring > two dose delays for the same event should discontinue nivolumab and ipilimumab.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 5-7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Patients may be dose-delayed for evaluation and restarted depending on results.
Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after a 2-week observation period without further symptoms at the discretion of the PI or investigator.

6.3 Nivolumab and Ipilimumab ((17-JAN-2023)

There are no dose modifications for nivolumab and ipilimumab.

6.3.1 Treatment of Nivolumab/Ipilimumab-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, urticaria, angioedema, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines.

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

Remain at bedside and monitor subject until recovery from symptoms.

For Grade 1 symptoms

(Mild reaction; infusion interruption not indicated; intervention not indicated)

Infusion rate may be slowed or interrupted and restarted 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 patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab and ipilimumab administrations, slowing infusion rate as above.

For Grade 2 symptoms

(Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [*e.g.*, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours).

Stop the nivolumab and ipilimumab infusions, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid 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 patient closely. If symptoms recur, re administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and (acetaminophen) (or paracetamol) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab and ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms:
(Severe reaction)

Grade 3 symptoms: prolonged [*i.e*., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [*e.g*., renal impairment, pulmonary infiltrates]).

Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated). Nivolumab and ipilimumab will be permanently discontinued

Immediately discontinue infusion of nivolumab and ipilimumab. Begin an IV infusion of normal saline, and bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 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. Patient should be monitored until the investigator is comfortable that the symptoms will not recur.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

Other guidance:
In the case of late-occurring hypersensitivity symptoms (*e.g*., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (*e.g*., oral antihistamine, or corticosteroids). Additional treatment prior to next dose as per guidelines above.

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

6.3.2 Nivolumab and Ipilimumab Overall Dosing Delays

All dose management decisions apply to both ipilimumab AND to nivolumab. **When assessing dose management, please use the tables below and refer to the Nivolumab/Ipilimumab Management Algorithms in Appendix II for further guidance.**

Decisions to delay nivolumab and ipilimumab dose must be made on specified safety criteria. Treatment with nivolumab and ipilimumab will be delayed (or discontinued)

if the subject experiences at least one adverse event, specified below, considered by the investigator to be **"possibly," probably," or "definitely" related to nivolumab and/or ipilimumab treatment.**

Adverse events considered "unlikely" or "unrelated" to nivolumab and ipilimumab treatment do not require a dose delay.

A delay of up to 6 weeks is permitted to allow for resolution of adverse events.

All Other Events	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	No change in dose.
Grade 2	Hold until Grade 1 OR baseline (exceptions as noted below).
Grade 3	Hold until Grade 1 OR baseline and patient no longer on steroid treatment if initiated (exceptions as noted below). Permanently discontinue for events with a high likelihood of morbidity or mortality with recurrent events.
Grade 4	Discontinue nivolumab/ipilimumab.
Recommended management: As clinically indicated	

- Any Grade 2 drug-related uveitis or 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 should discontinue nivolumab/ipilimumab.

- Any Grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should discontinue nivolumab/ipilimumab.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	Continue nivolumab/ipilimumab *. Consider symptomatic therapy (e.g., antihistamines, topical steroids).
Grade 2	Hold* until ≤ Grade 1 . Resume dose.
Grade 3	Hold* until ≤ Grade 1. Resume dose at investigator discretion
Grade 4	Discontinue nivolumab/ipilimumab
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, toxic epidermal necrolysis (TEN), and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and	

should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering. If Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS) is suspected, withhold nivolumab/ipilimumab and refer the patient for specialized care for assessment and treatment. If SJS, TEN or DRESS is diagnosed, permanently discontinue nivolumab/ipilimumab.
Recommended management: AE management guidelines

Liver Function: AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	Continue nivolumab/ipilimumab. Increase frequency of LFT monitoring.
Grade 2	Hold until Grade 1 or baseline. Increase frequency of monitoring to every 3 days. If returns to baseline, resume routine monitoring and resume nivolumab/ipilimumab. If elevations persist >5-7 days, start 0.5-1 mg/kg/day methylprednisolone or oral equivalent. Resume dose at investigator discretion.
Grade 3	Hold until Grade 1 or baseline. Start 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent.
Grade 4	Discontinue nivolumab/ipilimumab. Start 2 mg/kg/day methylprednisolone IV or IV equivalent.
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate liver function test (LFT) changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis. Please note: Grades for liver function follow UNL rather than multiples of baseline.	
Recommended management: see Hepatic AE management algorithm	

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	Continue treatment. Symptomatic treatment for diarrhea.
Grade 2	Hold nivolumab/ipilimumab. Symptomatic treatment for diarrhea. If improves to grade 1, resume dose. If symptoms persist >5-7 days, start 0.5-1 mg/kg/day methylprednisolone or oral equivalent. Resume dose at investigator discretion when improved to grade 1.
Grade 3	Hold nivolumab/ipilimumab. Start 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent. Resume dose at investigator discretion when improved to grade 1.
Grade 4	Discontinue nivolumab/ipilimumab.

See GI AE Algorithm for management of symptomatic colitis. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.
Recommended management: see GI AE management Algorithm

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	Continue dose if asymptomatic at investigator discretion.
Grade 2	Continue dose if asymptomatic at investigator discretion. If symptomatic, resume at same dose when resolved
Grade 3	Continue at same dose if asymptomatic at investigator discretion. Patients should have imaging study when clinically indicated (grade 3 symptomatic pancreatitis) before resuming treatment. Patients who develop diabetes mellitus should discontinue nivolumab/ipilimumab.
Grade 4	Hold until grade 2. Resume dose if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated. Patients who develop grade 4 symptomatic pancreatitis or diabetes mellitus should discontinue nivolumab/ipilimumab.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as diabetes mellitus and diabetic ketoacidosis (DKA). Lipase elevation may occur during the period of steroid withdrawal and with other immune-mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. Recommended management of symptomatic pancreatitis: see the Hepatic AE Management Algorithm.	

Pneumonitis	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO_2. Resume dose after pulmonary and/or infectious disease (ID) consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume dose after pulmonary and/or ID consultation excludes ipilimumab/nivolumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Resume nivolumab/ipilimumab if improves to grade 1. If symptoms persist >5-7 days, start 0.5-1 mg/kg/day methylprednisolone or oral equivalent. Resume dose at investigator discretion when improved to grade 1.

Grade 3	Hold dose pending evaluation. Resume dose after pulmonary and/or ID consultation excludes ipilimumab/nivolumab and associated lymphocytic pneumonitis as the cause of the pneumonitis; otherwise, discontinue nivolumab/ipilimumab. Hospitalize, start 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent.
Grade 4	Discontinue nivolumab/ipilimumab. Hospitalize, start 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent.
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified, including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please recommend seasonal influenza killed vaccine for all patients. Consult Pulmonary and Infectious Disease early.	
Recommended management: See Pulmonary AE Management Algorithm	

Other GI Nausea/Vomiting	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	Continue dose.
Grade 2	Hold pending evaluation for gastritis, duodenitis, and other immune AEs or other causes. Resume at same dose after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume dose. If symptoms do not resolve within 7 days with symptomatic treatment, patients should discontinue nivolumab/ipilimumab.
Grade 4	Discontinue nivolumab/ipilimumab
Patients with Grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 2	Continue dose.
Grade 3	Hold until ≤ Grade 2. Resume at same dose.
Grade 4	Discontinue nivolumab/ipilimumab.
Fatigue is the most common AE associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation.	

Neurologic events	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	Continue nivolumab/ipilimumab. Monitor symptoms.

Grade 2	Hold dose pending evaluation and observation. Start 0.5-1 mg/kg/day methylprednisolone or oral equivalent. Resume nivolumab/ipilimumab when improved to baseline. Resume nivolumab/ipilimumab for peripheral isolated n. VII (Bell's palsy).
Grade 3	Discontinue nivolumab/ipilimumab. Start 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent.
Grade 4	Discontinue nivolumab/ipilimumab. Start 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent.
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, and myasthenia gravis should be off study treatment.	
Recommended management: See Neurologic AE Management Algorithm	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	*Hold pending evaluation for evidence of adrenal insufficiency or hypophysitis. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment while evaluating the need for thyroid replacement.
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable on no more than physiologic replacement corticosteroids for 2 weeks. Resume dose.
Grade 3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable on no more than physiologic replacement corticosteroids for 2 weeks. Resume dose.
Grade 4	Discontinue nivolumab/ipilimumab.
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered Grade 3 events. Isolated thyroid or testosterone deficiency may be treated as Grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement. Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment. Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.	

Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events. Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.
Recommended management: See Endocrine Management Algorithm

Renal	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Start 0.5-1 mg/kg/day methylprednisolone or oral equivalent. Resume dose.
Grade 3	Hold until ≤ Grade 1. Start 0.5-1 mg/kg/day methylprednisolone or oral equivalent. Resume dose.
Grade 4	Discontinue nivolumab/ipilimumab. Start 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Fever	**Management/Next Dose for Nivolumab/Ipilimumab**
Grade 1	Evaluate and continue at dose.
Grade 2	Hold until ≤ Grade 1. Resume at dose.
Grade 3	Hold until ≤ Grade 1. Resume at dose.
Grade 4	Discontinue nivolumab/ipilimumab
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	
See section 6.4.1 – Treatment of Nivolumab/Ipilimumab -Related Infusion Reactions.	

Cardiac *	**Management/Next Dose for Nivolumab + Ipilimumab Cardiac Toxicities**
Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop then treat as below.

Cardiac *	Management/Next Dose for Nivolumab + Ipilimumab Cardiac Toxicities
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus. May resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Discontinue nivolumab and ipilimumab. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Discontinue nivolumab and ipilimumab.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agents administered in NRG-BN007, ipilimumab and nivolumab, are being made available under an IND sponsored by CTEP. For ipilimumab and nivolumab, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.4 of the protocol.

Commercial Agents

The commercial agent in NRG-BN007 is temozolomide. For temozolomide, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.4 of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no directed action will be taken. Patient responses to the PRO-CTCAE may lead to additional assessment by the clinician; the responses should be reviewed. PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action. PRO-CTCAE may lead to additional evaluation by the clinician; their response should not be overlooked.

7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List for CTEP Study Agents (09-FEB-2021)

7.3.1 Ipilimumab

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting

Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis[2] (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		General disorders and administration site conditions - Other (Systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders - Other (immune-mediated encephalitis)[2]	

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.3.2 Nivolumab (NSC 748726)

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Nivolumab (NSC 748726)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for Nivolumab.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, December 2, 2020[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		
GASTROINTESTINAL DISORDERS			

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-mediated hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoidosis)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocyte decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (immune-mediated nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Nivolumab being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.4 Adverse Events for Commercial Study Agents: Temozolomide
Refer to the package insert for detailed pharmacologic and safety information

7.5 Adverse Events and PRO-CTCAE (09-FEB-2021)

PRO-CTCAE

The PRO-CTCAE instrument will be used to assess patient reported toxicity outcomes.

PRO-CTCAE is a validated instrument developed by the National Cancer Institute to assess clinical trial toxicity outcomes by patient report; it complements information collected by physician-reported CTCAE. PRO-CTCAE is available in English and French for this study.

Assessments will be collected as specified in the Section 4 assessment tables.

The patient-reported AEs that will be assessed using PRO-CTCAE are listed in the table below. These adverse events are considered expected and, if reported, should also be clinician graded using the CTCAE v.5

CTCAE v.5	PRO-CTCAE Items With Attributes
Abdominal pain	Abdominal pain (frequency, severity, interference
Rash maculo-papular	Rash (presence)
Pruritus	Itching (severity)
Myalgia	Muscle pain (frequency, severity, interference
Arthralgia	Joint pain (frequency, severity, interference
Injection site reaction	Pain and swelling at injection site (presence)
Chills	Chills (frequency, severity)
Headache	Headache (frequency, severity, interference)
Mucositis oral	Mouth/throat sores (severity, interference)
Dry skin	Dry skin (severity)
Alopecia	Hair loss (amount)
Cough	Cough (severity, interference)
Dysgeusia	Taste changes (severity)
Dizziness	Dizziness (severity, interference)
Edema	Swelling (frequency, severity, interference)
Hot flashes	Hot flashes (frequency, severity)

7.6 Expedited Reporting of Adverse Events

All adverse events (AEs) are submitted for expedited reporting protocol-specific rules evaluation using the Medidata Rave data management system. All AEs will be evaluated by the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) to determine whether expedited reporting is recommended based on a set of programmed expedited reporting rules. AEs identified as meeting the programmed expedited reporting requirements can then be submitted in CTEP-AERS. A deep link in Rave will take the user directly to CTEP-AERS where the expedited report may be completed and submitted via CTEP-AERS.

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the link in RAVE.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP by telephone at 301-897-7497 and NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

7.6.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event Each CTEP-AERS-24-hour notification must be followed by a complete report within 5 days.

