NRG ONCOLOGY

NRG-BN005
(ClinicalTrials.gov NCT #03180502)

A PHASE II RANDOMIZED TRIAL OF PROTON VS. PHOTON THERAPY (IMRT) FOR COGNITIVE PRESERVATION IN PATIENTS WITH IDH MUTANT, LOW TO INTERMEDIATE GRADE GLIOMAS

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
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Agent	**Supply**	**NSC #**	**IND #**	**IND Sponsor**
Temozolomide	Commercial	362856	Exempt	N/A

Participating Sites

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

Document History

	Version/Update Date
Amendment 1	August 22, 2018
Activation	June 7, 2017

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<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>To submit site registration documents:</th><th>For patient enrollments:</th><th>Submit study data</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU Regulatory Submission Portal.

Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)
Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.
For regulatory questions call the CTSU Regulatory Help Desk at 1-866-651-CTSU</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at 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 log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> Contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU Website is located at https://www.ctsu.org.</td></tr>
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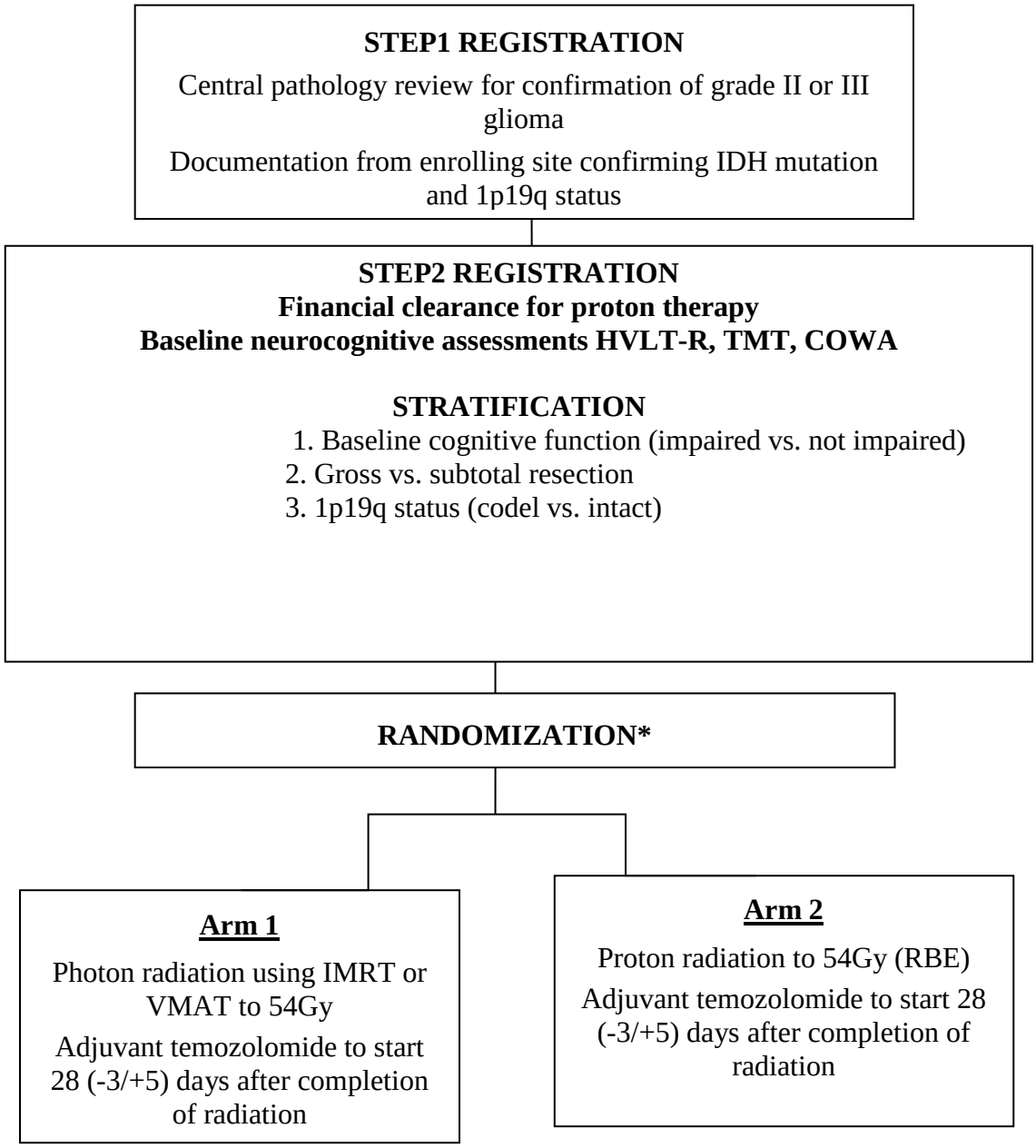
SCHEMA (22-AUG-2018)



***** Randomization is 2:1 in favor of protons

Impaired cognitive function requires a Clinical Trials Battery composite score < -0.5.

1. OBJECTIVES

1.1 Primary Objective

To determine whether proton therapy, compared to IMRT, preserves cognitive outcomes over time as measured by the Clinical Trial Battery Composite (CTB COMP) score (calculated from the Hopkins Verbal Learning Test Revised (HVLT-R) Total Recall, HVLT-R Delayed Recall, HVLT-R Delayed Recognition, Controlled Oral Word Association (COWA) test, Trail Making Test (TMT) Part A and Part B.

1.2 Secondary Objectives

1.2.1 To assess whether treatment with proton therapy preserves neurocognitive function as measured separately by each test, HVLT-R, TMT Parts A & B, and COWA.

1.2.2 To document and compare treatment related symptoms, overall symptom impact, and disease related factor groupings, utilizing the M.D. Anderson Symptom Inventory Brain Tumor (MDASI-BT), for both treatment arms.

1.2.3 To assess whether treatment with proton therapy, compared to IMRT, results in superior quality of life as measured by the LASA scale.

1.2.4 To compare local control patterns of failure and overall and progression-free survival between the two treatment arms.

1.2.5 To assess adverse events

1.2.6 To compare Illumnia MethylationEPIC beadchip array-derived IDH and 1p19q status determined centrally to that submitted by enrolling sites.

1.3 Tertiary Objectives

1.3.1 To assess the impact of chemotherapy use on cognitive outcomes, symptom outcomes and quality of life.

1.3.2 To assess dose-response relationships between neuro-anatomic dosimetry and cognitive outcomes within and between treatment arms

1.3.3 To evaluate the association between tumor molecular status and cognition at baseline and within and between treatment arms over time

1.3.4 To assess patterns of failure and pseudoprogression as a function of radiation delivery type and dose received.

1.3.5 To assess local control, overall survival and, progression free survival in IDH mutant grade II and III tumors.

1.3.6 To collect blood samples for future studies seeking to correlate changes in peripheral blood biomarkers (genes, microRNA, proteins, lymphocyte count, melatonin, etc) and the study endpoints.

1.3.7 To document and compare the impact of low to intermediate gliomas and therapy on patients' work and activity participation (The Work Productivity and Activity Impairment (WPAI:GH) Questionnaire: General Health version 2.0) as well as the relationship between changes in patients' work and activity participation and neurocognitive function and patient reported symptoms and interference.

2. BACKGROUND

2.2 Introduction

WHO grade II and III gliomas are commonly treated with radiation therapy. However, the utilization of radiation therapy is associated with the potential for radiation-induced

cognitive decline. Cognitive decline following cranial irradiation is especially problematic for brain tumor survivors as it is associated with reduced quality of life. (Kiebert 1998; Li 2008) Exposure of uninvolved normal brain, even to low doses of radiation, has a significant impact on cognitive function in patients with lower grade brain tumors. (Gondi 2013; Armstrong 2012) Proton therapy is a radiation modality, which spares uninvolved brain tissues from exposure to low dose radiation to a substantially greater degree compared to traditional photon radiation. Proton therapy has been safely used in the treatment of brain tumors, including WHO grade II and III gliomas, with low toxicity rates and excellent disease control. However, it is unknown if the improved sparing of normal brain tissues, relative to photon therapy, is associated with improved cognitive function or overall symptom burden. To this end, we propose a randomized phase II trial comparing intensity modulated radiation therapy, (i.e. best photon therapy, IMRT) and proton therapy in patients with IDH mutant, WHO grade II or III gliomas. Our long-term goal is to reduce the burden of radiation induced cognitive decline and symptom burden through the use of proton therapy, thereby improving long-term quality of life in brain tumor survivors. Our hypothesis is that the superior normal tissue sparing offered by proton therapy will lead to superior preservation of cognitive function in comparison to patients treated with photon-based therapy.

Despite the efficacy of radiation therapy in the treatment of central nervous system (CNS) tumors, substantial concerns exist regarding radiation adverse effects. Concerns regarding long-term radiation effects, including vascular damage, endocrine deficits, and secondary malignancies are often voiced. However, the potential for progressive cognitive decline following brain radiation is often a paramount concern for both patients and practitioners. Radiation-induced cognitive impairment is known to occur in up to 50-90% of adult brain tumor patients 6-months after radiation. (Meyers 2006; Johannesen 2003; Crossen 1994) Adults that receive radiotherapy for CNS tumors face significant effects on quality of life with the most commonly reported symptoms being fatigue, changes in mood and cognitive dysfunction. (Gleason 2007; Meyers 1998)

Historically, the overwhelming majority of radiation treatments have been delivered using photon based techniques. Douw et al retrospectively evaluated patients with low-grade gliomas treated with or without radiotherapy and found radiotherapy use to be associated with impaired attentional functioning and executive function. (Douw 2009) Gondi et al (2013) prospectively evaluated the effects of radiation on cognitive function in adult patients with low-grade brain tumors treated with advanced photon radiation techniques including IMRT. The trial included both baseline and post-radiotherapy assessments utilizing formal neurocognitive tests. Exposure of the bilateral hippocampi to doses as low as 7.3Gy was associated with long-term memory impairment. We retrospectively evaluated patients with grade II or III gliomas, treated with IMRT at The University of Texas MD Anderson Cancer Center and seen by the Neuropsychology service for formal cognitive testing. Testing included HVLT-R Total Recall, HVLT-R Delayed Recall, HVLT-R Delayed Recognition Discriminability, COWA and TMT Parts A and B. All patients had baseline and post RT testing. Given the retrospective nature of this analysis there was variability in the timing of post radiation assessments (mean 4.2mo, range 2 to 24). Patients with progressive disease (n=2) were excluded. One

patient, who underwent surgery and suffered a perioperative stroke, was excluded as well. Raw test scores were evaluated using reliable change index (RCI) criteria. Neurocognitive failure for each test was defined as the patient's raw score change greater than the RCI. Fifty-two patients with grade WHO II or III glioma, baseline and follow-up cognitive testing within 2 years of radiation therapy were evaluable. RCI results are as follows; HVLT-R Total Recall 25% declined, HVLT-R Delayed Recall 12% declined, HVLT-R Delayed Recognition Discriminability 21% declined, COWA 17% declined TMT Part A and B, 14 and 15% declined respectively.