- Supporting source documentation is requested by CTEP as the IND sponsor for this study and by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page; fax supporting documentation to CTEP at 301-897-7404 and contact NRG Oncology at 1-215-574-3191. A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action not recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.6.2 Expedited Reporting Requirements for Adverse Events

Arm 1 Expedited Reporting Requirements [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day		24-h/5 day	24-h/5 day

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of **possible, probable, or definite** require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- Unexpected Grade 4 and all Grade 5 AEs

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken.

Arm 2: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERs within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken.

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements

None

7.6.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.6.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

7.7 Routine Reporting Requirements for Adverse Events (09-FEB-2021)

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

7.7.1 Reporting PRO-CTCAE

Symptomatic Adverse Events reported by patients through PRO-CTCAE are not to be used for direct safety reporting.

7.8 NRG Responsibility for Reporting Serious Adverse Events to Health Canada

NRG will provide expedited reports of SAEs to Health Canada for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment.

7.9 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be

reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (17-JAN-2023)

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register and with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and;
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required		IVR	NPIVR	AP	A	AB
FDA Form 1572		✓	✓			
Financial Disclosure Form		✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)		✓	✓	✓		
GCP training		✓	✓	✓		
Agent Shipment Form (if applicable)		✓				
CV (optional)		✓	✓	✓		

An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for the new CTEP-IAM accounts, and by July, 2023 for all users) participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval) or consenting/treating/drug shipment investigator in OPEN or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures (17-JAN-2023)

This study is supported by the NCI CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to

submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-BN007 Site Registration

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only);
- Compliance with all applicable protocol-specific requirements (PSRs);

- Neurocognitive Function Testing Certification
  Institutions must meet certification requirements for administering neurocognitive assessments. Upon review and successful completion of the Neurocognitive Certification, Dr. Wefel will notify the certified examiner, NRG Headquarters, and CTSU that the examiner has successfully completed this requirement.

  See protocol-specific material on CTSU members' website for certification requirements

- Radiation/Imaging Requirements
  This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

  IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

  To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in protocol section 8.2 to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, the institution will need to upload their approval letter to the Regulatory and Roster Maintenance applications to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in the Regulatory application, enrolling site may access OPEN to complete enrollments. If the study is using the IROC integration suite, the enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

Additional Requirements for Sites in Canada

Prior to clinical trial commencement, sites in Canada must also complete and submit the following documents to the CTSU via the Regulatory Submission Portal:

- Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
- Protocol Signature Page
- Investigator Brochure Signature Page
- List of Laboratories
- SIV/Training Confirmation of Completion Form – Research Associate (please refer to the activation memo for details)
- SIV/Training Confirmation of Completion Form – Qualified Investigator (please refer to the activation memo for details)
- IRB/REB approved consent (English and native language versions*; Submit to NRG Regulatory (CanadianRegulatory@NRGOncology.org) prior to IRB/REB submission for review.

  *Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational letterhead/stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

The following items are collected By NRG Oncology Regulatory on a yearly or biyearly basis:

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password; or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- Click on *Protocols* in the upper left of the screen

- Enter the protocol number in the search field at the top of the protocol tree; or
- Click on the By Lead Organization folder to expand, then select *NRG* and protocol number *NRG-BN007*.

- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the site's 5-character CTEP Institution Code and click on Go:
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on

completing the DTL are available in the Help Topics button in the DTL application and describeDTL task assignments, CI signature, and CTEP registration requirements,as well as include a Master Task List.

8.2 RT-Specific Pre-Registration Requirements (17-JAN-2023)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. IROC will automatically send the approval to the Regulatory Support System (RSS) to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification..

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality	
	Photon	Key Information

Credentialing Status Inquiry Form	**X**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Facility Questionnaire	**X**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Phantom Irradiation	**X**	An IMRT Head & Neck phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org**).
IGRT	**X**	Only institutions interested in using reduced margins will be required to compete this credentialing step. Instructions for IGRT credentialing may be found on the IROC Houston website (**http://irochouston.mdanderson.org**).
Credentialing Notification Issued to:		
Institution	Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.	

8.2.1 Digital RT Data Submission to NRG Using TRIAD

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR;
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.3 Patient Enrollment (17-JAN-2023)Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.3.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023, for all users);
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- A Delegation of Tasks Log (DTL) is required for the study and the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. A DTL is required for the study, and the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.3.2 Patient-Initiated Consent Withdrawal from the Study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow up data to be submitted to NRG Oncology), the study applicable form should be completed in Medidata Rave to report the patient's consent withdrawal. NOTE: This should not be done if the patient has only chosen to stop protocol treatment and is willing to still be followed.

8.4 Medidata Patient Cloud ePRO Registration (08-APR-2022)

This study includes the use of Medidata's *Patient Cloud* mobile ePRO (electronic patient-reported outcomes) application. The *Patient Cloud* ePRO application allows patients to report clinical trial information (patient reported outcomes (PROs)) directly from their mobile devices into the Medidata Clinical Cloud. In this document ePRO application refers to the application accessed by the site via iMedidata (for patient registration) and Rave (to view completed ePRO forms), and *Patient Cloud* mobile app refers to the app accessed by the patient on a mobile device. After the patient is registered to the trial via OPEN, and if the patient is willing to participate in electronic data collection, the site staff will then complete a registration for the patient to the ePRO application through iMedidata. Site staff must complete the required eLearning (assigned in iMedidata) for the ePRO application before registering a patient. Information about the training is in the ePRO Appendix. The registration to the ePRO application will create a unique patient registration code that the *site staff will provide to the patient*. The patient (with assistance from the site staff) should be instructed to download the appropriate ePRO mobile app onto his/her own device (IOS, Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial.

There are multiple versions of the *Patient Cloud* mobile ePRO app available. Ensure that the correct version of the *Patient Cloud* mobile app is downloaded by the patient by verifying the correct version with the study team. Note only one version of the app is active per protocol and this protocol is using:

"Patient Cloud"

For sites providing a shared institutional device for use by multiple patients on site:

- The site staff should assist the patient with registration to the Patient Cloud mobile ePRO application and access to the Patient Cloud mobile app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

8.4.1 CRA Patient Registration Instructions for ePRO

Site staff must complete the required ePRO online training (assigned in iMedidata) for studies using the ePRO application before registering a patient. Reference materials for the Patient Cloud (current) app can be found at the link below; the landing page contains general information as well as links to additional resources on the left side of the screen:

- Patient Cloud (current) Medidata Learning Tool

The subject registration process starts in iMedidata. To register a patient log into iMedidata and perform the following steps:

i. Select the Patient Cloud Registration link for your study
ii. From the patient management app, select your STUDY and SITE from the drop downs and click Launch.
iii. Register your first patient. Create a subject ID and select a Country / Language from the drop down (required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.
iv. The subject will be added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

9. DRUG INFORMATION

9.1 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-

supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites may request an initial 4 vials of ipilimumab and 5 vials of nivolumab once a patient has enrolled to Step 1 registration.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9.2 Investigational Study Agent: Ipilimumab (NSC 732442)

(17-JAN-2023)

Sites must refer to the Investigator Brochure for detailed pharmacologic and safety information. The Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB). See Section 9.1.

Chemical Name or Amino Acid Sequence: 4 polypeptide chains, 2 identical heavy chains with 447 amino acids and 2 identical light chains consisting of 215 amino acids.

Other Names: Anti-CTLA-4 monoclonal antibody, MDX-010, Yervoy™

Classification: Human monoclonal antibody

M.W.: 147,991 Daltons

Mode of Action: Ipilimumab is specific for the CTLA4 antigen expressed on a subset of activated T-cells. CTLA4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate T-cell response. Ipilimumab is, thought to act by blocking the interaction of CTLA4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation. The CTLA4/B7 creates the interaction.

Description: Ipilimumab is a fully human immunoglobulin ($IgG_1\kappa$) with two manufacturing processes – ongoing trials have been using substances manufactured using Process B. New clinical trials will be using ipilimumab that is manufactured by Process C. The Process C has been developed using a higher producing sub-clone of the current Master Cell Bank, and modified cell culture and purification steps.

How Supplied:. In 2023, PMB will transition to a 50 mg/10 mL (5 mg/mL) vial, which will replace the 200 mg vial. The 50 mg vial is packaged in a 10-cc Type I flint tubing glass vial, stoppered with a 20-mm gray butyl rubber stopper, and sealed with a 20-mm aluminum flip-off seal. Each vial includes a 0.7-mL overfill for vial, needle, and syringe (VNS) holdup.

Eachvial is a Type I flint tubing glass vial with gray butyl rubber stoppers and sealed with aluminum flip-off seals.

	Process C
Component	**200 mg/ vial**[a]
Ipilimumab	213 mg
Sodium Chloride, USP	249 mg
TRIS-hydrochloride	134.3 mg
Diethylenetriamine pentacetic acid	1.67 mg
Mannitol, USP	426 mg
Polysorbate 80 (plant-derived)	4.69 mg
Sodium Hydroxide	QS to pH 7

Hydrochloric acid	QS to pH 7
Water for Injection	QS: 42.6 mL
Nitrogen[b]	Processing agent

[a]Includes 2.6 mL overfill.

[b]Nitrogen is used to transfer the bulk solution through the pre-filled and sterilizing filters into the aseptic area.

Preparation: Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 4 mg/mL. Ipilimumab is stable in a polyvinyl chloride (PVC), non-PVC/non DEHP (di-(2-ethylhexyl) phthalate) IV bag or glass container up to 24 hours refrigerated at (2^0 to 8^0 C) or at room temperature/ room light.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Storage: Store intact vials refrigerated at (2^0 to 8^0 C), protected from light. Do not freeze.

Stability: Shelf-life surveillance of the intact vials is ongoing. Solution as described above is stable up to 24 hours refrigerated at (2^0 to 8^0 C) or at room temperature/ room light.

CAUTION: Ipilimumab does not contain antibacterial preservatives. Use prepared IV solution immediately. Discard partially used vials.

Route*(s)* of Administration: Intravenous infusion. Do not administer ipilimumab as an IV push or bolus injection.

Method of Administration: Can use a volumetric pump to infuse ipilimumab at the protocol-specific dose(s) and rate(s) via a PVC IV infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (0.2 micron to 1.2 micron).

Patient Care Implications: Monitor patients for immune-related adverse events, e.g., rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypothyroidism. If you suspect toxicity, refer to the protocol guidelines for ruling out other causes.

9.3 Investigational Study Agent: Nivolumab (NSC 748726) (09-FEB-2021)

Sites must refer to the Investigator Brochure for detailed pharmacologic and safety information. The Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB). See Section 9.1.

Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

Other Names: BMS-936558, MDX1106

Classification: Anti-PD-1MAb

M.W.: 146,221 Daltons

Mode of Action: Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Description: Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), polysorbate 80 (Tween® 80) and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

How Supplied: Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7 mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Storage: Vials of Nivolumab injection must be stored at 2°- 8°C (36°- 46°F) and protected from light and freezing. Unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

Route of Administration: Intravenous infusion over 30 minutes. Do not administer as an IV push or bolus injection.

Method of Administration: Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter.

Potential Drug Interactions: The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Patient Care Implications: Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab.

Availability: Nivolumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Nivolumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix I).

9.4 Commercial Agent: Temozolomide

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.4.1 Adverse Events

Please refer to the package insert.

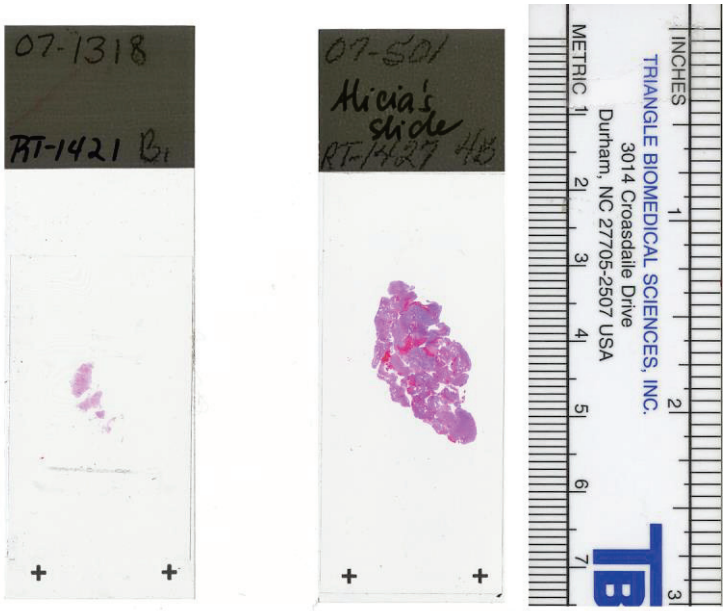
9.4.2 Availability/Supply

Drug will be supplied commercially. Please see Section 5.1 for administration instructions. Please refer to the current FDA approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug

preparation, handling and storage.

10. PATHOLOGY/BIOSPECIMEN

10.1 Central Histology Confirmation (see Section 10.3.1 for submission logistics)
Representative tissue blocks and corresponding H&E slides that contain diagnostic viable tumor are required. As a guide, at least 1 square centimeter of tissue composed primarily of tumor must be present when a slide is cut from the block. Note that the tissue blocks composed primarily of either normal tissue or necrotic tissue are inadequate for molecular analysis, as it depends on the presence of viable tumor tissue. In cases where a single block has insufficient tumor, tissue for multiple blocks can be combined to ensure specimen adequacy. Central pathology review will be conducted by the Neuropathology Co-Chair, Dr. Ken Aldape or another NRG Oncology-designated pathologist within 3 business days of receipt of the H&E slide, tumor block and required paperwork. If the pathologist determines that the block that was sent is insufficient, the pathologist will contact the site in an attempt to obtain additional tissue. Examples of adequate (RIGHT) and inadequate (LEFT) samples are shown below.



Examples of inadequate (*left*) and adequate (*right*) tissue samples for study entry. In both cases a slide was cut from the submitted block and stained with H&E. Even though the slide on the left had tissue diagnostic of glioblastoma, the amount of tumor will be insufficient for molecular testing

10.2 MGMT-STP27 Testing (see Section 10.3.1 for submission logistics) (08-APR-2022)
Central testing of tumor MGMT methylation status is now a standard in trials of newly diagnosed GBM. We will use of the Illumina EPIC whole genome methylation array to determine differences in response to standard of care +/- experimental therapy. The Illumina genome-wide methylation platform is a robust platform that is used at several centers for MGMT testing of glioma using the MGMT-STP27 measurement, and this model will be used for this protocol. It is considered a locked down assay and the use of the Illumina array to measure MGMT methylation determination has been previously validated (Bady 2016). It is compatible with the formalin-fixed, paraffin embedded tissue specimens that will be required for this trial and has the advantage to offer a rich source

of potential correlative biomarkers for retrospective analyses. MGMT testing will be performed after Step 1 registration. Tissue must be received by the central lab on or before postoperative calendar day 23. If tissue cannot be received by postoperative calendar day 23, then patients may NOT enroll on this trial as central pathology review will not be complete in time for the patient to start treatment no later than 6 weeks following surgery. Results will generally be conveyed to NRG Oncology within 10 business days of receipt of tissue. Patients with MGMT promoter without methylation will be randomized to a treatment arm. Patients with inadequate tissue for testing or with MGMT promotor with methylation status, indeterminate status, or with test failure will not be randomized and will not continue onto the treatment portion of the study. If the MGMT is methylated, the patient can be considered for enrollment on NRG-BN011. The MGMT-STP27 profiling will be performed at the Laboratory of the Biomarkers Co-Chair/designee who will be responsible for conducting these studies and evaluating the results. MGMT-STP27 testing was validated in the Clinical Laboratory Improvement Amendments (CLIA) laboratory at NYU Langone under CLIA ID number 33D2063212, expiration date at time of protocol activation: 6/30/2020.

- Required Paperwork: ST, P4 forms and pathology report must be included with the pathology shipment and must include the NRG protocol number, patient case number, patient's initials, and NRG institution number and name. Specimen Transmittal Form listing pathology materials being submitted for Central Tissue Evaluation
- Central Pathology Review Form (P4) must be completed by the local pathologist. Include on the P4 form the name, telephone number, email, and fax number of the person to notify with the results of the tissue evaluation.
- Pathology Report documenting that the submitted material contains tumor; the report must include the NRG protocol number, patient case number, and the patient's initials. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- Tissue evaluation will be required for every case. Dr. Aldape or another NRG Oncology designated pathologist will review these materials. See protocol cover page for additional contact information.
- Ship pathology material submissions Monday-Friday by overnight courier:
- Notify NYU Center for Biospecimen Research and Development (CBRD) (cbrdtissuerequest@nyulangone.org) on or before the day of submission: (1) the case # that is being submitted for review; (2) the name of the contact person; (3) when to expect the sample; and (4) the shipping carrier and tracking number.
- Central pathology (P4) results will be submitted electronically into the NRG database. An email notification about central pathology review results will be sent to the site when the P4 form is completed. If the patient is deemed eligible per pathology results, the lab will proceed with MGMT testing.
- MGMT (P5) results will be submitted electronically into the NRG database. A second email notification with results of MGMT analysis will be sent to the site when the P5 has been completed. The site may then proceed to step 2 registration. Only Unmethylated cases may be randomized at step 2. Any other MGMT result would require step 2 registration to be reported as a "central review failure". If

there is any tissue related-issue (e.g. not enough tissue), the site will be notified.

- Since there is a narrow time window within which the review must be completed, submission of H& E and tumor blocks should be done as soon as possible to ensure sufficient time for review. NYU CBRD must receive the H&E and tumor block within 23 days of surgery, to allow time for review and molecular testing. Samples received after this time cannot be accepted. If a sample is received beyond day 23 post op, the site will be notified and the tissue will be returned.
- If the patient does not meet eligibility requirements, all tissue and forms will be returned to the participating submitting institution. The site must provide a return airbill.
- If the tissue has already been evaluated by NYU Langone for enrollment to NRG-BN011 and resulted as unmethylated, those results can be used for enrollment to NRG-BN007. The aforementioned paperwork (ST/P4/redacted Pathology report) must still be submitted to NYU Langone for NRG-BN007. An email with the attached paperwork must be sent to NYU Langone **#mgmttesting@nyulangone.org** and the **NRG data managers** indicating that the tissue has already been processed and the previous results should be used for enrollment to NRG-BN007.The following templated email can be used to notify the lab:
  Please find attached paperwork for
  BN007 case # __ __ __ __ __- BN007- _0_ _0_ _0_ __ __.

  This tissue for this case was processed for enrollment to
  BN011 case # __ __ __ __ __- BN011- _0_ _0_ _0_ __ __.

  Please transfer the results from the NRG-BN011 database to the NRG-BN007 database.

10.3 Biospecimen Submission Tables (09-FEB-2021)

10.3.1 Mandatory Specimen Submissions

See detailed specimen collection/processing/shipping instructions on the protocol-specific website.

Mandatory Tissue Submission for Histology Confirmation and MGMT-STP27 Testing (per Sections 10.1-10.2)

1) Required Forms: ST form, pathology reports with accession number and date of procedure with all other PHI redacted, P4 form with local pathologist review filled out.
2) Shipping costs: Sites pay for FFPE shipping costs and returns.
3) Residual Material: Will be shipped from NYU to the NRGBB-SF once testing is completed and banked for patients who consented to banking. If requested by site, the block will be punched using three 2mm punches to create a new block and the original block can then be returned to the site. For patients who did not consent to banking, the block will be returned when requested by the site. H&E slides will remain at the bank for all patients and cannot be returned.

For shipments and questions, contact:

NYU Center for Biospecimen Research and Development (CBRD)
Medical Science Building

550 First Ave, MSB 238 New York, NY 10016 646-501-4268 Email: #MGMTTesting@nyulangone.org			
Specimen Type	**Collection Time Points**	**Collection Information and Requirements/ Instructions for Site**	**Shipping**
H&E slide(s) of Primary tumor for central review	Pre-treatment at time of surgery	Can be duplicate cut H&E slide, does not have to be the diagnostic slide.	Ship ambient to NYU CBRD by overnight courier
FFPE Block (same as H&E)	Pre-treatment at time of surgery	FFPE block must be submitted for this trial. Blocks can be returned after testing is completed upon request. For patients who consented to banking the NRGBB will obtain 2mm punches prior to returning.	Ship by overnight carrier to NYU CBRD (use cold packs during warm weather)

10.3.2 Optional Specimen Submissions

(Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.)

See detailed specimen collection/processing/shipping instructions on the protocol-specific website.

This study will include collection of biospecimens for future analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

Specimen Submission for Biobanking for Future Research

1) Kits are available for frozen biospecimens from the NRGBB-SF. Send an email to NRGBB@ucsf.edu requesting a kit. Allow 5-10 business days for kits to arrive by Fed EX Ground delivery.
2) Shipping days for frozen specimens: Monday-Wednesday (US sites); Monday-Tuesday (Canadian sites).
3) Shipping costs: One prepaid return label per case for batch shipping of frozen specimens will be provided in the US kits from the NRGBB-SF.
4) Brief processing instructions are provided with kits, and complete versions are available in NRG-BN007 Pathology and Correlative Science Instructions document posted on the CTSU website.

For questions, contact:
NRG Oncology Biospecimen Bank – San Francisco
UCSF Department of Radiation Oncology
2340 Sutter Street- Room S341
San Francisco, CA 94115
415-476-7864/Fax 415-476-5271; NRGBB@ucsf.edu

Specimen	Collection Time Points	Collection Information and Requirements/Instructions for Site	Shipping
H&E slide(s) of Primary tumor for central review	Pre-treatment at time of surgery	**Pretreatment:** Residual from histology/MGMT studies	N/A for site; to be batched shipped by NYU to NRG Oncology Biospecimen Bank San Francisco for patients who consent to biobanking of residual material.
FFPE Block (same as H&E)	Pre-treatment at time of surgery	**Pretreatment:** Residual from histology/MGMT studies	N/A for site; to be batched shipped by NYU to NRG Oncology Biospecimen Bank San Francisco for patients who consent to biobanking of residual material.
Serum- 10 ml Red top tube	Pre-treatment- Prior to radiation During Treatment: Before initiation of cycles 1 and 3 of adjuvant therapy	Process serum and aliquot a minimum of 0.5 ml into each of five (5) 1 ml cryovials Storage: Freeze and store at -80°C and ship frozen on dry ice	Batch Ship frozen on dry ice by overnight courier NRG Oncology Biospecimen Bank San Francisco.
Whole blood for	Pre-treatment- Prior to	Collect blood in EDTA tube,	Batch Ship frozen on

DNA 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	radiation *-note: If site missed this collection, they may collect at any other time but must note this on the ST form when submitting*	mix and aliquot a minimum of 1.5ml blood into three (3) 2ml cryovials. Freeze and store at -80°C and ship frozen on dry ice	dry ice by overnight courier to NRGBB-SF
Plasma- 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Pre-treatment- Prior to radiation During Treatment: Before initiation of cycles 1 and 3 of adjuvant therapy	Frozen plasma samples containing a minimum of **0.5 mL** per aliquot into five (5) 1 mL cryovials Storage: -80°C and ship frozen Forms: ST form Kits: request from NRG BB-San Francisco Shipping: One prepaid label provided for each case for batch shipping	Ship on dry ice by Priority Overnight Courier to NRG BB-SF

11. SPECIAL STUDIES (NON-TISSUE/BIOSPECIMEN)

11.1 Neurocognitive Function (NCF) and Patient-Reported Quality of Life (QOL)

(08-APR-2022)

11.1.1 Background

Toxicities seen with immune checkpoint inhibitor (ICI) therapies are much less predictable than with other cancer-directed therapies such as chemotherapy and are the result of immune activation against other organ systems. The combination of ipilimumab /nivolumab (ipi/nivo) has a 59% rate of Grade III/IV immune related adverse events (irAEs) (Larkin 2019). Up to 12% of patients with non-central nervous system disease treated with ipi/nivo experience neurologic AEs (nAEs) including encephalopathies, hypophysitis, meningitis and headache, though the incidence of nAEs is likely underestimated (Cuzzubbo 2017). QOL measures have demonstrated clinically meaningful deterioration with this combination for role functioning as well as fatigue in patients with melanoma (Schadendorf 2017). Given the high frequency of AEs with immunotherapy, patient-reported outcomes have been shown to be an effective complementary approach to early toxicity monitoring (Tolstrup 2019). Additionally, prior phase III have shown greater adverse symptom burden and functional interference, as well as decreased global health and motor function, following intensification of systemic therapy for newly diagnosed glioblastoma (Armstrong 2013).

The occurrence of neurocognitive dysfunction as assayed by rigorous, clinically relevant and validated objective neurocognitive tests has not been systematically evaluated. Bartels et al (2019) found cognitive impairment in 37% of a heterogeneous sample of melanoma patients studied cross-sectionally. They also found evidence of neuronal autoantibodies (e.g., anti-NMDAR) associated with history of ICI treatment, and a threefold higher odds of cognitive impairment in antibody positive versus negative

patients. Preclinical mouse models have shown that treatment with ICI therapy produces untoward effects on brain including mood disturbance, cognitive impairment, and neuroinflammation proving insight on a plausible mechanistic link between ICI therapy and nAEs that can influence QOL and cognitive dysfunction (McGinnis 2016).

We hypothesize that the experimental ICI arm will be impact QOL and/or neurocognitive function in either of two ways: 1) due to augmented toxicity and neuroinflammation, the experimental ICI arm may demonstrate greater decline in QOL and/or neurocognitive function; or 2) due to enhanced tumor control, the experimental ICI arm may lead to better preservation of QOL and/or neurocognitive function. Assessment of this hypothesis will provide important complementary information to the primary endpoints of this trial. In addition, this study will provide the first opportunity in a randomized control trial in GBM to evaluate these QOL and neurocognitive function impact of this immunotherapeutic approach.