Patients with lower grade glioma are younger, have longer survival times than many patients with more malignant glioma, and often try to return to regular life roles including employment. Yet very little is known about the impact of their disease or their treatments on their ability to work and participate in their usual activities. Moreover, we do not have information on the relationship between NCF or symptoms and patients' work and activity participation. The Work Productivity and Activity Impairment (WPAI:GH) Questionnaire: General Health version 2.0 (Reilly, 1993) is a brief 6 item patient reported outcome measure that asks about the effects of health problems on ability to work and perform regular activities. The WPAI:GH produces outcome variables that include Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment. As a tertiary aim we will explore the impact of low and intermediate grade gliomas as well as therapies used to treat these tumors on work and activity participation, and the relationship between these with cognitive function and symptom burden.

2.3 Proton Therapy

While treatment planning and delivery have advanced dramatically, the physical limitations of photon interactions within the body may now preclude further sparing of normal tissues. Photons deposit dose as they travel through normal tissues both upon entrance and exit after passing through the target. In contrast to photons, which are absorbed exponentially throughout the course of the beam path, protons have a finite range that is dependent on their initial energy. Protons traverse the beam path and then deposit most of their energy in the target near the Bragg peak with no exit dose. Exploring potential therapeutic alternatives to photon therapy, Dennis et al. (2013) published a dosimetric comparison of passive scattering proton therapy (PSPT) vs. IMRT in patients with brain tumors and found superior sparing of both contralateral and ipsilateral normal brain structures. The decreased dose to critical normal brain tissue resulting from protons is predicted to translate into improved cognitive function based on radiation dose cognitive effect models. (Merchant 2008)

In addition to compelling dosimetric studies, initial clinical studies of proton therapy have suggested efficacy and indicate that further study is warranted. Investigators from the Massachusetts General Hospital first utilized mixed photon/proton treatments for dose escalation studies including patients with WHO grades II and III gliomas. (Fitzek 2001) Investigators from the University of Heidelberg, which employs scanning beam proton delivery technology, have also reported on 19 patients treated for low-grade gliomas. Similar to photon-based treatments, their initial results suggest high rates of tumor control and acceptable toxicity rates. (Hauswald 2012) In a recent study Shih et al. (2015)

reported results of a prospective trial, which enrolled patients with grade II gliomas. In addition to reporting excellent disease control rates, they assessed cognitive function and quality of life following proton therapy. Twenty patients, all with supra-tentorial tumors were enrolled. With a median follow-up of 5.1 years, as compared to baseline, measures of cognitive function were stable to improved with no patients experiencing cognitive failures. However, as this was an uncontrolled, non-comparative trial it is unclear if this relative stability reflects the absence of an expected practice effect in this treated population. Sherman et al. (2015) reported that compared to normative practice effects, these patients exhibited less improvement in the domains of processing speed, executive function, and verbal memory. In summary, in order to document the potential benefits of proton therapy in comparison to best photon therapy (IMRT), prospective randomized trials are necessary.

2.4 WHO Grade II and III Gliomas

Radiation therapy plays an integral role in the treatment of gliomas. As survival rates increase the potential impact of radiation induced adverse effects, including cognitive dysfunction, grows. For WHO grade II gliomas, combined modality therapy has contributed to improved survival rates and early radiation therapy is associated with improved progression-free survival. (Shaw 2012; van den Bent 2005) However, the timing of radiotherapy, i.e. whether delivered as adjuvant or salvage, remains controversial. The existing controversy centers on the negative effects of radiation on cognitive function and quality of life, which are of special importance in a patient population with a long life expectancy. For patients with WHO grade III tumors adjuvant radiation therapy is considered standard. Increasingly, mutational profiling allows for the prediction of favorable outcomes for subsets of patients. In particular, grade III gliomas with an IDH mutation have favorable outcomes and numerous patients will achieve long-term survival similar to that seen for patients with WHO grade II tumors. (Olar 2015; Brat 2015; Eckel-Passow 2015) As such these patients are at substantial risk for cognitive decline following radiation therapy.

2.5 Radiation dose for IDH mutant gliomas

For WHO grade II gliomas, dose escalation has not proven to be beneficial. The EORTC 22844 trial compared 45 vs. 59.4 Gy doses each delivered in 1.8 Gy fraction sizes in patients with WHO grade I or II lesions. Overall and progression free survival rates were not significantly different and patients treated to the higher dose had inferior quality of life scores (Kiebert 1998). Including only WHO grade II lesions, the Intergroup trial randomized between 50.4 and 64.8Gy (Shaw 2002). Here again the delivery of higher radiation doses was not associated with improved disease control with the overwhelming majority of patients experiencing disease recurrence within the primary radiation field. Given the lack of evidence for dose escalation, in clinical practice, grade II gliomas are commonly treated to 54Gy delivered in 30 fractions.

For WHO grade III tumors there is no randomized evidence to guide radiation dosing. Historically, given the potential for a more aggressive course, practitioners have delivered higher doses, 59.4 to 60 Gy, similar to those used for glioblastoma. However, as described previously, our understanding of the biology of gliomas, particularly grade II

and III has undergone a significant transformation. This is reflected in the revised WHO classification (Louis 2016). In the 2016 classification, molecular parameters, particularly IDH status, along with descriptive histologic criteria are used to describe gliomas. This is reflective of newer data described above which indicate that in the presence of an IDH mutation, grade WHO II vs. III is not predictive of outcome.

In the current trial by including only patients with IDH mutated tumors, we have identified a population in which a relatively indolent course is predicted. It is anticipated that outcomes from EORTC and Intergroup trials discussed previously, will apply to such patients. As such in this protocol both grade II and III patients will receive 54Gy or Gy(RBE) and a planned secondary analysis will assess progression-free survival rates.

2.6 Chemotherapy for Low and Intermediate Grade Gliomas

Whereas the use of chemotherapy in addition to radiotherapy became standard of care treatment for glioblastomas over a decade ago (Stupp 2005), the role of adjuvant chemotherapy for lower grade gliomas has been the subject of much debate for years. However, more recent randomized clinical trials evaluating the use of adjuvant chemotherapy in certain lower grade glioma subgroups have demonstrated a statistically significant benefit in progression free and overall survival.

In high-risk low-grade gliomas, defined as subtotally resected and/or occurring in patients $\geq$ 40 years of age, the RTOG 9802 randomized trial demonstrated a major increase in survival after adjuvant chemotherapy with procarbazine, CCNU and vincristine (PCV). (Buckner 2016) Median overall survival increased from 7.8 years with radiation alone (54 Gy) to 13.3 years when radiation was followed by PCV, with a hazard ratio of death of 0.59 (log rank: P=0.003). The rate of progression-free survival at 10 years was 51% in the group that received radiation plus chemotherapy versus 21% in the group that received radiation therapy alone. This increase in survival was observed despite the fact that 77% of patients who progressed after radiotherapy alone received salvage chemotherapy.

In 1p19q codeleted anaplastic oligodendrogliomas and mixed gliomas, two cooperative group randomized phase III trials (RTOG 9402 and EORTC 26951) provided strong evidence that a combination of radiation and PCV is associated with an improvement in survival. In the RTOG9402 trial, overall survival was significantly prolonged in patients treated with intensified PCV followed by radiation compared to those given only radiation initially (median 14.7 versus 7.3 years, HR 0.59, 95% CI 0.37-0.95). (Cairncross 2013) In patients with IDH mutant tumors overall survival was significantly prolonged by the addition of PCV to radiation, both in codeleted (14.7 versus 6.8 years, HR 0.49, 95% CI 0.28-0.85) and non-co-deleted tumors (5.5 versus 3.3 years, HR 0.56, 95% CI 0.32-0.99) (Cairncross 2014). In EORTC 26951, among 80 patients with the 1p19q codeletion, PFS was significantly increased when patients were treated with radiation plus PCV compared with radiation alone (median 157 versus 50 months, HR 0.42, 95% CI 0.24-0.74), and there was a trend towards increase in overall survival (median not reached versus 112 months, HR 0.56, 95% CI 0.31-1.03). In patients without codeletion, there was a modest benefit in PFS (15 versus 9 months, HR 0.73, 95% CI

0.56-0.97), but no statistically significant benefit in overall survival. In the subset of patients with known IDH1 mutation status, the presence of an IDH mutation was associated with significantly improved median overall survival (8.4 versus 1.4 years) (van den Bent 2013).

In non-codeleted anaplastic gliomas, the cooperative group trial CATNON provided evidence at interim analysis that a combination of radiation and 12 cycles of adjuvant temozolomide improves both progression free survival (HR 0.59, 95% CI 0.47-0.73) and overall survival (HR 0.65, 95% CI 0.45-0.93) compared to radiation alone. (van den Bent ASCO 2016).

For WHO grade II and III gliomas, the optimal adjuvant chemotherapy regimen has not been determined. While the use of PCV is supported in this patient population, PCV is associated with significantly more toxicity including nausea, fatigue peripheral neuropathy, encephalopathy and myelosuppression. Temozolomide has been shown to be also very active in lower grade gliomas, particularly oligodendrogliomas (Brandes 2006; van den Bent 2003; Wick 2009). Even though results of randomized trials comparing PCV and temozolomide are not available at present, given the high toxicity burden of PCV chemotherapy, in many clinical practices temozolomide alone is used as the standard adjuvant treatment regimen. Moreover, the higher rates of toxicity with PCV could impact performance on cognitive testing and would negatively impact symptom burden as measured by the MDASI, quality of life, etc in this trial. Potential issues with neuropathy might also adversely impact testing. For these reasons, in the current trial patients will receive only adjuvant temozolomide.

2.7 Summary

It is well established that exposure of uninvolved normal brain, even to low doses of radiation, has a significant impact on cognitive function in patients with brain tumors. (Gondi 2013; Armstrong 2012) The overall goal of this trial is to reduce the burden of radiation induced cognitive decline through the use of proton therapy, thereby improving long-term quality of life in brain tumor survivors. *Our hypothesis is that the normal tissue sparing offered by proton therapy will lead to superior preservation of cognitive function and reduced symptom burden in comparison to patients treated with photon-based therapy in patients with IDH mutant, WHO grade II and III gliomas.*

We propose a randomized phase II trial comparing IMRT and proton therapy in patients with IDH mutant, WHO grade II or III gliomas. We will assess whether treatment with proton therapy results in longer time to cognitive failure compared with IMRT. In conjunction, we will determine if the low dose sparing afforded by proton therapy, is associated with reduced symptom burden and a superior quality of life in comparison to patients treated with IMRT. Additional secondary endpoints will include comparisons of local control, survival, and patterns of cognitive change and symptom burden as a function of volumetric disease and chemotherapy use.