11.1.2 Neurocognitive Function (NCF) Assessments

Neurocognitive function will be assessed using the Hopkins Verbal Learning Test – Revised (Benedict 1998), Trail Making Test (Tombaugh 2004), and the Controlled Oral Word Association test (Ruff 1996). These tests were selected because they are widely used and standardized psychometric instruments that have been shown to be sensitive to the impact of cancer and the neurotoxic effects of cancer treatment in other clinical trials (Gilbert 2014; Meyers 2004; Wefel 2011). The tests have published normative data that take into account age and, where appropriate, education and gender. The tests must be administered by a healthcare professional (eg, psychologist, physician, research associate, nurse) who is pre-certified by Dr. Wefel (see Section 8.1).

11.1.3 Patient-Reported Quality of Life (QOL) and Adverse Events Assessments

Symptom burden will be assessed using the MDASI-BT-modified (Armstrong. 2006). The MDASI-BT has demonstrated reliability and validity in the primary brain tumor patient population, including predictive validity for tumor recurrence (Armstrong, Mendoza et al. 2006, Armstrong, Vera-Bolanos et al. 2011). The MDASI-BT was developed and validated for use in the brain tumor patient population and typically requires less than 4 minutes to complete. It consists of 23 symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being “not present” and 10 being “as bad as you can imagine.” Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument are those commonly associated with cancer therapies and those associated with neurologic and cognitive symptoms associated with the tumor itself. The MDASI-BT also includes ratings of how symptoms have interfered with different aspects of the patient’s life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0-10 scales.

Selected PRO-CTCAE items that have demonstrated sensitivity to immunotherapy-related toxicities but do not overlap with MDASI-BT will be used to complement

MDASI-BT in assessing immunotherapy-related adverse events. Tolstrup and colleagues highlighted PRO-CTCAE items that correlate with CTCAE toxicities that very commonly or commonly occur with immunotherapy for melanoma patients. Removing items that overlap with MDASI-BT, the following PRO-CTCAE items will be monitored: abdominal pain, rash, itching, muscle pain, joint pain, pain and swelling at injection site, headache, chills, mouth/throat sores, skin dryness, hair loss, cough, taste changes, dizziness, swelling, and hot flashes. The combination of these selected PRO-CTCAE items in addition to the MDASI-BT will address all FDA-recommended patient-reported outcomes for PD1/PDL1-directed immunotherapy trials (King-Kallimanis 2019).

11.1.4 Administration of NRG-BN007 Patient-Completed Questionnaires and Neurocognitive Function (NCF) Assessments

Patient Population

All patients enrolled in NRG-BN007 who read English or French will be required to participate in the QOL/NCF study.

Time Points for Administration

See Section 4.

Administration Instructions

After the baseline assessment, questionnaires may be completed using ePRO (discussed in Section 8) or on paper at the visit. If the patient chooses to complete on paper, questionnaires are to be administered at follow-up visits, so that when a follow-up visit is delayed, completion of QOL may also be delayed. QOL should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaires are completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by mail or phone. The completed form will then be data entered into Medidata Rave.

The QOL Coversheets must be completed in Medidata Rave for each scheduled patient assessment regardless of whether the assessment was completed or not. The Coversheets notify the NRG SDMC that an assessment either has or has not been completed and collects other important information. If the assessment was completed, the Coversheet collects the date of completion and method of completion. If the assessment was not completed, the Coversheet collects the reason it was not completed. The questionnaires can be completed by phone or mail if they are not completed at an office visit.

The Neurocognitive Function Verification form must also be completed in Medidata Rave whether or not the Neurocognitive Function assessment was completed.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

The Radiation Oncology Co-Chairs (Minesh Mehta, MD; Tony J. C. Wang, MD) or NRG Oncology Headquarters approved designee will perform an RT Quality Assurance

Review after IROC Philadelphia-RT has received complete data in TRIAD. The RT reviews will be ongoing and performed remotely. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as IROC-Philadelphia RT has received complete data in TRIAD for all cases enrolled, whichever occurs first. The scoring mechanism is: **Per Protocol, Variation Acceptable, and Unacceptable Deviation**.

12.2 Medical Neuro-Oncology Modality Quality Assurance Reviews

The Principal Investigator/Neuro-Medical Oncology Co-Chairs (Andrew B. Lassman, MD; Fabio Iwamoto, MD) or NRG Oncology Headquarters approved designee will perform a Systemic Therapy Assurance Review for temozolomide, ipilimumab, and/or nivolumab for all patients who receive systemic therapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of systemic therapy treatment data. The scoring mechanism is: **1) Per Protocol, 2) Acceptable Variation, 3) Unacceptable Deviation, and 4) Not Evaluable**.

Drs. Lassman/Iwamoto/designee will perform a Quality Assurance Review after NRG Data Management Center has received complete data for cases enrolled. The reviews will be ongoing and performed remotely. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Data Management Center has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

13.1 Data Management/Collection (17-JAN-2023)

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as aNon-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those individuals requiring

write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in, the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name. Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

13.2 Summary of Data Submission (09-FEB-2021)

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting.

Summary of All Data Submission: Refer to the CTSU website

See Section 8 for TRIAD account access and installation instructions. See data submission table for TRIAD below.

DICOM Items	DICOM CT Image	**Due Within 1 week of start of RT.** Triad Time Point: *RT Digital Plan*
	DICOM Structure	
	DICOM Dose (2) Initial & Boost	
	DICOM Plan (2) Initial & Boost	
All required structures must be labeled per the tables in Sections		

5.2.4 **5.2.5**	
Imaging needed for RT review:	
Preoperative MR (in its entirety) Postoperative MR (in its entirety) Additional MRI if used for RT Planning See tables in Section 4 for diagnostic MRI sequence requirements	Triad Time Points: *Preoperative* *Postoperative* *Other*
Upon submission of the digital data via TRIAD, complete an online **Digital Data Submission Information Form (DDSI)**: https://www.irocqa.org/Resources/TRIAD	

NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

DIAGNOSTIC MRI IMAGING REQUIRED FOR SUBMISSION TO TRIAD

MRI Brain in its entirety: See bullets below for required and strongly suggested acquisition of MRI sequences. Please still submit ENTIRE MRI Brain exam □MRI with Axial T2 weighted FLAIR{preferred} or T2 TSE/FSE and 3D contrast-enhanced T1 sequences are required. □3D pre contrast-enhanced T1 sequences are strongly suggested.	TRIAD Time Points: Pre-treatment During Treatment Baseline (4 wks post RT) Follow Up Progression Other Note: For Phase II only, imaging for all time points must be submitted via TRIAD until progression has been confirmed by central review. Sites will be notified if central review of progression does not agree with site review. For Phase III, imaging for all time points must be submitted via TRIAD until progression.

NOTE: Please refrain from anonymizing the DICOM header of any exam prior to uploading into the TRIAD application. Custom DICOM editing can exclude an exam from the final analysis, due to the omission of technical data elements. These elements include, but are not limited to, the study date (0008,0020), acquisition date (0008,0022) scanner station name (0008,1010), scanner serial number (0018,1000), and any scan acquisition parameter. TRIAD has been uniquely configured to locate and

scrub all PHI from the exam's DICOM header, during the image transfer to ensure the anonymity of our trial patients.
**Please ensure selection of the correct imaging time point in TRIAD

13.3 Data Quality Portal (17-JAN-2023)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help icon Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.4 Rave-CTEP-AERS integration (17-JAN-2023)

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave**.

Treatment-emergent AEs: All AEs that occur after the start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*; and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

13.5 Global Reporting/Monitoring

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment

Status, Abbreviated Treatment and Course information, and Adverse Events as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: https://ctep.cancer.gov/protocolDevelopment/dmu.htm.

Note: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

NRG-BN007 is a randomized phase II/III trial. The randomized phase II/III trial design will provide the opportunity to discontinue further enrollment (if applicable) and follow-up for the definitive endpoint (overall survival) in the event that there appears to be no benefit from the experimental regimen.

14.1.1 Stratification

Upon entry for randomization, patients will be stratified by 1) RPA class (III vs. IV vs. V), and 2) Intent to use the Optune device.

14.1.2 Randomization

Patients will enter Step 1 to undergo central pathology review of tumors to establish histology and MGMT status. Permuted-block randomization based on above stratification factors will allocate patients meeting histology, MGMT status, and other eligibility criteria to one of two treatment arms in a 1:1 ratio.

14.1.3 Sample Size Overview

The total sample size (phase II and III combined), as described and justified in Section 14.3.2 below, is **485** randomized patients with follow-up information. The accrual rate for newly diagnosed GBM patients with unmethylated MGMT for this study is expected to be 15 eligible and randomized patients per month after a 6-month ramp-up period. Therefore, it is projected that the target total accrual will be met approximately 39 months after study activation. Further details are provided in Section 14.5.

The phase II portion of the trial will enroll 150 randomized patients. Accrual will be suspended at that time and these patients will be followed until a total of 100 PFS events have been observed. The primary analysis for the phase II portion of the trial will be performed to determine if the trial should proceed to phase III. This analysis is projected to take place around 23 months after study activation. If there is sufficient evidence based on the phase II endpoint (progression-free survival, PFS) for potential superiority for the experimental treatment, the study will then continue and complete accrual for the phase III portion of the study. If the PFS null hypothesis is not rejected, then the trial will discontinue at the end of phase II. Thus, if the study ultimately ends at Phase II, a decrease in sample size of approximately 350 patients will result, providing efficiency in the case of lack of apparent benefit.

If the study continues to Phase III, the required number of deaths for the final analysis for the phase III portion of the study is expected to be reached approximately 18 months after phase III accrual completion.

Patients who participate in phase II will contribute to phase III accrual and efficacy goals and analyses, including PFS, OS, PROs, and Neurocognitive Function.

14.2 Study Endpoints

14.2.1 Primary Hypothesis Endpoints

- Phase II: Progression-free survival (PFS), defined as time from randomization to disease progress or death.
- Phase III: Overall survival (OS), defined as time from randomization to death from any cause.

14.2.2 Secondary Endpoints

- PFS for the entire cohort (phase II/III)
- Two-year OS proportion
- Comparative frequency of specific adverse events of interest; frequency summaries for all adverse event types
- Patient Reported Outcomes (MDASI)
- Neurocognitive function (NCF)
- Selected PRO-CTCAE items (abdominal pain, rash, itching, muscle pain, joint pain, pain and swelling at injection site, headache, chills, mouth/throat sores, skin dryness, hair loss, cough, taste changes, dizziness, swelling, and hot flashes)

14.2.3 Exploratory Endpoints

- OS (if the study discontinues in phase II)
- Tumor biomarker analyses, specifically but not limited to
    - PDL-1 expression
    - Mutational burden
- MGMT protein expression

14.3 Primary Objectives Study Design (09-FEB-2021)

14.3.1 Primary Hypothesis and Endpoints

The primary endpoint for the randomized phase II portion of the study is PFS. As it can be complex to distinguish true disease progression from treatment effects (e.g., pseudoprogression) by conventional MRI scans, this trial will utilize the "PFS resolution" guidance provided in the ALLIANCE A071102 study, the updated RANO criteria (Wen, Macdonald et al. 2010) and additional recent efforts (Ellingson, Wen et al. 2017) to help distinguish between progression and pseudoprogression. In addition, the investigators will have access to an online module that will be accessible from the protocol page to help guide in making the determination of true progression versus pseudoprogression.

Based on observations from prior NRG Oncology/RTOG GBM trials among patients with MGMT unmethylated tumors, it is assumed that the median time to PFS failure is 5.7 months from randomization for the control group (Arm 1 – TMZ). It is projected that the experimental treatment with the combination of ipilimumab and nivolumab (Arm 2 – ipi + nivo) will increase the median PFS time to 9.7 months, corresponding to a 42% relative hazard reduction (HR of 0.58) in favor of the experimental arm.

The primary endpoint for the phase III study is OS. The control group median survival

time is expected to be about 14.5 months, based on prior NRG Oncology/RTOG experience in MGMT unmethylated tumors. The alternative hypothesis is that patients receiving the experimental treatment (ipi + nivo) will have a median survival time of at least 20.0 months, corresponding to a 28.0% relative hazard reduction (HR of 0.72) in favor of the experimental arm

14.3.2 How Primary Endpoints Will Be Analyzed

The phase II portion of this trial will enroll 150 randomized patients. Accrual will be suspended at that time. The definitive analyses for the phase II trial will be conducted after 100 PFS events (among both treatment arms) have been observed and central reviews of progression are completed, which is projected to take place around 23 months after study activation. The analysis will be performed on the intent-to-treat basis, including all randomized patients with follow-up information. PFS distributions for each treatment group will be estimated via the Kaplan-Meier survival function. If the stratified analogue of the log-rank (Mantel 1966) statistic has associated one-sided p-value is 0.15 or less, then the trial will conclude that continuation to the phase III portion of the trial is warranted. Detailed information on censoring rules for PFS evaluation is given in Appendix VI, in accordance with the FDA *Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ UCM071590.pdf).

The definitive primary endpoint analyses for the phase III trial will be conducted after 363 deaths (among both treatment arms) have been recorded, and will be performed on the intent-to-treat basis, including all randomized patients with follow-up information. Overall survival distributions for each treatment group will be estimated via the Kaplan-Meier survival function. If the stratified log-rank statistic has associated one-sided p-value is 0.024 or less, then the trial will conclude that the experimental arm results in improved OS over the control arm.

Additional analyses will involve statistical models to evaluate factors related to the hazard of failure for PFS and OS. These models will be used to estimate treatment effects adjusting for patient and tumor characteristics that may be imbalanced by arm, or suggest a differential treatment effect by characteristic (e.g., treatment-covariate interactions). The Cox proportional hazards regression model will be the principal approach, however, in the case that the proportional hazards assumption is inadequately met, other modeling approaches will be applied as appropriate.

14.3.3 Sample Size and Power Calculations:

This trial will provide for a reliable evaluation of whether radiation therapy in combination with ipilimumab and nivolumab will improve outcomes in newly diagnosed MGMT unmethylated GBM relative to treatment with radiation therapy and temozolomide.

For the phase II endpoint, observation of 100 PFS events among the 150 randomized patients (from both arms) provides 95% statistical power to detect an improvement in median PFS from 5.7 months in the control arm to 9.7 months in the experimental arm, corresponding to a hazard reduction of 42% (hazard ratio 0.58) at one-sided significance

level of 0.15 (and 87% power for HR of 0.65 at this same alpha). It is anticipated that at the expected accrual and control group PFS failure rate, this analysis will occur when the first 100 patients have been followed for approximately 7 months after phase II accrual completion.

For the Phase III evaluation, a total of 363 deaths are required to detect the hypothesized survival benefit of a 28% reduction in hazard of death with 85% statistical power at significance level is 0.024 (one-sided). If the study continues to Phase III, the required number of deaths for the final analysis for the phase III portion of the study is expected to be reached within approximately 18 months after phase III accrual completion (58 months from study initiation).

With regard to number of patients required and the accrual rate, given that MGMT is unmethylated in about 65% of all newly diagnosed GBMs, it is estimated that approximately 750 patients need to be screened for MGMT methylation status to obtain the targeted 485 randomized patients for the phase III trial. All patients included in the phase II PFS evaluation will be included in the primary endpoint analysis of OS for the phase III portion of the trial. Total accrual time (phase II and III combined) is anticipated to require up to 39 months (10 months phase II accrual + 7 months accrual suspension and follow-up for required PFS events + 22 months phase III accrual).

14.4 Study Monitoring of Primary Objectives (17-JAN-2023)

The trial is monitored on a continuous basis during conduct, including a monthly tally of accrual, real-time oversight of serious adverse events as required, and regular meeting of the study team to track progress and identify problems.

Interim Reports to Monitor Study Progress

Reports will be prepared twice per year and provided to the NRG Oncology external Data Monitoring Committee (DMC) until the initial treatment results have been presented/published. The interim reports will contain at a minimum the following information:

- Total patients accrued, patient accrual rate and projected accrual completion date (while the study is still accruing), and information on trial eligibility of patients enrolled
- Frequency distributions of important patient and disease characteristics by treatment arm
- Frequencies and severity of adverse events by treatment arm
- Information on timeliness of data reporting

The DMC will review the scheduled interim efficacy/futility analyses to be carried out during the Phase III portion of the trial. The DMC will also review the trial on an 'as needed' basis at any time between regularly scheduled meetings.

14.4.1 Interim Efficacy/Futility Monitoring

Phase II Monitoring

The phase II portion of the trial will enroll 150 randomized patients. Accrual will be suspended at that time and these patients will be followed until 100 PFS events have been observed (expected to be reached approximately 23 months (= 6 months ramp-up period + 10 months accrual + 7 months follow-up) from trial activation. The PFS (experimental/control) hazard ratio will be estimated. A 1-sided 0.15 level stratified log-rank test will be employed to determine if the trial should proceed to the phase III portion of the study. The trial will proceed to phase III accrual if the 1-sided p-value from the stratified log-rank test is less than 0.15; otherwise, the trial will discontinue early (at the end of phase II).

If the study continues to phase III based on either the PFS analyses above, patients on active treatment will remain on their assigned treatment arm. All patients accrued to phase II are included in the phase III accrual cohort and will be included in all further analyses.

Phase III Monitoring

Interim analyses for the OS endpoint are planned after observing approximately 50% and 75% of the required number of deaths. The futility boundary is based on the method of Freidlin, Korn, and Gray (2010) (using the 20% of target efficacy criterion) for early determination of treatment inefficacy. The efficacy boundary is derived from the method by Fleming, Harrington, and O'Brien (1984), and provides a boundary that requires a less extreme boundary for early looks than the traditional O'Brien Fleming method, at the cost of a slightly more conservative boundary for later looks. This table summarized the analyses to be conducted and the criteria for possible early determination of efficacy or futility for the primary endpoint.

Analysis	Time (mos) (from Ph II accrual inception)	Prop. Total Events	Cumulative Events (Both Arms)	Efficacy Boundary		Futility Boundary	
				Z<	P<	Z>	P>
Interim 1	33	0.50	181	3.03	0.001	0.059	0.477
Interim 2	42	0.75	272	2.97	0.002	0.298	0.383
Final	54	1.00	363	1.98	0.024	-	-

p-values one-sided

The results of the interim analyses will be reported to the NRG Oncology DMC, along with all other information described earlier. The NRG Oncology statistician will provide a provisional recommendation to the DMC, who will deliberate and ultimately render a recommendation regarding actions on the trial to the NRG Oncology Group leadership.

14.5 Accrual/Study Duration Considerations

Previously conducted trials in GBM by RTOG/NRG Oncology have achieved and sustained accrual of 39 patients/month. Screening for histology and sufficient tissue reduces the available patients by about 32%, resulting in 26 patients/month. Of these, about 65% are anticipated to be MGMT unmethylated, yielding 17 patients/month.

Monthly accrual is expected to be negligible for the first 6 months after study activation while sites obtain IRB approval and activate the trial. We conservatively assume 15 patients/month accrual. Thus, total time required to reach the accrual goal (phase II and III combined) is anticipated to be about 39 months (10 months phase II accrual + 7 months accrual suspension and follow-up for required PFS events + 22 months phase III accrual).

If at any point accrual is terminated for lack of efficacy in the treatment arm, patients remaining on study treatment who are felt to be benefiting may continue at the discretion of the treating investigator in discussion with the patient and a revised written informed consent form that will be generated as needed.

14.6 Secondary Objectives Study Design

14.6.1 Secondary Hypotheses and Endpoints

Endpoints for the secondary objectives of this trial include PFS in the entire cohort (phase II and III combined), the OS proportion (% alive) at 2 years, summary statistics on adverse event frequencies, the MDASI-BT patient-reported outcome (PRO) measure, neurocognitive function (NCF) measures, and evaluation of a novel method to detect disease progression. The following hypotheses will be evaluated:

- To determine if adding ipilimumab and nivolumab to radiotherapy significantly prolongs PFS versus adding temozolomide to radiotherapy in patients with newly diagnosed GBM without MGMT promoter methylation for the phase III part of the study
- To determine if adding ipilimumab and nivolumab to radiotherapy significantly increases the 2-year OS rate versus adding temozolomide to radiotherapy in patients with newly diagnosed GBM without MGMT promoter methylation
- To evaluate the safety of adding ipilimumab and nivolumab to radiotherapy via comparative frequency between arms of specific adverse events of interest and frequency summaries for all adverse event types
- To evaluate the effect of adding ipilimumab and nivolumab to radiotherapy versus adding temozolomide to radiotherapy on patient reported outcomes (PROs), as measured by the MD Anderson Symptom Inventory - Brain Tumor (MDASI-BT) in patients with newly diagnosed GBM without MGMT promoter methylation
- To evaluate the effect of adding ipilimumab and nivolumab to radiotherapy versus adding temozolomide to radiotherapy on selected PRO-CTCAE items (abdominal pain, rash, itching, muscle pain, joint pain, pain and swelling at injection site, headache, chills, mouth/throat sores, skin dryness, hair loss, cough, taste changes, dizziness, swelling, and hot flashes) in patients with newly diagnosed GBM without MGMT promoter methylation
- To evaluate the impact of adding ipilimumab and nivolumab to radiotherapy versus adding temozolomide to radiotherapy on neurocognitive function (NCF) in patients with newly diagnosed GBM without MGMT promoter methylation

14.6.2 Definition of Secondary Endpoints and How These will be Analyzed

Progression-Free Survival, as defined in 14.3.1, will be evaluated among all trial participants in the event that the trial proceeds to phase III (485 patients). Analysis for this endpoint will consist of estimation of the PFS curves via the Kaplan-Meier method and a stratified log-rank test. Statistical power will depend on the total PFS events accumulated at trial end, as well as any convergence of PFS curves that may occur late in follow-up, as is frequently observed in GBM trials. As it is anticipated that PFS events will exceed 375, there will be approximately 90% power to detect the 33% failure rate reduction specified for the phase II portion at one-sided alpha of 0.005.

Additional analyses may consist of estimating the hazard ratio via the Cox proportional hazards model, accounting for other prognostic covariates (and evaluating whether the proportional hazards assumption holds or whether any treatment effect is notably time-varying), and evaluating for potential treatment by prognostic covariate interactions.

Overall Survival at 2 Years

Because of concerns about a possible 'late emerging' effect of immunotherapy, estimates of 2-year OS will be compared between treatment arms, to determine whether the proportion surviving to this landmark is increased in the experimental (ipi + nivo) arm. Estimates will be obtained from the Kaplan Meier curves, and a test comparing the proportion surviving with an appropriate variance term that accounts for censoring (Greenwood's formula) will be used. The current hypothesized 2-year survival estimates based on the assumed failure rates are 30.4% in the standard arm and 42.5% in the experimental arm. These estimates depend on time-independent treatment benefit (i.e., proportional hazards) and exponential hazards, and thus realized estimates may differ.

Adverse Events

Adverse events (AEs) will be graded according to CTCAE v5.0 and PRO-CTCAE. Comprehensive summaries of all AEs by treatment arm will be generated and examined. Counts and frequencies of worst (highest score) AE per patient will be presented overall and by AE type category, separately by assigned treatment group. Complementing physician-assessed AEs will be selected PRO-CTCAE symptom items that have demonstrated sensitivity to immunotherapy-related toxicities (Tolstrup 2019) but do not overlap with MDASI-BT. The following PRO-CTCAE symptom items will be monitored: rash, itching, muscle pain, joint pain, headache, chills, mouth/throat sores, skin dryness, hair loss, cough, taste changes, dizziness, swelling, hot flashes. The PRO-CTCAE will be administered according to the schedule described in Section 4.

The proportion of patients with at least one grade 3 or higher AE will be compared between treatment arm. Similarly, frequencies for specific potentially treatment related AEs where grade 3 or higher events are noted may be compared. Any frequencies to be tested will be evaluated using the chi-square or exact test as appropriate, with two-sided significance level 0.05. It noted that no hypotheses are specified regarding expected differences in AE frequency, and that given that power can be high for frequency tables with large sample size, only clinically material differences that represent potential patient risk will be of interest.

Patient-Reported Symptom Burden

As described in (11.2), symptom burden will be assessed using the MDASI-BT-modified (Armstrong 2006). The MDASI-BT consists of 23 symptoms rated on an 11-point ordinal scale (0 to 10) to indicate the presence and severity of the symptom in the last 24 hours, with 0 being "not present" and 10 being "as bad as you can imagine." Symptoms included on the instrument are those commonly associated with cancer therapies and those associated with neurologic and cognitive symptoms associated with the tumor itself. The MDASI-BT also includes ratings of how symptoms (on 0-10 scale) have interfered with different aspects of the patient's life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. Complementing MDASI-BT will be selected PRO-CTCAE symptom items that have demonstrated sensitivity to immunotherapy-related toxicities (Tolstrup 2019) but do not overlap with MDASI-BT. This is referenced under Adverse Events. The MDASI-BT will be administered according to the schedule described in Section 4.