A positive result from the proposed trial would support the routine use of proton therapy for patients with WHO grade II and III, IDH mutant gliomas in order to

preserve cognitive function and quality of life. This would directly influence clinical practice and contribute to improved survivorship outcomes. Moreover, a positive result would potentially influence referral patterns and allow for the earlier introduction of radiation therapy, which is known to improve disease control and potentially survival. A negative result would suggest that advanced photon treatment using IMRT, is sufficient. This would also be an important contribution, indicating that existing technologies, which are currently less costly, can offer outcomes equal to those seen with more expensive proton therapy.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

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

3.1 Patient Selection Guidelines (22-AUG-2018)

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception during the trial.

3.1.3 Submission of tumor tissue is required for all patients in order to confirm the histologic diagnosis and for future translational studies. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. Biopsy only patients are eligible (See details in Section 10.)

3.1.4 Patients with suspected WHO grade IV, glioblastoma, should not be enrolled. For example patients who have undergone biopsy revealing only grade II or III disease, but with substantial areas of enhancement on MRI suggestive of glioblastoma should not be enrolled.

3.1.5 Submission of serum, plasma, and whole blood are strongly encouraged for all patients. Samples will be submitted for banking for the translational research portion of this protocol and future studies. (See details in Section 10.)

3.2 Eligibility Criteria (22-AUG-2018)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to STEP1 REGISTRATION

3.2.1 Tumor tissue must be available for submission for central pathology review (see Section 10 for details).

3.2.2 Grade II and III gliomas IDH mutant gliomas including; diffuse astrocytoma, anaplastic astrocytoma, oligodendroglioma, anaplastic oligodendroglioma, oligoastrocytoma, anaplastic oligoastrocytoma;

3.2.3 Documentation from the enrolling site confirming the presence of IDH mutation and 1p/19q status. The provided information must document assays performed in CLIA-approved laboratories and be uploaded prior to Step 2 registration (see Section 10 for details);

3.2.4 Age ≥ 18;

3.2.5 The trial is open to both genders;

3.2.6 Only English or French speaking patients are eligible to participate as the cognitive assessments are only available in these languages;

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

3.2.8 History & physical exam, and Karnofsky Performance Status of ≥70 within 30 days prior to registration;

3.2.9 Adequate hematologic and hepatic and renal function within 60 days prior to registration defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3
- Platelets ≥ 100,000 cells/mm3
- Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable)
- Bilirubin ≤ 1.5 upper limit of normal (ULN);
- ALT and AST ≤ 3 x ULN
- BUN < 30mg/dl
- Serum creatinine <1.5 mg/dl

3.2.10 Pre-operative MRI imaging of the brain available for radiation planning

3.2.11 Post-operative MRI imaging with contrast is mandatory obtained for radiation therapy planning. Enrolling sites are not mandated although highly encouraged to obtain Thin-slice (<1.5mm) 3D T1 pre and post contrast and Axial T2/FLAIR sequences for planning purposes.

3.2.12 Patients must be able to swallow capsules.

Prior to STEP2 REGISTRATION

Note: Step 2 registration must occur no later than 30 calendar days after Step 1 registration.

3.2.13 Histologically proven diagnosis of supratentorial, WHO grade II or III astrocytoma, oligodendroglioma or oligoastrocytoma, with IDH mutation **confirmed by central review** (See Section 10 for details).

3.2.14 The following baseline neurocognitive assessments must be completed and uploaded prior to Step 2 registration: HVLT-R (recall, delayed recall, and recognition), TMT Parts A and B, and COWA. The neurocognitive assessment will be uploaded into a folder in the NRG Medidata RAVE System for central evaluation. Once the upload and scoring of the tools are complete, a notification will be sent within 3 business days to the Research Associate (RA) to proceed to Step 2. In order for the patient to be eligible, at least 5 of the 6 neurocognitive assessments must be able to be scored (i.e. free of any errors).

3.2.15 Completion of all items on the following baseline quality of life forms: MDASI-BT, LASA QOL, WPAI-GH and Employment Questionnaire. These quality of life forms will

be required and data entered at step 2 registration.

3.2.16 Financial clearance for proton therapy treatment prior step 2 registration.

3.2.17 Women of childbearing age must have a negative serum pregnancy test within 14 days prior to step 2 registration.

3.3 Ineligibility Criteria

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

3.3.1 Definitive clinical or radiologic evidence of metastatic disease; if applicable

3.3.2 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years. (For example, carcinoma in situ of the breast, oral cavity or cervix are permissible);

3.3.3 Prior cranial radiotherapy or radiotherapy to the head and neck where potential field overlaps would exist;

3.3.4 Prior chemotherapy or radiotherapy for any brain tumor;

3.3.5 Histologic diagnosis of glioblastoma (WHO grade IV) or pilocytic astrocytoma (WHO grade I);

3.3.6 Definitive evidence of multifocal disease;

3.3.7 Planned use of cytotoxic chemotherapy during radiation (only adjuvant temozolomide therapy will be used on this protocol);

3.3.8 Patients with infra-tentorial tumors are not eligible;

3.3.9 Prior history of neurologic or psychiatric disease believed to impact cognitive function;

3.3.10 The use of memantine during or following radiation is NOT allowed;

3.3.11 Severe, active co-morbidity defined as follows:

- Unstable angina or congestive heart failure requiring hospitalization within 6 months prior to enrollment
- Transmural myocardial infarction within the last 6 months prior to registration
  Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of $\geq$ 2 mm using the analysis of an EKG performed within 28 days prior to registration. (Note: EKG to be performed only if clinical suspicion of cardiac issue).
- New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to registration.
- Serious and inadequately controlled arrhythmia at step 2 registration
- Serious or non-healing wound, ulcer or bone fracture or history of abdominal fistula, intra-abdominal abscess requiring major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to registration, with the exception of the craniotomy for surgical resection
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
- HIV positive with CD4 count < 200 cells/microliter. Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS

from this protocol is because the treatments involved in this protocol may be significantly immunosuppressive with potentially fatal outcomes in patients already immunosuppressed.

- Any other severe immunocompromised condition.
- Active connective tissue disorders, such as lupus or scleroderma that in the opinion of the treating physician may put the patient at high risk for radiation toxicity.
- End-stage renal disease (i.e., on dialysis or dialysis has been recommended).
- Any other major medical illnesses or psychiatric treatments that in the investigator's opinion will prevent administration or completion of protocol therapy.

3.3.12 Inability to undergo MRI with and without contrast (e.g. claustrophobia, non-MRI compatible implant or foreign body, gadolinium allergy or renal dysfunction preventing the patient from receiving gadolinium- institutional guidelines should be used to determine if patients are at risk for renal dysfunction). Note that patients with severe claustrophobia are permitted on this study if they are willing and able to undergo MRI with adequate sedation or anesthesia.

3.3.13 Patients known to have hypersensitivity to dacarbazine (DTIC) are not eligible.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (22-AUG-2018)

Highly recommended evaluations/management includes;

- CD4 lymphocyte count prior to and at completion of radiotherapy
- Pre-radiation therapy thin-slice volumetric (<1.5mm) 3D T1 pre and post contrast and Axial T2/FLAIR sequences for planning purposes. For post-operative patients, because the surgical cavity may change in size over time, the planning MRI should be obtained as close to the start of radiation as feasible. Sites are also encouraged to specifically obtain pre and post gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan and an axial T2 FLAIR sequence. To yield acceptable image quality, the gadolinium contrast-enhanced three-dimensional SPGR, MP-RAGE, or TFE axial MRI scan should use the smallest possible axial slice thickness not exceeding 1.5 mm. Such sequences aid in target delineation as well as normal tissues including the hippocampi.

PRE-TREATMENT ASSESSMENTS	
Prior to *Step 1* Registration *(required for eligibility)*	
Tissue available for central pathology review and confirmation of IDH mutation and 1p19q status	Prior to step 1 registration
Informed consent	Prior to step 1 registration
Confirmation of English or French as primary language	Prior to step 1 registration
Employment status recorded	Prior to step 1 registration
Karnofsky performance status	Prior to step 1 registration
History/physical exam	Prior to step 1 registration
Pre-surgery Magnetic Resonance Imaging	Available for radiation planning
Post-surgery Magnetic Resonance Imaging-to be used for radiation therapy treatment planning	Prior to the start of radiation therapy
CBC with differential (ANC, hemoglobin, platelets, lymphocyte count)	60 days prior to step 1 registration
Serum creatinine, BUN, total bilirubin, ALT, AST	60 days prior to step 1 registration
Prior to *Step 2* Registration	
Central pathology confirmation and documentation of IDH and 1p19q status	Prior to step 2 registration
Financial clearance for proton therapy	Within 30 days following step 1 registration
Baseline neurocognitive assessment	No more than 7 days prior to or 21 days after step 1 registration *
Patient reported outcomes: LASA, MDASI-BT, WPAI:GH, Employment Questionnaire, AHS, PHQ2	No more than 7 days prior to or 21 days after step 1 registration **
Specimen collection *(If patient consents to optional banking)*	Prior to start of radiation therapy
Serum pregnancy test *(if applicable)*	14 days prior to step 2 registration
CD4 lymphocyte count is highly encouraged (but not required)	Prior to the start of radiation therapy

* Neurocognitive assessments can be uploaded immediately after step 1 registration.

** Completion of LASA, MDASI-BI, WPAI:GH, Employment Questionnaire, AHS and PHQ2 can be completed with the neurocognitive testing then be data enterer on step 2 registration.

ASSESSMENTS DURING TREATMENT

Assessments	**Weekly during Treatment**
Monitoring for radiation acute effects	Weekly during Radiation Treatment
CD4 lymphocyte count is highly encouraged (but not required)	After the completion of radiation therapy
Monitoring for hematologic and non-hematologic toxicities	Throughout adjuvant chemotherapy (see Section 5)
Report of number of chemotherapy cycles and tolerance (up to 12 cycles)	At the completion of chemotherapy

ASSESSMENTS IN FOLLOW UP	
Assessments	**Timeframe**
Patient reported outcomes: LASA, MDASI-BT	Within 5 days of completion of radiation
CBC with differential (ANC, hemoglobin, platelets, lymphocyte count)	
Specimen collection *(If patient consents)*	
Patient reported outcomes: LASA, MDASI-BT, WPAI:GH*, Employment Questionnaire, AHS*, PHQ2*	At 6 months, 12 months, then annually** for 10 years after completion of radiation
Neurocognitive assessment	
History/physical exam	
Karnofsky performance status	
Brain MRI w/ contrast	
Neurologic exam	
CBC with differential (ANC, hemoglobin, platelets, lymphocyte count)	
AE collection	
Specimen collection *(If patient consents)*	12 months

* AHS and PHQ2 are only collected at 6 months; WPAI:GH and Employment Questionnaire are only collected at 6 months, 1 and 2 years after completion of radiation

**+/- 4 month window for completing PRO and neurocognitive assessments; CBC is not required after 12 months unless clinically indicated.