The expected difference in symptom burden between treatment arms will partly depend on relative disease control benefit as well as the different adverse events associated with temozolomide versus the immunotherapy combination. Of primary interest is the difference in change in symptom burden from baseline to 6 months (from the start of treatment) between the two treatment arms. While scales for the individual instrument questions are quantitative, they represent ordinal values on a bounded range rather than continuous quantities. Nonetheless, in aggregate these scores approximate continuous distributions, and appropriate transforms will be applied to improve consistency with model assumptions for the outcome measure. The mean score changes from baseline to 6 months and standard deviations will be calculated for the two treatment arms. A two-sample t-test will be used to evaluate the difference between two arms. Note that the meaningful effect size for these tools is still in debate. Cohen's widely used rules of thumb for interpreting the magnitude of difference define 0.8 standard deviation (SD) as a "large" effect size, 0.5 SD as a "medium" effect size, and 0.2 SD as a " small" effect size (Cohen 1988). Effect size below 0.5 SD, supported by data regarding the specific characteristics of a particular quality of life assessment or application, may also be clinically meaningful (Sloan 2005). Assuming 390 patients (~80% of the patients enrolled in the treatment trial) will participate in the QOL study and have both baseline and 6-month follow-up data, the study will have over 80% statistical power to detect effect sizes (mean difference between arms / standard deviation) of 0.30 or greater.

In addition to investigating the difference in score change from baseline to 6-months between two arms, we will also conduct a longitudinal analysis that will focus on patterns of score change over time points (baseline, t1, t2,) in MDASI-BT. It is posited that patients undergoing immunotherapy may experience fewer of the traditional 'side-effects' associated with cytotoxic cancer therapies, but may have greater neurologic and cognitive effects during active treatment. Over the longer period, greater disease control due to immunotherapy may lead to more favorable outcomes with respect to symptoms burden. This trial is uniquely positioned to evaluate this experience. To this end, we will implement mixed effects models for repeated measures to evaluate the MDASI-BT scores longitudinally. Mixed effects models describe the rate of change in scores over time for each treatment arm (fixed effect), taking into account the between-patient variability by incorporating each patient's individual starting point and individual rate of change (random effect) into the model. The MDASI-BT scores will be the dependent variables in these models. Independent variables will include time, study arm, baseline stratification factors, and the interaction between time and study arm. An unstructured correlation matrix will be used to model the correlation between repeated observations. Of particular interest is the treatment group by time interaction effect, representing a difference in symptom burden experience over time among patients in the two groups. To control for multiple comparisons among time points and treatment groups, a hierarchical analytic approach described below will be undertaken:

a) Perform an overall (omnibus) test of the treatment group by timepoint interaction effect. Prior to this test, model characteristics, including trajectories of scores may be examined via regression diagnostics within treatment arm, and appropriate functional form for the models then specified.
b) If an overall difference in score trajectories by arm is confirmed, then
    a. test timepoint-specific differences between arms
    b. characterize treatment-arm specific patterns over time within the group treatment groups (changes from baseline, shape of the trajectory, etc.)
c) If overall differences by arm cannot be established, then further characterization of the symptoms experience within the immunotherapy arm may be undertaken, to provide a detailed history of the experience.

Neurocognitive Function

As described in (11.1), neurocognitive function (NCF) will be assessed using the Hopkins Verbal Learning Test – Revised (Benedict 1998), Trail Making Test (Tombaugh 2004), and the Controlled Oral Word Association test (Ruff 1996). These widely used and standardized psychometric instruments have been shown to be sensitive to the impact of cancer and the neurotoxic effects of cancer treatment in other clinical trials (Gilbert 2014; Meyers 2004; Wefel 2011). The tests have published normative data that account for age and, where appropriate, education and gender. The NCF assessments will be administered according to the schedule described in Section 4.

The established metric for clinically significant change is the Reliable Change Index (RCI; Jacobson 1991). The RCI is derived from the standard error of measurement of each test

and represents the 90% confidence interval for the difference in raw score from baseline to the next assessment that would be expected if no real change occurred:

RCI = 1.64(standard error of difference), where standard error of difference
= $[2(\text{standard error of measure}^2)]^{1/2}$, and standard error of measure
= $\text{standard deviation}_1[(1 - r_{xy})^{1/2}]$

This yields the following RCI values for each test in the Clinical Trial Battery:

NCF Test	RCI Value
HVLT-R Total Recall	5
HVLT-R Delayed Recall	3
HVLT-R Delayed Recognition	2
TMT Part A	12
TMT Part B	26
COWA	12

At each assessment, change in raw test score relative to baseline are calculated, and declines in a score that meets or exceeds the RCI value is categorized as a failure. Cognitive failure (CF) is defined as a decline on at least one of the Clinical trial Battery tests (HVLT-R, TMT, COWA) that meets or exceeds the RCI value.

The key objective for the NCF analysis is to compare the **cognition failure free (CFF) rate** between the two treatment arms. The primary comparison of treatment effect on CFF rates will be based on a 2-sided 0.05-level test for cause-specific hazard ratio (CHR) in a Cox proportional hazards model. A 2-sided test is selected because the impact of the experimental ICI on neurocognitive function in comparison to the control arm is uncertain (Section 11.1.1).

Participation in the neurocognitive function study is mandatory for all patients that are proficient in English and French-Canadian, given that the psychometric properties for translated tests are either not known or not as robust. Thus, we very conservatively estimate at least 70% of patients will be eligible and evaluable for the primary analysis of CFF rate (with exception of patients who are not English or French-Canadian speaking (~2-5%), early withdrawal of consent, lack of follow-up, or refusal to participate, etc.) but there could be as high as 90% of the full trial population. We assume that 6-month CF rate in the experimental ICI arm is 30%, which translates to 12-months CF rate of 51% assuming exponential distribution. We expect that the control arm will improve 12-month CFF by 11% (i.e. from 49% to 60%). This difference translates to a hazard ratio (TMZ vs. ICI) of 0.72. Assuming uniform accrual of 32 months with an additional follow-up of 18 months after accrual completion, the following table describes the percentage of patients evaluable for CFF, the effective sample size, expected number of CFF events by the end of the trial, and statistical power to detect the hypothesized effect size, using a 2-sided 0.05 level test, assuming the percentage of patients evaluable for the CFF endpoint ranges between 70% and 90%. Note that the timing of this analysis will be based on the timing for primary analysis of NRG-BN007.

Percentage of patients evaluable for CFF endpoint	Effective sample size evaluable for CFF endpoint	Estimated number of CFF events by the end of the trial	Power to detect hypothesized effect in CFF (HR = 0.72)
70%	340	271	80%
80%	388	310	84%
90%	437	348	88%

As a secondary analysis, the cumulative incidence function estimator will be used to estimate the median time to cognitive failure in the presence of precluding disease progression or death (Korn and Dorey 1992). Gray's test will be used to test for a statistically significant difference in the distribution of CFF (Gray 1988). Results will be interpreted in light of competing disease progression and death, which may be frequent.

Additional exploratory analysis will involve assessing the change in cognitive failure over time. For each NCF test, patients will be categorized as deteriorated (decline per the reliable change index [RCI]) or not deteriorated at each assessment. A generalized estimating equations (GEE) model with a binary response will be used to assess if there is difference between the experimental and control arms in terms of RCI-determined NCF decline over time. The GEE model will include fixed effects for treatment, assessment time point, and the treatment-by-time interaction, controlling for baseline score stratification variables and other covariates of interest.

Missing Data Considerations for PRO and NCF Studies
A certain degree of attrition from the PRO and NCF studies, due to both patient refusal or other reasons for missed assessments, and deterioration/mortality due to disease, is expected. Characteristics of patients with missing data will be evaluated to identify imbalance in factors such as treatment, baseline scores, and other clinical and demographic features. Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 2010, Verbeke 2000. If missing data are MCAR or MAR, then a mixed model using maximum likelihood is sufficient because all available data can be used. A joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

14.7 Gender/Ethnicity/Race Distribution

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**		
	Ethnic Categories		
	Not Hispanic or Latino	Hispanic or Latino	Total

	Female	Male	Female	Male	
American Indian/Alaska Native	1	2	0	0	3
Asian	3	5	0	0	8
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	6	9	0	0	15
White	156	231	9	15	412
More Than One Race	2	5	0	0	5
Total	169	253	9	15	445

Racial Categories	**INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	
Asian	0	0	0	0	
Native Hawaiian or Other Pacific Islander	0	0	0	0	
Black or African American	0	0	0	0	
White	15	22	1	2	40
More Than One Race	0	0	0	0	
Total	15	22	1	2	40

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APPENDIX I: CTEP COLLABORATIVE AGREEMENTS LANGUAGE

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually*

Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX II: NIVOLUMAB/IPILIMUMAB MANAGEMENT ALGORITHMS (INVESTIGATOR BROCHURE V. 20) (08-APR-2022)

Note that the algorithms below are to help guide therapy. If the algorithms recommend management that conflicts with other sections of the protocol, follow the directives in the other sections of the protocol.

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.

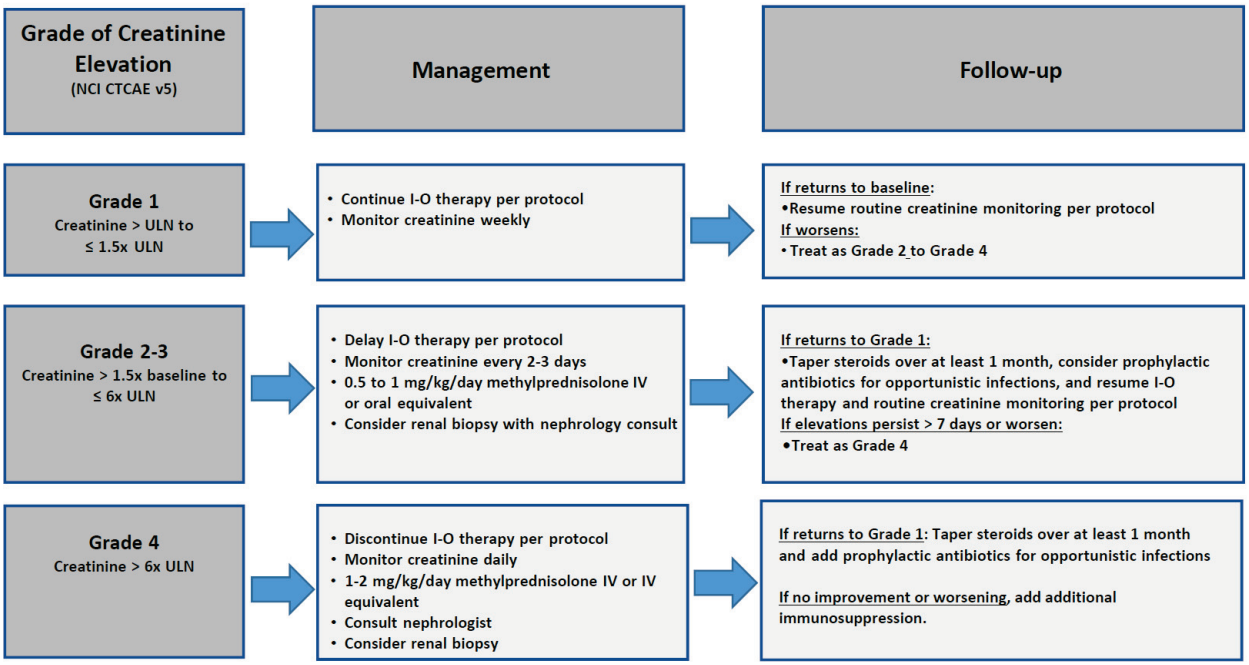
Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: 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 (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

Renal Adverse Event Management Algorithm

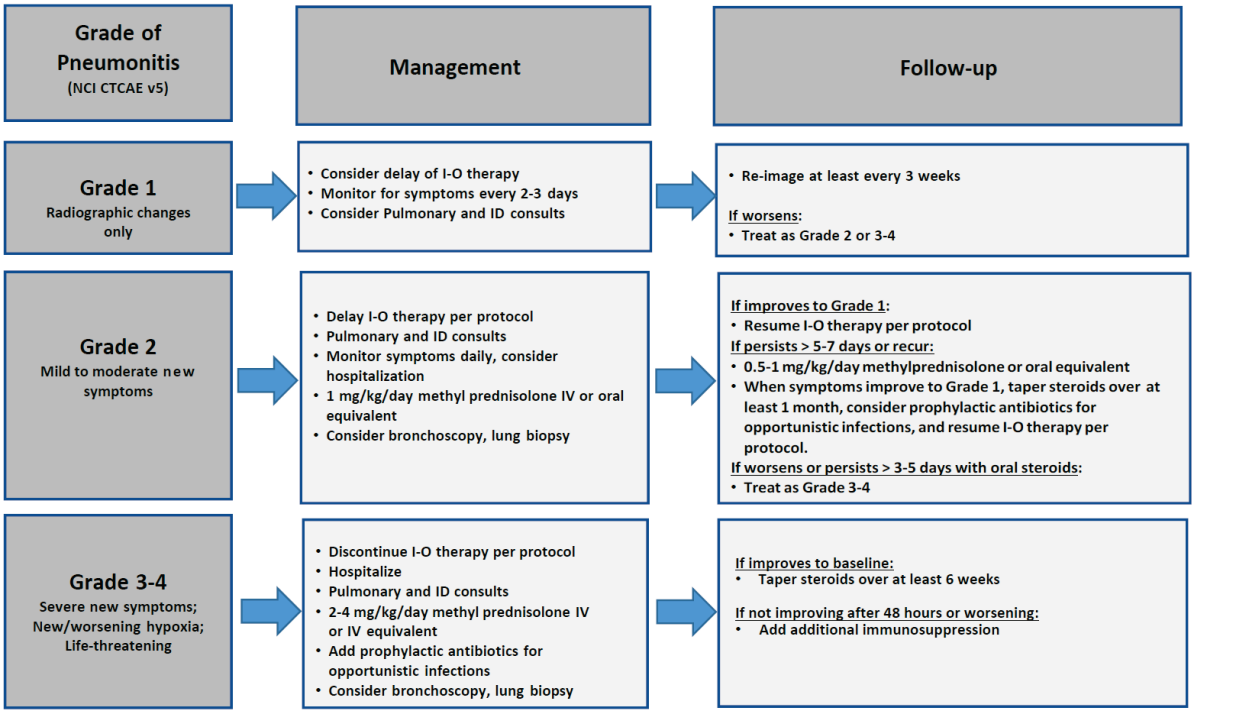
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