Definition of Disease Assessments

Local control and distant control in the brain will be measured by MRI scans using Response Assessment in Neuro-Oncology (RANO) Criteria for low-grade glioma, as follows (1, 2).

Complete Response (CR): Requires all of the following 1) complete disappearance of the lesion on T2 or FLAIR, if enhancement was present it must have resolved completely, 2) no new lesions or T2/FLAIR abnormalities apart from those consistent with radiation effects, 3) patients must be off corticosteroids (unless on physiologic replacement doses only) and 4) stable or improved clinically.

Partial Response (PR): Requires all of the following: 1) ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable T2 or FLAIR lesions sustained for at least 4 weeks; 2) no new lesions or enhancement apart from those consistent with radiation effect; 3) the same or lower dose of corticosteroids compared with the baseline scan and stable or improved clinically.

Minor Response: Requires all of the following: 1) 25 to 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable T2 or FLAIR lesions 2) no new lesions or enhancement apart from those consistent with radiation effect; 3) dose of corticosteroids not greater than the dose at the time of the baseline scan and stable or improved clinically.

Progressive Disease (PD): Defined as any of the following 1) development of new lesions or increase of enhancement (possible malignant transformation); 2) ≥25% increase in T2 or FLAIR lesions on stable or increasing steroid doses, not attributable to radiation or other effects; 3) definite clinical deterioration not attributable to other causes or decrease in steroid use; (4) failure to return for evaluation due to death or deterioration in clinical condition unless due to non-related causes. *****For suspected pseudo progression or necrosis see below.

Stable Disease (SD): Requires all of the following 1) does not qualify for complete response, partial response, or progression; 2) stable FLAIR/T2 lesions; 3) no new lesions apart from those consistent with radiation effect; 4)on corticosteroid dose no greater than at baseline and stable or improved clinically.

For local control, PD is considered local failure, or stable disease with deterioration of the neurological examination with a grade III or worse toxicity on the CTCAE (v. .0 scale through April 12, 2018; v. 5.0 beginning April 13, 2018). All others (CR, PR, minor response, asymptomatic SD) are deemed success.

*****If pseudoprogression (an increase in tumor size or edema in response to treatment which may mimic tumor progression) or radiation necrosis are suspected, all efforts should be made to further document the event and differentiate it from real tumor progression. This may include surgical resection or biopsy if warranted, advance imaging such as MR perfusion, spectroscopic or diffusion weighted imaging or PET imaging. At the discretion of the treating physician, patients with suspected pseudoprogression or necrosis may remain on trial and on treatment. If a surgical procedure is performed, results of the pathologic evaluation will be collected. . If true tumor progression is confirmed by advanced imaging or resection, the date of progression will be the date of the scan that first showed imaging worsening.

5. TREATMENT PLAN/REGIMEN DESCRIPTION (22-AUG-2018)

Participants randomized to Arm 1 will receive photon radiation using IMRT or VMAT to 54Gy. Adjuvant temozolomide will begin 28 (-3/+5) days after completion of radiation.

Participants randomized to Arm 2 will receive proton radiation to 54Gy(RBE). Adjuvant

temozolomide will begin 28 (-3/+5) days after completion of radiation.

Randomization will be 2:1 in favor of protons.

5.1 Chemotherapy

Chemotherapy treatment must begin within 28 (-3/+5) days of completing radiation.

5.1.1 In all treatment arms Temozolomide will be administered during the adjuvant post radiation phase at 150 mg/m^2 by mouth once daily for 5 consecutive days followed by a 23-day rest period for a 28-day cycle (up to 12 cycles) in the absence of tumor progression and/or limiting toxicity. Capsules should be swallowed whole with a glass of water. Absorption is affected by food, so administer consistently either with food or without food. May administer on an empty stomach and/or at bedtime to reduce nausea and vomiting.

Do not repeat dose if vomiting occurs after dose is administered and wait until the next scheduled dose.

For cycle 2, increase dosage to 200 mg/m^2 by mouth once daily for 5 days *only if* nonhematologic toxicity (excluding alopecia, nausea, and vomiting) from cycle 1 is ≤ grade 2, ANC ≥1500/mm^3, and platelet count ≥100,000/mm^3. For cycles 3–12, continue dosage of 200 mg/m^2 by mouth once daily for 5 consecutive days of each 28-day cycle, unless toxicity occurs. If dosage was not increased for cycle 2, do *not* increase dosage for subsequent cycles.

Monitoring and management of side effects including dose reduction and/or dose delay will be performed as per local standard practice. Periodically monitor CBC; do not resume dosing until criteria for continuance of therapy are met.

5.2 Radiation Therapy (22-AUG-2018)

Protocol treatment must begin within 30 calendar days (+ 14 days) after baseline cognitive testing, and administration of MDASI-BT and WPAI:GH.

5.2.1 Treatment Technology

IMRT

Photon beam energies of 6-10 MV may be used. IMRT is required for patients randomized to this arm. IMRT may be delivered using multiple fixed fields employing dynamic multi-leaf collimation, helical arc therapy or volumetric modulated arc therapy using any of the commercially available delivery systems. 3D Conformal Radiation Therapy is not allowed.

Proton therapy

Proton dose shall be reported in Gy (RBE) where the physical proton dose is multiplied by a uniform RBE value equal to 1.1. Proton dose in Gy (RBE) and photon doses in (Gy) are considered equivalent in terms of biological response for this protocol.

Pencil beam scanning, passive scatter, or uniform scanning proton therapy are allowed. Proton treatment plans should use no fewer than 2 fields per fraction. For proton planning, special attention should be made in selecting the beam angles to be utilized for treatment. In general beams with short radiologic path lengths as well as trajectories avoiding the greatest amount of uninvolved normal tissues and avoiding passage through complex heterogeneities should be favored. For lesions localized to one side of the brain, beams entering through the contralateral are not permitted. Beam angles should be selected to avoid tangential incidence to the skull or being parallel to a heterogeneous tissue interface, such as along the ear canal or nasal septum, as such beams are less robust in the presence of rotational errors in patient setup not accounted for in currently available commercial treatment planning systems (TPS). Beams flashing the skull and depositing doses to low neck/shoulders should be avoided. Lastly, beams in which the distal edge is within or near critical normal tissues should be avoided given the possible increased biologic effectiveness of such regions as well as physical uncertainties.

<u>3D conformal proton therapy (3DCPT)</u>
3DCPT delivery techniques, including passive scattering and uniform scanning both use high-Z metal field apertures/blocks for lateral beam conforming and low-Z range compensators/boluses for distal beam range conforming to the target. Either beam delivery technique is acceptable for use in this protocol. Adequate aperture margins to account for beam lateral penumbra are required in the design of treatment plans, in a manner similar to photon-based 3DCRT block margins. Such margins may be specified as a distance away from the PTV (please see section 5.2.4 for target volume definitions) used in IMRT treatment planning, or from the CTV with additional consideration for setup errors and other geometric uncertainties of CTV within the beam's eye view (BEV). Distal and proximal beam margins are necessary to account for uncertainties in beam range calculations due to those of CT number to proton relative linear stopping power (RLSP) calibration; immobilization devices; and inter- and intra-fraction errors that may cause range changes. In commercial treatment planning systems, distal and proximal margins may be specified as a percentage of the maximum water-equivalent-depth of the CTV, or as an addition to beam range in mm.

Proton beam distal and proximal margins: Proton beam specific distal and proximal margins will be determined based on the water equivalent thickness of the most distal and most proximal part of the CTV respectively. Additional distal and proximal margin amounts should be calculated using the following formulas.

Distal margin (DM): DM = (0.025 x distal CTV depth) + 2 mm

Proximal margin (PM) = (0.025 x proximal CTV depth) + 2 mm

These margins are intentionally made smaller than historically used margins calculated using 0.035 x distal or proximal CTV depth + 3 mm to avoid over generous margins around CTV for this protocol. Use of this reduced margin is also in good agreement with the suggestions in the recent review in the literature (Durante M., Paganetti H. Nuclear

Physics in Particle Therapy. Rep. Prog. Phys. 79; 2016: 096702 (59 pp)). The adequacy of the use of these lower distal and proximal margins will be confirmed by the robustness analysis of the CTV coverage for +/- 3.5% range uncertainties.

Range compensator smearing and border smoothing are necessary to maintain the robustness of 3DCPT plans. Due to the increased radiobiological effectiveness (RBE) at the end of the spread-out-Bragg-Peak produced by each passive scattering or uniform scanning treatment field, as well as the possibility of beam range delivered in patient may be higher than the TPS calculated value, a scenario of multiple beams directed and stopping in front of a high-importance OAR, such as the brainstem, optic chiasm or optic nerves should be avoided. In general, this would call for no more than 1 beam in a 3-field treatment plan should be allowed to stop on the same OAR. The range compensator thickness may be increased locally in front of the OAR ("distal blocking") to reduce beam ranges in such areas to further assure adequate protection of the OAR. Beam patching techniques will be allowed.

Intensity-Modulated Proton Therapy (IMPT)

Proton therapy may be delivered with intensity-modulated proton therapy (IMPT) technique using scanning proton beams. IMPT plans using either single field optimization (SFO), in which dose from each field in the plan encompasses the entire target volume, or multi-field optimization (MFO), in which heterogeneous dose distributions from individual beams combine to produce a conformal dose to the target. The choice between SFO and MFO will be decided by the treating physician and medical physicist. In general SFO plans are considered to be more robust in the face of physical uncertainties. However, for brain tumor patients the target is typically homogenous and radiographic path-length short. For this protocol if the MFO plan demonstrates superior normal tissue sparing with similar target coverage, practitioners are highly encouraged to use MFO. For the plan selected, either SFO or MFO, the plan selected for treatment should meet robustness evaluation criteria, as discussed in the paragraphs below.

For IMPT planning, particularly MFO-IMPT, robust optimization is strongly recommended. Robust optimization should be done using values of range uncertainty and setup errors identical to those used for 3DCRT. With robust optimization, a number of potential sources of uncertainties are included and addressed by the treatment planning system. If robust optimization is not available consideration should be given to the use of appropriate target volume for optimization. Use of beam specific margins with appropriate distal, proximal and lateral margins around the CTV may not be feasible or appropriate in IMPT planning. An expanded target volume with a small isotropic margin around the CTV (as much as 3 mm) can be used as a starting volume for IMPT optimization. It is mandatory that the generated plan with an expanded target volume must be evaluated for robustness (robust evaluation). For robust evaluation, dose distributions for a number of uncertainty scenarios (setup, range etc.) are calculated and the resulting dose volume histogram (DVH) bands evaluated by physics and clinical staff. Robust evaluation is available for all commercial proton treatment planning systems. If the worst-case dose distribution is found to be not acceptable, alternative strategies, including re-planning using alternative or additional beam angles, or optimizing to an

expanded planning target volume with adequate additional margins around the CTV, should be attempted. Practitioners are encouraged to contact the protocol chairs with questions.

Note; robustness evaluation and robust optimization both utilize CTVs and organs at risk (OARs). These structures, in contrast with PTV and organ at risk planning volumes (ORVs), exclude margins for uncertainties in set up and range. This requires special care when comparing results of IMPT robust optimization or robustness evaluation with IMRT or IMPT dose distributions optimized and evaluated based on traditional PTV (and ORV)-based methods. An effective approach that has been reported is to perform robustness evaluation for all competing dose distributions and compare the worst case DVHs and DVH bandwidths (Malyapa 2016, Fredriksson 2012).. Practitioners are encouraged to contact the protocol chair with questions. For robustness evaluation, the CTV and GTV should be used as the target.

Dose Prescription

Both grade II and III tumors the total dose will be 54 Gy(RBE) delivered in 30 fractions.

Proton and photon dose will be reported in Gy (relative biological effectiveness, RBE), where 1 Gy(RBE) = dose in Gy x RBE. For protons, RBE = 1.1 and for photons, RBE =1. So the unit Gy(RBE) may be used for both protons and photons.

Target Standard Name	**Dose [Gy(RBE)]**	**Fraction Size [Gy(RBE)]**	**# of fractions**	**Dose specification technique**
CTV_5400	54	1.8	30	should receive the prescription dose with at least 95% probability under robustness evaluation for proton plans
PTV_5400	54	1.8	30	≥95% should receive 54 Gy for IMRT plans only

Radiation doses shall be prescribed using the protocol specified definitions for GTV, CTV and PTV as described below.

For IMRT, at least 95% of the PTV_5400 should receive the prescription dose. IMRT plans shall be normalized such that 95% of the PTV_5400 volume receives prescription dose of 54 Gy.

For proton plans, the CTV_5400 should receive the 54 Gy (RBE) with at least 95% probability under robustness evaluation i.e., in the worst case DVH, 95% of CTV_5400 should receive 54 Gy (RBE). IMPT plans optimized using robust optimization method shall be normalized such that 95% of CTV_5400 receives 54 Gy (RBE). Passive scattering plans or IMPT plans without robust optimization should be normalized to meet the same criteria for the worst case of target coverage under robustness evaluation.

Treatment Planning Priorities and Instructions

Depending on the arm to which the patient has been randomized, an optimized IMRT or proton plan meeting the tumor and normal tissue constraints per protocol will be produced.

Treatment plans will be evaluated using dose distributions superimposed on images, dose-volume histograms (DVHs) and other appropriate tools to ensure adequate coverage of the target and sparing of normal tissues per protocol. If normal tissue constraints listed above are not meet treating physicians my chose to reduce target coverage at their discretion. In such circumstances the treating physician is encouraged to contact the study chair and/or physics co-chairs for input and guidance.

Patients will be treated once per day five days per week (with the exception of holidays as observed by the treating institution or patients preferences).

The treatment of single fields for proton therapy is not allowed.

For patients randomized to the proton arm of the trial and whom have started proton therapy, up to 10% of total dose may be delivered using an IMRT plan in the event that proton therapy is not available due to machine down events. If prior to treatment start slots are not available on the proton therapy unit, sites should not start with IMRT but instead make every effort to secure a proton therapy treatment slot in a reasonable amount of time.

Dose Calculations

All existing photon and proton dose calculation algorithms available from commercial vendors are acceptable for plan calculations of this trial, provided that the participating institution is credentialed by the IROC for use of their applicable delivery techniques for brain/H&N treatments. Dose calculations shall be performed with heterogeneity corrections applied for photons. Heterogeneity corrections are inherent in all proton dose calculations. Dose calculations should be performed with no greater than 3 mm dose grid spacing.

Proton dose will be reported in Gy (relative biologic effectiveness, RBE), where 1 Gy

(RBE) = proton dose Gy x RBE, RBE = 1.1.

Primary dataset for dose calculation
Planning CT image is the primary dataset for dose calculation.

5.2.2 Immobilization
For both proton therapy and IMRT, patients will be simulated and treated in the supine position. A thermoplastic mask and headrest will be utilized for baseline immobilization. Additional immobilization devices such as bite blocks are permitted.

5.2.3 Simulation Imaging
A planning CT, encompassing the entire cranium, must be obtained. Fusions of pre-and or post-operative MRI scans will be performed. Practitioners are encouraged to utilize all imaging resources available, including pre-operative imaging, to assist with target volume delineation. The use of postoperative MR imaging for the facilitation of radiation therapy planning is required. Sites are encouraged to obtain MR imaging for radiation planning as near the time of simulation as feasible (in order to allow for potential collapse of the surgical cavity, resolution of edema etc.). The inclusion of volumetric sequences both thin slice volumetric (<1.5mm) 3D T1 pre and post contrast and Axial T2/FLAIR imaging is highly encouraged.

For proton therapy treatments, the CT scanner utilized for simulation must have been calibrated appropriately to establish a relationship between CT numbers and proton stopping power ratios.

Imaging for Structure Definition, Image Registration/Fusion
MR sequences from an MRI obtained within 4 weeks of radiation therapy must be fused to the treatment planning CT. Structures should be delineated using both, information from the CT as well as MRI. Because CT data is used to calculate range and errors in image registration may occur, the CT should be considered the primary data set. Practitioners are encouraged to contour structures such as the optic chiasm and brainstem on CT, verifying contours then on MR. MR images will be essential for contouring of the hippocampal formations as well as target volumes as described below.

5.2.4 Definition of Target Volumes and Margins

Standard Name	Description	Validation Required/Required when applicable/Optional
GTV_5400	GTV to receive 54 Gy (RBE)	Required
CTV_5400	CTV to receive 54 Gy (RBE)	Required
PTV_5400	PTV to receive 54 Gy (RBE)	Required

DetailSpecifications
Target volumes will include:

Gross Tumor Volume (GTV)

The GTV will contain the edematous volumes as visualized on FLAIR or T2 weighted MR images. Following surgical resection, the GTV will include the resection cavity as well as remaining FLAIR or T2 abnormalities suspected of harboring disease. If the patient has undergone a gross total resection, the operative bed will define the GTV. GTV size should be recorded and reported in cubic centimeters.

Clinical Target Volume (CTV)
For grade II and III tumors, the CTV will be generated by the addition of a 1.0 cm margin from the GTV. Following this expansion practitioners are encouraged to customize the generated target. This includes removing expansions past the inner calvarium, and reducing expansions in areas of anatomic barriers to tumor spread including the ventricles and falx etc. If concern exists for subclinical spread beyond the 1cm margin corresponding adjustments are also permitted. CTV size should be recorded and reported in cubic centimeters.

Planning Target Volume (PTV)
For IMRT, the PTV will be generated by a 3 to 5mm expansion of the CTV in all directions. While the concept of PTV is not directly applicable to IMPT, a PTV may be generated for reporting purposes, even though it is not expected to meet the same evaluation criteria as for IMRT plans. For SFO-IMPT, definition of beam-specific PTVs for planning and plan robustness evaluation will be necessary. For MFO-IMPT planning, robust optimization is highly recommended and robustness evaluation is required If robust optimization is not feasible, an expanded target volume with appropriate margin around the CTV will be used for optimization as described in Section 5.2.1.

5.2.5 Definition of Critical Structures and Margins

Critical structures should be labeled as listed below with standard DICOM names used.

Standard Name	Description	Validation
Brain	The whole brain parenchyma includes all intracranial contents, inclusive of target volumes, contoured using the CT dataset.	Required
BrainStem	The brainstem is bordered superiorly by the tentorial incisure and inferiorly by the foramen magnum. It can be visualized on postoperative MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.	Required
Hippocampus_L	The left hippocampus should be defined utilizing the most recent, fused MRI according to the online RTOG atlas (http://www.rtog.org/corelab/contouringatlases/hippocampalsparing.aspx). Practitioners are encouraged to request SPGR (three dimensional spoiled gradient), MP-RAGE (magnetization-prepared rapid gradient echo) or TFE (turbo field	Required

	echo) MR sequences to best identify the hippocampus.	
Hippocampus_R	The right hippocampus should be defined utilizing the most recent, fused MRI according to the online RTOG atlas (http://www.rtog.org/corelab/contouringatlases/hippocampalsparing.aspx). Practitioners are encouraged to request SPGR (three dimensional spoiled gradient), MP-RAGE (magnetization-prepared rapid gradient echo) or TFE (turbo field echo) MR sequences to best identify the hippocampus.	Required
Hippocampi	Bilateral hippocampal contours will be manually generated on the fused planning MRI/CT image set by the treating physician according to contouring instructions specified on http://www.rtog.org//corelab/contouringatlases/hippocampalsparing.aspx.	Required
OpticChiasm	Located above the pituitary fossa, the optic chiasm includes both anterior and posterior limbs. It is best visualized on postoperative T2/FLAIR MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.	Required
OpticNrv_L	Due to variance in eye position between the CT and MRI, if possible, the left optic nerve should be contoured using the CT dataset only.	Required
OpticNrv_R	Due to variance in eye position between the CT and MRI, if possible, the right optic nerve should be contoured using the CT dataset only.	Required
SpinalCord	Spinal cord should be contoured, wherever possible, on the CT dataset only.	Required

5.2.6 Compliance Criteria

Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Notes
PTV_5400	D95% [Gy(RBE)]	54	>= 50	For IMRT only
CTV_5400	D95% [Gy(RBE)]	54	>= 50	

Normal tissue constraints and compliance criteria are as follows:

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
SpinalCord	D0.03cc[Gy(RBE)]	<=50	
BrainStem	D0.03cc [Gy(RBE)]	<=55	55-60

OpticChiasm	D0.03cc[Gy(RBE)]	<=55	55-60
OpticNrv	D0.03cc[Gy(RBE)]	<=55	55-60

*for proton plans the nominal plan values of OAR doses shall be used for this purpose.

Delivery Compliance criteria

	Per Protocol	Variation Acceptable
Start date	Within 30 days of cognitive testing	Within 44 days of cognitive testing
Interruptions	<= 4 days	5 to 7 days

5.2.8 Patient-Specific QA

Phantom plans of IMRT and IMPT plans shall be created, with the resultant planar fluencies or doses, or 3D doses measured in a corresponding phantom, to assure plan and delivery accuracy, prior to start of patient treatment. All plans shall be deemed acceptable for treatment with gamma pass rate of 90% or higher using 3% and 3mm criteria for all treatment fields. 3DCPT treatment plans shall have field-specific output factors measured in phantom, and patient specific treatment accessories of apertures and range compensators shall have been verified for accuracy prior to start of treatment. For IMPT plan QA, measurement in multiple layers is required.

5.2.9 Daily Treatment Localization/IGRT

Daily image guidance is required for all proton therapy treatments and highly recommended for IMRT. 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.

At the discretion of the treating physician, if concerns arise regarding potential anatomic changes which could impact treatment delivery, CT images will be acquired and dose distributions will be recalculated using them and the beam configuration being used at the time to produce a verification plan.