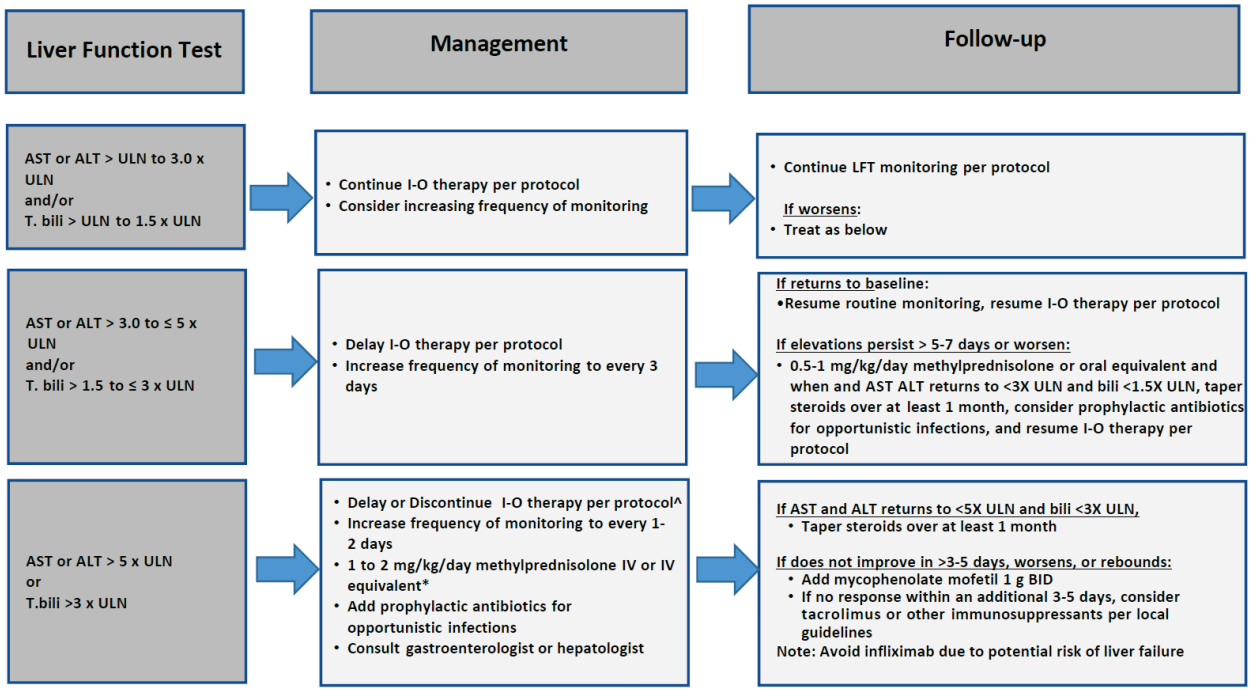
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



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

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.



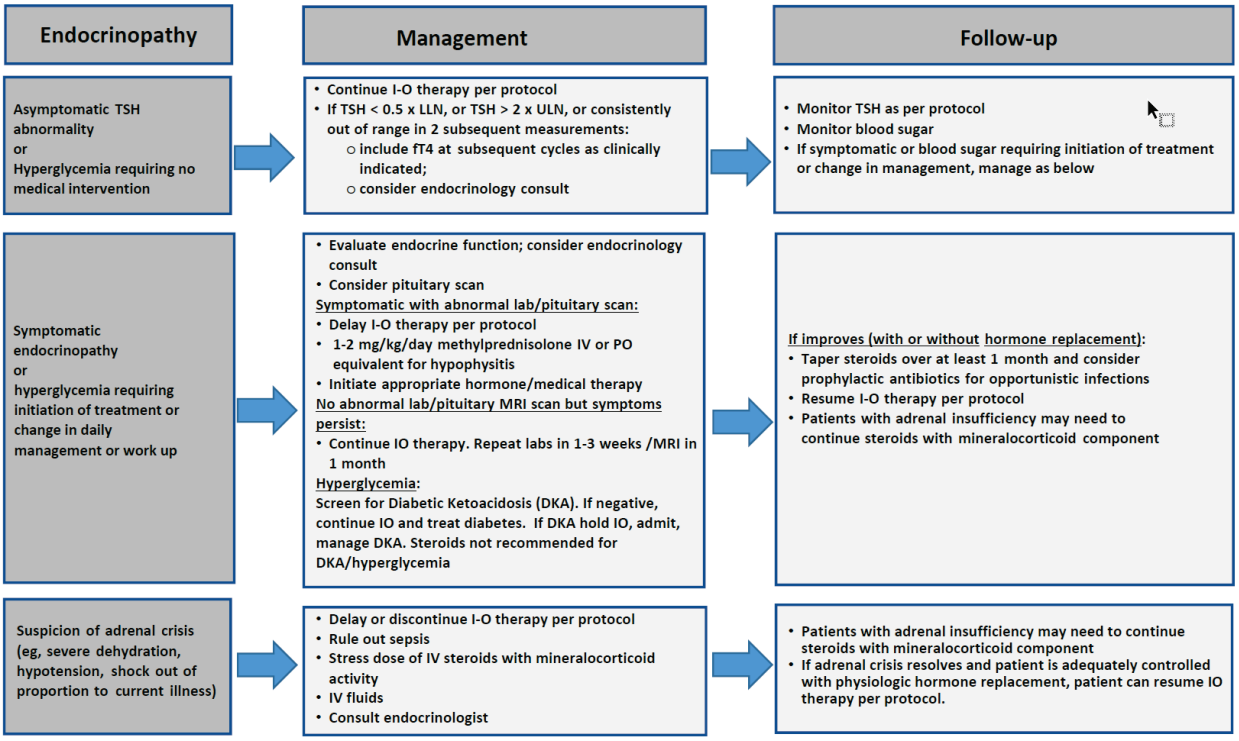
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

^ Please refer to protocol dose delay and discontinue criteria for specific details.

*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

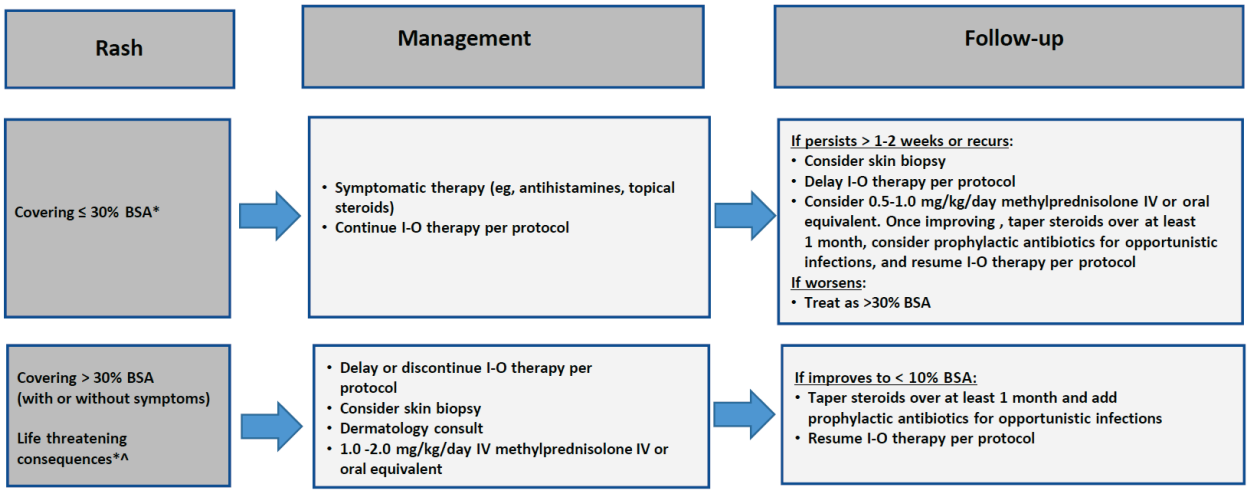
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



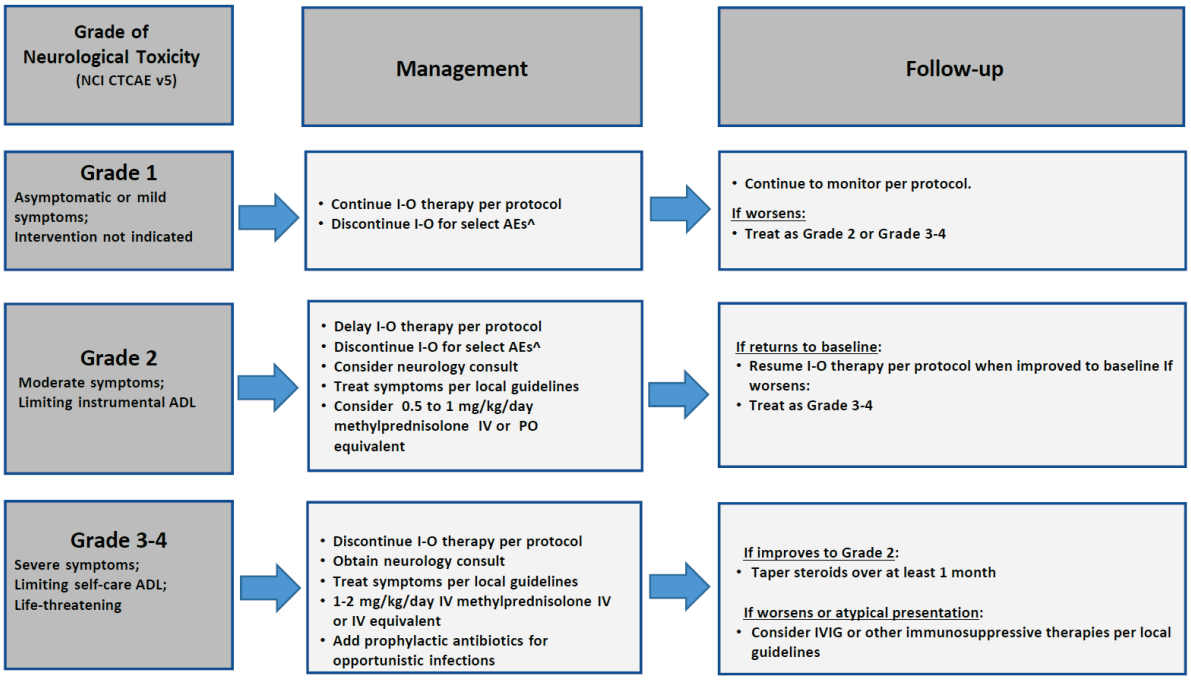
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

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

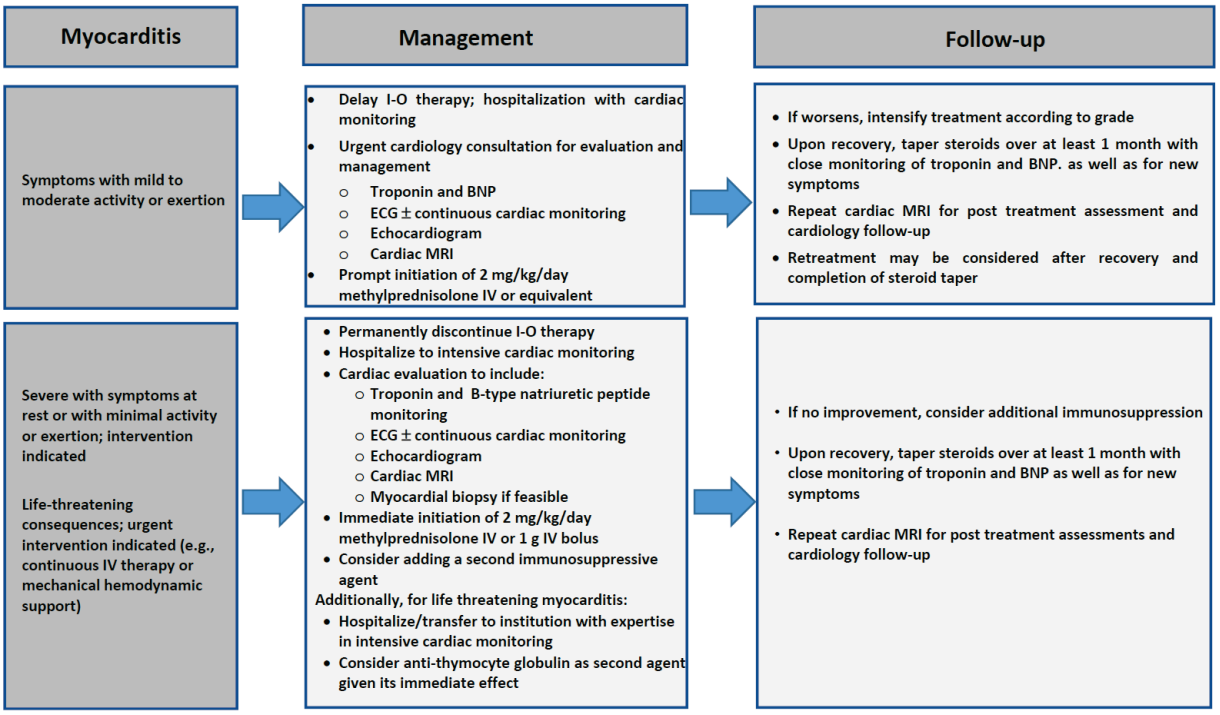


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

Myocarditis 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 (eg, prednisone) at start of tapering or earlier, after 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.