If the verification plan indicates deviation from the original target coverage or normal tissue sparing objectives, re-planning is indicated. In which case, an adaptive plan on the new CT image will be created with goal of delivering the remaining dose within the original constraints. The new plan will be used to deliver the rest of the treatment or until another re-plan is indicated.

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.

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

Management of Radiation Dose to the Patient from IGRT
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.

5.3 General Concomitant Medication and Supportive Care Guidelines

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.

- Anticonvulsants: Anticonvulsants may be used as clinically indicated. The regimen and dosing schedule at study entry and any subsequent changes in the anticonvulsant regimen and/or dosing schedule must be recorded.
- Corticosteroids: Corticosteroids may be administered at the treating physician's discretion. The goal is to use the lowest clinically necessary dose of corticosteroids.
- Antiemetics: Prophylactic antiemetics may be administered at the treating physician's discretion.
- Pneumocystis Carinii Prophylaxis:
  Both corticosteroid therapy and continuous temozolomide therapy induce lymphopenia. Patients receiving any of these drugs or both concomitantly are at an increased risk for opportunistic infections.

  The following drugs can be used for prophylaxis against P. carinii pneumonia:: 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).

  During the adjuvant chemotherapy phase, it is strongly recommended that CD4 quantification is obtained at day 1 of each cycle. In addition, CD4 quantification is mandatory if **lymphocyte count < 500/mm3.** If the CD4 is ≤ 200, then *P. carinii* prophylaxis is recommended and the CD4 is required to be quantified every 2 weeks until CD4 is > 200, at which point *P. carinii* prophylaxis can be stopped. If the lymphocyte count is ≥ 500 or the CD4 is > 200, then prophylaxis and CD4 quantification are no longer mandatory.

5.3.2 Prohibited Therapies

- The use of memantine during or after radiation therapy is NOT allowed.
- Growth factors are not permitted to induce elevations in neutrophil count for the purposes of: (1) administration of temozolomide on the scheduled dosing interval; (2) allowing treatment with temozolomide at a higher dose; or (3) avoiding interruption of the treatment during concomitant radiotherapy.
- No other investigational drugs will be allowed.
- Surgical procedures for tumor debulking, other types of chemotherapy, and

immunotherapy or biologic therapy must not be used. Further, additional stereotactic boost radiotherapy is not allowed. All further therapy is at the treating physician's discretion, but should be recorded in the CRF.

- Carmustine wafers or any form of brachytherapy is not permitted prior to study entry or while the patient is on study.

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,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 7
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Interruptions in radiotherapy should be avoided. Early delayed effects during, or shortly after, the course of radiation may include fatigue and a worsening of existing neurologic symptoms. Acute reactions such as hair loss, fatigue, erythema or nausea are common and should not be reason to interrupt therapy. If radiation is to be held for concerns regarding toxicity, please contact the chair or radiation oncology co-chairs.

Temozolomide dose modifications should be consistent with the FDA-approved package insert.

ANC <1,000/mm3 or platelets <50,000/mm3 on day 22 or day 29 (day 1 of next cycle), or grade 3 nonhematologic toxicity related to temozolomide (excludes alopecia, nausea/vomiting) during previous cycle: Postpone therapy until ANC >1,500/mm3 and platelets >100,000/mm3, and non-hematological toxicity recovered to grade 2 or less; reduce dose by 50 mg/m2/day (but not below 100 mg/m2) for subsequent cycle.

ANC 1,000 to 1,500/mm3 or platelets 50,000-100,000/mm3 on day 22 or day 29 (day 1 of next cycle): Postpone therapy until ANC >1,500/mm3 and platelets >100,000/mm3; maintain initial dose

If dose reduction <100 mg/m2/day is required or grade 4 nonhematologic toxicity (excludes alopecia, nausea/vomiting), or if the same grade 3 nonhematologic toxicity occurs after dose reduction: Discontinue therapy

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Commercial Agent

The commercial agent in NRG-BN005 is temozolomide**.**

7.2 Adverse Events and Serious Adverse Events (22-AUG-2018)

7.2.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for AE reporting. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; study case report forms will use CTCAE version 5.0 beginning April 13, 2018. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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.

7.3 Adverse Events for Commercial Study Agents

Refer to the package insert for detailed pharmacologic and safety information

7.4 Expedited Reporting of Adverse Events

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 CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

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.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Biostatistical/Data Management Center by phone, 215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event Supporting source documentation is requested by NRG as needed to complete adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Biostatistical/Data Management Center (215-574-3191) for source document submission.
- 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.

7.4.2 Expedited Reporting Requirements for Adverse Events

Any Phase Study Utilizing a Commercial Agent (including Standard RT)[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

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements

Not applicable.

7.4.3 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.

7.4.4 Secondary Malignancy

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 reporting via CDUS unless otherwise specified.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (22-AUG-2018)

CTEP Registration Procedures and Access requirements for OPEN, Medidata Rave, and TRIAD Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to

renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

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

8.1 Site Registration Requirements (22-AUG-2018)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for

this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:
Site registration forms may be downloaded from the **NRG-BN005** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the NRG Oncology link to expand, then select trial protocol NRG-BN005
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For NRG-BN005 Site Registration Prior to Step 1 Registration:

- IRB approval letter (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted). *Non English speaking international institutions must translate all regulatory documents to English. See below for details.
- Letter of Intent (LOI) – See Section 8.2.3 for details.

- IRB approved consent (International sites only: English and native language versions*****) **Note**: International sites must provide certification/verification of IRB consent translation to NRG Oncology (described below).
- The enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.
- Credentialing documentation received from IROC Houston for this trial- See Section 8.3 Table for details.

Non-English Speaking International Institutions:
*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.

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' section) → Regulatory Tab → Regulatory Submission Portal
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:
You can verify your site registration status on the members' section of the CTSU website.
- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM

username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

8.1.1 Pre-Registration Requirements FOR ALL INSTITUTIONS (Prior to Step 1 Registration)
All sites must submit a Letter of Intent (LOI) to NRG Oncology Regulatory to receive approval to participate in this trial. Centers, which are not capable of delivering proton therapy should the patient be randomized to the proton arm, are encouraged to discuss logistics for with a partnering proton center prior to registering patients. For more details and the LOI form with instructions see the NRG-BN005 protocol page on the CTSU website.

8.2 Pre-registration Requirements (Prior to Step 1 Registration)

8.2.1 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 both the certified examiner and NRG Headquarters that the examiner has successfully completed this requirement.

See protocol-specific material on the CTSU website for Neurocognitive Certification requirements.

8.3 RT-Specific Pre-Registration Requirements (Prior to Step 1 Registration) (22-AUG - 2018)

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. This document must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

Proton centers wishing to participate in this study must comply with the NCI proton guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, which are available on the IROC Houston (http://irochouston.mdanderson.org and IROC (https://www.irocqa.org) websites. These requirements include, but are not limited to, completion of a proton facility questionnaire, a successful IROC Houston site visit, which identifies the proton technique(s) which can be used, annual monitoring of the proton beam calibration, e.g. IROC Houston's monitoring program, and successful digital data submission to the TRIAD. Once these requirements

are successfully met, the proton center is approved to use proton therapy in NCI sponsored clinical trials. Each trial may require additional proton therapy credentialing steps prior to being allowed to enter a patient treated with protons onto a specific study. The IROC Houston's will coordinate the completion of the proton therapy use approval process in conjunction with the appropriate other IROC QA Offices for any additional protocol specific credentialing requirements. See the table below for the credentialing requirements of this study.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions http://irochouston.mdanderson.org		
	Treatment Modality		
	Photon	Proton	Key Information
Facility Questionnaire	x	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.
Credentialing Status Inquiry Form	x	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).
Phantom Irradiation	x	x	An IMRT 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).
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. The institution will need to upload a PDF of the approval email to the CTSU Regulatory Portal for RSS to be updated.

8.3.1 Digital RT Data and Standard of Care Imaging Submission to NRG Using TRIAD
TRIAD is the image exchange application used by the NRG. TRIAD provides sites

participating in NRG clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP), have a valid and active CTEP Identity and Access Management (IAM) account and be registered as an AP, NPIVR or IVR. Please refer to the CTEP Registration Procedures for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging to IROC Diagnostic Imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the IROC website **https://www.irocqa.org/Resources/TRIAD**.
This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

8.4 Patient Enrollment (22-AUG -2018)

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.

8.4.1 Oncology Patient Enrollment Network (OPEN)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. . To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or

investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: [email to come] or call the NRG Registration Desk at [phone number to come], Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

9.0 DRUG INFORMATION

9.1 Commercial Agent: Temozolomide

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

9.1.1 Adverse Events

Please refer to the package insert.

9.1.2 Availability/Supply

Please see Section 5.1 for administration instructions. Temozolomide capsules will be used for this study the following strengths are commercially available: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. Calculated doses should be rounded up to the nearest 5 mg. 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 (22-AUG-2018)

10.1 Central Pathology Review Guidelines

10.1.1 Prospective Review of Primary Tumor

- Enrolling sites will be required to submit H&E slide(s) containing tumor tissue for use in central histologic review after to Step 1 registration.
- Sites must include the required P4 form filled out by the local pathologist and a redacted pathology report. Accession number and date of procedure and all test

results must remain visible on the pathology report.

- Central review will be completed within 2-3 business days following receipt of the H&E stained slides. Slides can be recuts from the tumor blocks; they do not have to be the diagnostic H&E slides.
- In such an instance where the diagnosis between central review and original review is different, the pathologist responsible for the central review will contact the original pathologist immediately in order to adjudicate any such discrepancy.

10.2 Testing requirements and reporting for IDH and 1p19q Status

Each enrolling institution will be responsible for obtaining IDH and 1p19q status based on testing in a CLIA-certified laboratory. Results of this testing will be submitted along with the study specific P4 forms (see "Pathology Forms" in table under section 10.3.1). IDH and 1p19q testing recommendations: Testing will evaluate known IDH mutational hotspots. Sequencing is encouraged for patients with a negative immunohistochemistry using antibodies to mutant IDH R132H only. Evaluation of chromosomes 1p and 19q copy number utilizing either fluorescence in situ hybridization (FISH) or other assay of DNA copy number.

10.3 Biospecimen Submission Tables

10.3.1 Mandatory Specimen Submissions

See detailed specimen collection/processing/shipping instructions on the protocol specific page of the CTSU website.

1) Forms: P4 amd ST forms are required with each FFPE submission. The local pathologist is responsible for filling out the needed information prior to shipment.
2) Samples being submitted cannot be returned. They must be able to be banked for all consenting patients. Blocks can be returned upon request but the block will be punched prior to returning to the site.
3) Shipping: Sites pay for shipping of FFPE materials.
4) Contact the NRGBB at San Francisco with any questions. NRGBB@ucsf.edu

Ship Material to:
NRG Oncology Biospecimen Bank—San Francisco
2340 Sutter Street, Room S341
University of California San Francisco
San Francisco, CA 94115
415-476-7864; NRGBB@ucsf.edu

Specimen Type	Collection Time Points	Collection Information and Requirements/ Instructions for Site	Shipping
Specimen 1 H&E stained slide(s) of Primary tumor for central review	Pre-treatment	H&E slide- can be duplicate cut slide, does not have to be the diagnostic slide. See Section 10.1.1 for pathology central review requirements Forms: *ST, Pathology forms, and Study specific P4 form*	Ship ambient by overnight courier to NRGBB-San Francisco.
Specimen 2	Pre-treatment	Site should make every effort to submit the block for this study. If Site is unable to submit a Block then the following alternative is acceptable for the mandatory	Ship ambient or with cold pack by overnight courier to

FFPE Block (same as H&E)		integral marker portion of the study: One - two 3mmpunches (tumor size dependent) embedded in paraffin with a corresponding H&E slide. (punch kits available from NRGBB-SF). Note: Unstained slides are not an acceptable alternative submission for this study.	NRGBB-San Francisco.

- If sites do not have the facilities to embed the punches, the tissue bank can punch the blocks (one- two 3mm punches) and return the blocks to the submitting sites upon request. Sites pay for return shipping costs.

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 CTSU website.

Optional Study: Correlation of biomarkers to the development of neurocognitive decline after brain irradiation

5) Forms: ST forms are required with each submission.
6) The specimens are being collected in order to be prepared to correlate biomarkers to the development of neurocognitive decline after brain irradiation
7) 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.
8) Shipping days: Monday-Wednesday (US Sites). Monday-Tuesday (overseas)
9) Shipping costs- One prepaid return label per case for batch shipping of frozen specimens will be provided in the US kit from the NRGBB-SF
10) Processing instructions are located on the CTSU website.

For questions, contact:
NRG Oncology Biospecimen Bank—San Francisco
2340 Sutter Street, Room S341 (Box 1800)
University of California San Francisco
San Francisco, CA 94115
415-476-7864; NRGBB@ucsf.edu

Specimen 1: Serum-red top tube Spin and process serum at site	Baseline: Prior to radiation Post Treatment: End of radiation Post Treatment: 12 months.	Frozen serum samples containing a minimum of 0.5 mL per aliquot in five (5) 1 mL cryovials Storage: -80°C and ship frozen	Serum sent frozen in batches on dry ice via overnight courier to NRG Biospecimen Bank
Specimen 2 Plasma- EDTA	Baseline: Prior to radiation	Frozen plasma samples containing a minimum of 0.5	Plasma sent frozen in batches on dry

tube	Post Treatment: End of radiation Post Treatment: 12 months	mL per aliquot in five (5) 1 mL cryovials Storage: -80°C and ship frozen	ice via overnight courier to NRG Biospecimen Bank- San Francisco
Specimen 3: Whole Blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube (purple/lavender top) and mix	Baseline: Prior to radiation	Frozen whole blood samples containing 1.5 mL per aliquot in three (3) 2 mL cryovials Storage: -80°C and ship frozen	Whole blood sent frozen on dry ice by overnight courier to NRG Biospecimen Bank- San Francisco

11. SPECIAL STUDIES (NON-TISSUE) (22-AUG-2018)

Symptom Burden (NOTE: Translations not available for this protocol; enrollment restricted to English and French-speaking participants).

As a secondary aims, we will assess quality of life between the treatment arms using the LASA scale and measures of patient-reported symptom burden using the MDASI-BT. As symptom burden and quality of life are of great importance and likely inter-linked with cognitive function, positive findings for either or each of these secondary aims when combined with a positive outcome for cognition would make the trial even more impactful. In these exploratory aims we will test the hypothesis that compared to IMRT, patients treated with proton therapy will experience less symptom burden and have better quality of life. In a tertiary aim, we will also document and compare the impact of low to intermediate gliomas and therapy on patients' work and activity participation

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 also are measured on 0-10 scales.

Linear Analog Scale Assessment (LASA)
Linear Analog Scale Assessment (LASA) includes one question, which targets overall

QOL. The Likert scales run from 0 (as bad as it can be) to 10 (as good as it can be). Thus, higher ratings suggest higher QOL. Normative data for the single item of overall QOL data has normative data for cancer patients and normal volunteers (Locke, et al 2007; Singh et al 2014).

Work Productivity and Activity Impairment

The Work Productivity and Activity Impairment Questionnaire General Health (WPAI:GH) V2.0, a validated instrument to assess work and productivity (Reilly 1993), will be used to assess patient lost wages and productivity. It consists of 6 questions utilizing a recall period of the last 7 days. The WPAI has 4 outcomes: absenteeism (work time missed), presenteesism (impairment at work/reduced on-the-job effectiveness), work productivity loss, and activity impairment. These outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

Hopefulness

The hippocampus, in addition to impacting cognitive function by virtue of its mediation of memory, has been implicated as a mediator of emotional regulation, especially during stress (e.g., cancer and the treatment of cancer) and the hippocampus has therefore been posited to be a neuropsychological "hope center" (Godsil 2013). Indeed, smaller hippocampal volume has been correlated with greater vulnerability to psychological trauma (Gilbertson, 2002). NRG-CC003 (a prospective trial randomizing between prophylactic cranial irradiation alone or PCI with hippocampal sparing) included testing of hopefulness before treatment and 6 months following PCI in an effort to assess whether hopefulness is preserved in those who had protection of the hippocampus. The latter would offer thought-provoking evidence for the hippocampus as a hope center. However, the dose for PCI was relatively low (25 Gy total) in NRG-CC003 and might be below the threshold of hippocampal tolerance. Accordingly, NRG-BN005 (which calls for total doses of 54 Gy) has been amended to include hope testing at the same time points noted above. Meticulous correlation will then be made between hopefulness and hippocampal dosimetry.

The Adult Hope Scale (AHS) was developed by Snyder and colleagues at the University of Kansas (Snyder, 1989). The tool, designed to be completed in approximately five minutes, assesses the core components of hope theory: goal-setting, path establishment and agency (i.e., motivation) to attain said goals by pursuing an establish pathway. The instrument has been validated and utilized in oncology studies where links between levels of hopefulness with post-traumatic growth and positive coping skills have been found (Ho 2012, Clayton 2008). To avoid the confounding effect of depression on hope, a 2-item tool (PHQ 2) will be administered to determine if underlying depression is present among subjects (Gilbody, 2007). The PHQ 2 has already been used in a depression screening trial mounted by the RTOG and was found to be remarkably robust in detecting depressive symptoms. Note: there is no French version of the PHQ2 so the first two questions of the PHQ9 (French version) will be used in its place.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

The Radiation Oncology Co-Chair, David Grosshans, M.D., Vinai, Gondi, M.D. and Helen

Shih, M.D. will perform an RT Quality Assurance Review on an ongoing basis once complete RT data is received at NRG Headquarters. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

13.1 Data Management/Collection (22-AUG-2018)

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). To access iMedidata/Rave, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users 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 will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts also will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2 Summary of Data Submission

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.

For reporting of second primary cancers or other report forms available in Rave: Indicate form for reporting in Rave, timeframes; add if loading of the pathology report is

required.

Summary of Data Submission: Refer to the CTSU website.

See Section 8.4.1 for TRIAD account access and installation instructions.

13.3 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

This is a randomized phase II study in which patients will register to step 1, complete neurocognitive assessments and then move to step 2 randomization. Step 2 will stratify patients according to baseline cognitive function (impaired vs not impaired), resection status (gross vs. subtotal), and 1p19q status (co-deleted vs. intact) and randomize 2:1 to protons or photons, respectively, using permuted block randomization (Zelen 1974). Impaired cognitive function is determined by a composite z-score < -0.5. This trial is not blinded. The target accrual is 120 patients and is based off of step 2 enrollment. All analyses will be conducted on an intent-to-treat basis of all at-risk patients (regardless of eligibility). The primary endpoint analysis will take place once all patients have been on study for 24 months from the end of treatment.

14.2 Study Endpoints

14.2.1 Primary Endpoint

Cognition, as measured by the CTB COMP score (Clinical Trial Battery composite) (calculated from HVLT-R, TMT Parts A and B, and COWA standardized scores).

14.2.2 Secondary Endpoints

- Cognition, as measured individually by HVLT-R, TMT Parts A and B, and COWA
- Symptoms, as measured by MDASI-BT
- Quality of life, as measured by the LASA scale
- Overall survival
- Local control
- Progression-free survival
- Site vs central IDH and 1p19q status

14.3 Primary Objectives Study Design

14.3.1 Primary Hypothesis and Endpoints

The primary hypothesis is that proton therapy will result in improved cognition, as measured by the CTB COMP, over time.

14.3.2 How Primary Endpoints Will Be Analyzed

The primary endpoint will be assessed with a general linear model with maximum likelihood estimation. Three models will be conducted. Baseline CTB COMP score, treatment arm, time, treatment by time interaction (if significant) and stratification factors will be included in the model for the primary endpoint. A second model will be built with these same variables and relevant covariates, such as total volume of intracranial disease, GTV and CTV size, histology, anti-epileptic use, and disease response to therapy (as measured by RANO criteria). Other than baseline score CTB COMP, treatment arm, and time, only covariates with a p-value < 0.10 will be retained in the model. A third model will be conducted at 10 years using the additional time points of neurocognitive assessments that will incorporate as covariates baseline CTB COMP score, treatment arm, time, treatment by time interaction (if significant), stratification factors, and other relevant covariates as listed above. Similar to the second model, only covariates with a p-value < 0.10 will be retained in the model other than baseline score, treatment arm, and time.

Radiation induced cognitive deficits have been best documented decades following the completion of therapy. Moreover, for patients with IDH mutant tumors survival can often be measured in decades. Therefore, data collection will continue for up to 10 years. However, 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 $\geq$15% of the data is missing at any time point for the any of the neurocognitive assessments, patient characteristics will be compared between patients with completed assessments and those with missing assessments. If any are found to differ significantly, they will be included in the longitudinal model which assumes that the data is MAR. Graphical methods may also be used to determine the type of missingness. If the missingness is determined to be ignorable, no additional analyses need to occur. If the missingness is determined to be non-ignorable, other methods, such as imputation, may be performed. Specifically, 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). Since survival may reduce the number of completed assessments as well as impact the results, a sensitivity analysis will be performed using patients alive at 2 years.

Missing data will be assessed. If $\geq$15% of the data is missing at any time point for the any of the neurocognitive assessments, patient characteristics will be compared between patients with completed assessments and those with missing assessments. Graphical methods may also be used to determine the type of missingness. If the missingness is

determined to be ignorable, no additional analyses need to occur. If the missingness is determined to be non-ignorable, other methods, such as imputation and pattern mixture models, may be performed.