Today's Date _____/_____/_____ Patient Initials _____ Patient Study ID _____

APPENDIX III: TEMOZOLONIDE PILL DIARIES

TEMOZOLOMIDE PILL DIARY

NRG-BN007

A RANDOMIZED PHASE II/III OPEN-LABEL STUDY OF IPILIMUMAB AND NIVOLUMAB VERSUS TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED MGMT (TUMOR O-6-METHYLGUANINE DNA METHYLTRANSFERASE) UNMETHYLATED GLIOBLASTOMA

Concurrent Treatment Phase

INSTRUCTIONS TO THE PATIENT:

- Complete one form during the radiation treatment phase and bring to your clinic visits.
- Take Temozolomide each day starting on the first day of radiation until the last day of radiation
- Your dose is _____ mg. You will take _____ capsules daily:

  ____ 5 mg _____ 20 mg _____100 mg _____140 mg _____180 mg _____250 mg
  .
- Record the date, the number of pills you took, and the time you took them.
- If you have any comments or notice any side effects, please record them in the Comments column.

Today's Date _____/_____/_____ Patient Initials _____ Patient Study ID _____

Day	Date	# Pills Taken						Time	Comment
		5mg	20mg	100mg	140mg	180mg	250mg		
1									
2									
3									
4									
5									
6									
7									
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Patient's Signature: _____ Date: _____

Today's Date _____/_____/_____ Patient Initials _____ Patient Study ID _____

TEMOZOLOMIDE PILL DIARY

NRG-BN007

A RANDOMIZED PHASE II/III OPEN-LABEL STUDY OF IPILIMUMAB AND NIVOLUMAB VERSUS TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED MGMT (TUMOR O-6-METHYLGUANINE DNA METHYLTRANSFERASE) UNMETHYLATED GLIOBLASTOMA

Adjuvant Treatment Phase

INSTRUCTIONS TO THE PATIENT:

- Complete one form for each cycle (28 days) and bring to your next clinic visit.
- Take Temozolomide on day 1-5 every 28 days for 6-12 cycles.
- Your dose is _____ mg. You will take _____ capsules daily:

  ____ 5 mg _____ 20 mg _____100 mg _____140 mg _____180 mg _____250 mg
- Record the date, the number of pills you took, and the time you took them.
- If you have any comments or notice any side effects, please record them in the Comments column.

Today's Date _____/_____/_____ Patient Initials _____ Patient Study ID _____

Day	Date	# Pills Taken						Time	Comment
		5mg	20mg	100mg	140mg	180mg	250mg		
1									
2									
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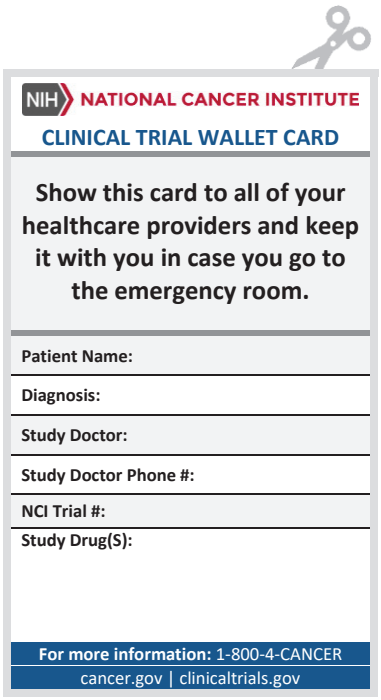
Patient's Signature: _____ Date: _____

APPENDIX IV: PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

APPENDIX V

RECURSIVE PARTITIONING ANALYSIS (RPA) CLASSIFICATION

Class III	Age < 50 and KPS 90-100
Class IV	Age < 50 and KPS < 90; **OR** age ≥ 50 and KPS 70-100 and partially or total resected with no worse than minor neurologic function impairment
Class V	Age ≥ 50 and KPS 70-100 and underwent prior partial or total tumor resection with worse than minor neurologic function impairment

APPENDIX VI (09-FEB-2021)

CENSORING RULES FOR PROGRESSION-FREE SURVIVAL (PFS) ENDPOINT

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of documented progression with protocol specified continued follow-up in all treatment arms	Progressed
New anticancer treatment started	Date of documented progression with protocol specified continued follow-up in all treatment arms	Progressed
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of documented progression, or if this date is unknown, date of death	Progressed

APPENDIX VII (08-APR-2022)

MEDIDATA PATIENT CLOUD EPRO OPERATIONAL INSTRUCTIONS

Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata's *Patient Cloud* application is preferred but not mandatory. Patients who will be submitting PRO data via the *Patient Cloud* mobile ePRO app must be registered to the ePRO application by an authorized site staff after the patient has been registered to the study. Patients may use their own mobile device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to the ePRO mobile app with their passwords or their PIN codes on the same device.

Patient Cloud Mobile ePRO Application Download

Note that there are multiple versions of the *Patient Cloud* mobile ePRO app. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error upon logging into the ePRO mobile app if the wrong version is downloaded. This protocol is using the current version with the following logo:

Search "Patient Cloud" in the app store and select the app with this icon

CRA Site Users

Site staff require access to the ePRO application. This access is granted through iMedidata, and is similar to the process of obtaining access to Rave studies. Site staff will receive an invitation to the ePRO application which they must accept in order to begin registering patients. Staff that have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Medidata Account Activation and Study Invitation Acceptance instructions are located on the CTSU members' website under Data Management > Rave Resource Materials. Site staff will not be able to access the study in the ePRO application until all required Rave and study specific trainings (eLearnings assigned in iMedidata) are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the Data Management tab and further under the Rave subtab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

CRA Instructions for Preparing a Site Device
Sites conducting studies entirely on-premises, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to the *Patient Cloud* mobile ePRO app with their passwords or their PIN codes on the same device. If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the *Patient Cloud* mobile ePRO app to the device and set the mobile app to multi-user mode if applicable. **Verify that the correct ePRO mobile app (*Patient Cloud* OR *Patient Cloud ePRO*) is downloaded by verifying the correct version with the study team. Note only one version of the mobile app is active per protocol. This protocol is using the current version with the cloud and dot logo. It is named simply "Patient Cloud" in the app stores.

To switch from personal mode (default setting) to multi-user mode:

1. Tap *About* at the bottom of the log in screen.
2. Scroll to the bottom and tap *Advanced User*.
3. Tap *Mode*, then select *Multi-User*.
4. Tap *Yes* to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

PATIENT USERS
To use the *Patient Cloud* mobile ePRO app, patients will need to use their own device (IOS, Android phone or tablet) or one provided by the site.

In both cases, short term data will only appear on the device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "*Submit*" button and data will no longer be visible on the device.

Quick Reference Cards (QRCs) are available to download and print for use by the site, and to hand out to the patient if desired. The QRCs can be found here and include: *Patient Cloud,* iOS App Download, Account Activation with Email and Password, Account Activation with Multiple Studies Using Existing Email Address, and Troubleshooting. **A Medidata login is required to access the Quick Reference Cards so sites must provide them to study participants, if desired.**

PATIENT INSTRUCTIONS FOR ACCESSING *PATIENT CLOUD* USING YOUR PERSONAL DEVICE

Downloading the Patient Cloud ePRO App
If you are using your personal device, and you do not have the *Patient Cloud* mobile ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google

account associated with the device. If the *Patient Cloud* mobile app is already on the device, or if you are using a provider's device, you can skip this section. There are multiple versions of the mobile app available. Ensure that the correct version of the ePRO mobile app is downloaded (see below).

You will need an email address that you agree to use for this purpose. The e-mail address is needed to uniquely identify you on the ePRO Application, and to reset your password if needed. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS (Apple mobile devices):

1. An Apple ID is required for downloading the *Patient Cloud* mobile ePRO app.
2. Tap the *App Store* icon.
3. Search for the appropriate mobile app (named "Patient Cloud" and using the following ico) and follow the installation instructions. 

For Android:

1. A Google account is required for downloading the *Patient Cloud* mobile ePRO app
2. Tap the *Play Store* icon.
3. Search for the appropriate mobile app (named "Patient Cloud" and using the following icon) and follow the installation instructions. 

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the *Patient Cloud* mobile ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud mobile app.

1. If registering from the Patient Cloud mobile app, **tap *Register* on the bottom of the log in page.** If registering on the web, open the URL shield.imedidata.com on a web browser.

2. Enter your activation code and tap *Activate*.
3. On the next page, read the instructions and tap *Next*.
4. Read the privacy notice and tap *I agree*. Then tap *OK* to confirm.
5. Enter and confirm your email address. Tap *Next*.
6. Enter and confirm your password. Tap *Next*.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap *Create my account* to complete your registration.

If you registered on the *Patient Cloud* mobile ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the *Patient Cloud* mobile ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap *Log in*.

Note: If you do not remember your password, tap *Forgot Password*, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the *Patient Cloud* mobile ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the *Patient Cloud* mobile ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap *Yes* when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu (three vertical dots) on the top right corner of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap *Forgot PIN* and you can access the app using your email and password. If you are logged in to the app you may reset your PIN by tapping the options menu (three vertical dots) in the top right corner of most pages and selecting *Set PIN*.

Resetting Your Password

If you are logged on to the mobile app you can reset your password by using the options menu at the top right of most pages.

1. Tap the options menu icon (three vertical dots) in the top right corner of most pages.
2. Tap Reset Password.

3. Follow the instructions to reset your password.

If you are not logged on to the mobile app you can reset your password by selecting *Forgot Password?* on the app's home screen.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a + icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

To complete and submit form(s):

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. If given the opportunity to review and update, review your responses by scrolling down the list; if you need to change an answer, tap the question to go back and change the answer.
4. When you are ready to submit, tap *Submit Your Data*.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

PATIENT COMPLIANCE

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

You can determine if a patient has already submitted an assessment via ePRO by looking in the patient's chart in Rave for the folder labelled "ePRO…" followed by the appropriate assessment time. If there is a completed icon ( ) the assessment was completed via ePRO.

Security
All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks "Submit," the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email address is stored for what purpose? The patient's email links the device used and ePRO account to where the data is stored. The patient's email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.

The Patient Cloud ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud ePRO are encrypted and therefore this information cannot be read if intercepted while in transit.

Site checklist for activities prior to consenting a patient

- ☐ Accept study invitation at iMedidata.com
  - Site staff must be rostered in RSS and have received an invitation to the ePRO application
- ☐ Site staff must have already completed required eLearning assigned in iMedidata for the ePRO application before gaining access to the study in Rave. Contact the LPO to request appropriate Rave access to register patients in the ePRO application.
- ☐ Verify the iOS or Android operating system is using the most current version
- ☐ Verify that the correct ePRO mobile app is being used. Note only 1 version of the ePRO mobile app is active per protocol. This protocol uses the current version named "Patient Cloud" with the cloud and dot icon . 
- ☐ If using institutional shared devices, for the first patient only: Verify the ePRO mobile app is in Multi-User mode.

Note: Sites should consider copying this site checklist and placing it in the clinic or area where site is consenting patients to ePRO and also copy the correct image and name of the ePRO mobile app version with it to help remind staff and patients of the correct version being used in the protocol. Sites should also inform patients that short term data will only appear on the device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and data will no longer be visible on the

device.

Patient withdraws study consent or withdraws consent from participating on ePRO
CRA must instruct the patients that are participating on ePRO who decide to withdraw consent to delete the App from their smart phones. This will prevent QOL reminders from being sent to the patient.