14.3.3 Sample Size and Power Calculations

Patients will complete the HVLT-R, TMT Parts A and B, and COWA test prior to start of treatment and 6 months, 1 year, then annually from the end of treatment until 10 years. The CTB COMP score, which is calculated using standardized scores from these tests (Benedict 1998; Ruff 1996; Tombaugh 2004), will be the primary endpoint. The first 3 follow-up time points (6, 12, and 24 months) will be of interest. Cohen's widely used guidelines 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). A moderate effect size of 0.5 will be used in this study due to the lack of prior data. It is assumed that there is an effect size of 0.5 at 6, 12, and 24 months. An attrition rate of 15% at 6 months, 27.7% at 12 months, and 38.6% at 24 months (15% of patients lost between each time point) is expected, due to non-compliance and loss to follow-up. An autoregressive correlation structure is assumed with ρ=0.4 due to the correlated nature of the data at consecutive time points. This means that the further out the time points go, the weaker the correlation. Using the method of Hedeker et al. (1999) with a one-sided $\alpha = 0.05$ and 2:1 randomization, 120 patients will provide 90% power. It is expected that very few patients (5%) will be registered to Step 1 and not proceed to randomization on Step 2.

14.4 Study Monitoring of Primary Objectives

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

Interim Safety Analysis

Since this trial compares two different RT methods, PFS is also of interest. Due to limitations in prior data, PFS, defined as the time from date of randomization to date of progression (defined using the local control definition in Section 4) or death, whichever occurs first, will be used. A confidence interval will be used to determine if the PFS rate in the proton arm is greater than that in the photon at 1 year. Specifically, the PFS rate in the photon arm is expected to be 78% at 1 year, using data obtained from the RT + PCV arm of RTOG 9802. The table below depicts the 95% confidence intervals around the 78% rate for increasing sample sizes. Each time 40 patients have at least 1 year of follow-up on the proton arm, the PFS rate for these patients will be compared to the appropriate lower bound from the table below. Therefore, if the proton arm has a PFS rate below the lower confidence limit, then the PFS rate and corresponding 95% confidence interval in the photon arm will be calculated and compared to that of the proton arm. If the rate in the proton arm falls below the 95% lower confidence limit in the photon arm, then proton therapy would be deemed unacceptable. The results from each of these looks will be presented to the NRG Oncology DMC to determine if the study can proceed as planned. The first look is projected to occur prior to study closure. The second look will occur approximately 1 year prior the primary endpoint analysis.

95% Confidence Intervals for 78% PFS Rate			
n	Lower Bound	Upper Bound	Projected Time of Analysis from Activation
40	65.2%	90.8%	33 months
80	68.9%	87.1%	48 months

14.5 Accrual/Study Duration Considerations

Based upon accrual to similar trials at MD Anderson, it is estimated that the monthly accrual will be 4 patients. Assuming a 6 month period of negligible accrual, it will take an additional 30 months to accrue 120 patients. Thus it will be 36 months from activation to study closure. The primary endpoint analysis will take place approximately 2 years from the end of treatment of the last patient which is projected to be just over 5 years from study activation. This study will be monitored according to accrual guidelines set by DCP.

14.6 Secondary or Exploratory Endpoints (22-AUG-2018)

14.6.1 Secondary Hypotheses and Endpoints: The expected level of detail for secondary hypotheses will be less than for the primary hypothesis and endpoint.

- Comparison of cognition, as measured individually by HVLT-R, TMT Parts A and B, and COWA, between treatment arms
- Comparison of symptoms, as measured by MDASI-BT, between treatment arms
- Comparison of quality of life, as measured by the LASA scale, between treatment arms
- Comparison of overall survival, between treatment arms
- Comparison of local control, between treatment arms
- Comparison of progression-free survival, between treatment arms
- Evaluation of adverse events
- Comparison of Illumnia MethylationEPIC beadchip array-derived IDH and 1p19q status to that submitted by enrolling sites.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Cognition

The HVLT-R, TMT Parts A & B, and COWA will be analyzed independently using a general linear model with maximum likelihood estimation. Standardized scores will be used (Benedict 1998; Ruff 1996; Tombaugh 2004). Baseline CTB COMP score, treatment arm, time, treatment by time interaction (if significant), stratification factors, and relevant covariates, such as total volume of intracranial disease, GTV and CTV size, histology, anti-epileptic use, and disease response to therapy (as measured by RANO criteria) will be included as covariates. Other than baseline score, treatment arm, and time, only covariates with a p-value < 0.10 will be retained in the model.

In addition to the longitudinal analysis, change, as defined by the Reliable Change Index (RCI), will be assessed at each time point and compared between treatment arms using a chi-square test or fisher's exact test if the cell size is < 5 (Jacobson 1991; Chelune 1993). This will be conducted at each follow-up time point for the HVLT-R, TMT Parts A & B, and COWA test along with the CTB COMP e score. Missing data will be assessed as

described in Section 14.3.2, including the sensitivity analysis for patients surviving 2 years. A reduced one-sided significance level, 0.01, will be used for these multiple comparisons due to the correlated nature of each endpoint. Given the 2:1 randomization, statistical tests will only be performed if the sample size in the control arm is sufficient for testing.

Patient-Reported Outcomes (PROs)
The MDASI-BT will be used to measure symptoms and the LASA scale will be used to measure quality of life (QOL). These will be collected at the same time as the neurocognitive assessments plus an additional time point: prior to start of treatment, end of treatment and 6 months, 1 year, then annually from the end of treatment until 10 years. Assessment of symptoms will focus on disease related factor groupings (activity subdimension, neurologic factor, and cognitive factor), treatment related symptoms (constitutional, general), and overall impact (total symptom burden and total interference). The LASA is a single numerical outcome variable that will be analyzed.

A general linear model with maximum likelihood estimation will be used to assess symptom and QOL trends across time as the primary PRO endpoint. Baseline score, treatment arm, time, treatment by time interaction (if significant), stratification factors, and relevant covariates, such as total volume of, GTV and CTV size, histology, anti-epileptic use, and disease response to therapy (as measured by RANO criteria) will be included as covariates in each model. Other than baseline score, treatment arm, and time, only covariates with a p-value < 0.10 will be retained in the model. Missing data will be assessed as described in Section 14.3.2, including the sensitivity analysis for patients surviving 2 years.

The following analyses will be exploratory in nature. The change from baseline to each follow-up time point (calculated as baseline score subtracted from follow-up score) will be compared between treatment arms using a t-test, or Wilcoxon test if the data is not normally distributed. A one-sided significance level of 0.05 will be used for these analyses since they are exploratory. Given the 2:1 randomization, statistical tests at each follow-up time point will only be performed if the sample size in the control arm is sufficient for testing.

Efficacy Endpoints
Overall survival (OS) is defined as the time from randomization to the date of death, or last known follow-up time. Progression-free survival (PFS) is defined as the time from randomization to the death of progression or death, or last known follow-up time. OS and PFS will be estimated using the Kaplan-Meier method and compared between arms using the log rank test (Kaplan 1958; Mantel 1966). Cox proportional hazards models will be used for OS and PFS adjusting for treatment arm and stratification factors (Cox 1972). Local control is defined using RANO criteria as described in Section 4. Local control will be estimated using cumulative incidence, treating death prior to an event as a competing risk. Gray's test will be used to compare local control rates between arms (Gray 1988). Cause-specific Cox proportional hazards models will be used for local control, adjusting for treatment arm and stratification factors. A two-sided significance

level of 0.05 will be used for comparisons between arms.

Adverse events
Adverse events (AEs) will be graded according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 through April 12, 2018; v. 5.0 beginning April 13, 2018. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. Grade 3+ treatment related AEs will be compared between arms using a chi-square test, or Fisher's exact test if cell frequencies are < 5, at the one-sided 0.05 significance level.

Comparison of site and central IDH and 1p19q status
A different method will be utilized for site vs. central IDH and 1p19q status as described in Section 10. Specifically, a single test will be done for both IDH and 1p19q testing centrally while sites will perform a separate test for IDH and 1p19q. The results from the central and site testing will be compared using the kappa statistic (Viera 2005). The asymptotic test of H_0: $\kappa=0$ will be performed using the Z-statistic to determine the strength of agreement. Concordance and discordance rates will be tabulated.

14.6.3 Power Calculations for Secondary Objectives

PROs and Symptom Burden
The primary PRO analysis will be a longitudinal model of the first 4 time points (end of RT, 6, 12, and 24 months) of the single-item LASA for QOL and symptom burden score from the MDASI-BT for symptoms. Cohen's widely used guidelines 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). A moderate effect size of 0.5 will be used in this study due to the lack of prior data. It is assumed that there is an effect size of 0.5 at end of RT, 6, 12, and 24 months. A slightly greater attrition rate is expected for this component as compared to the neurocognitive tests since those are the primary endpoint of the trial. Therefore, an attrition rate of 15% at the end of RT, 27.7% at 6 months and 38.6% at 12 months, and 47.8% at 24 months (15% of patients lost between each time point) is expected, due to non-compliance and loss to follow-up. An autoregressive correlation structure is assumed with $\rho=0.4$ due to the correlated nature of the data at consecutive time points. Using the method of Hedeker et al. (1999) with a one-sided $\alpha = 0.025$ (using a Bonferonni adjustment resulting in an overall type I error of 0.05) and 2:1 randomization, 120 patients will provide >90% power.

Collection of neurocognitive tests and PROs extends to 10 years from the end of treatment. Due to the concerns of a high rate of patient non-compliance at later time points, assessment of compliance rates at 5 years and later will be done on a routine basis and shared with the study investigators. If the compliance rate drops to < 50% of expected patients for the neurocognitive tests or one of the PROs, LASA and MDASI-BT, then that assessment will be removed for all future data collection. A time window of +/- 4 months (+/- 122 days) will be used when assessing compliance at these later time points (annually years 5-10 from the end of treatment). Expected patients include all randomized alive patients and exclude those that have withdrawn consent. Note that if compliance falls below 50% on only one or two of the three assessments (neurocognitive

tests, LASA, and MDASI-BT), only that assessment(s) will be eliminated from the study.

14.7 Exploratory Hypothesis and Endpoints

14.7.1 Exploratory Hypotheses and Endpoints

- Impact of chemotherapy use on cognition
- Assessment of dose-response relationships between dosimetry and cognitive outcomes
- Assessment of tumor molecular status and cognition
- Assessment of patterns of failure and pseudoprogression as a function of radiation delivery type
- Local control, overall survival, and progression free survival by tumor grade
- Work and activity participation, as measured by the WPAI:GH

14.7.2 Definitions of Exploratory Endpoints and How These Will Be Analyzed

Chemotherapy Use

Cognition, using the CTB COMP and each individual test score, will be compared between patients who have completed chemotherapy per protocol (defined as receiving a full dose of temozolomide as specified in Section 5.1) and those who have not or have received non-temozolomide based chemotherapy. If chemotherapy use is highly imbalanced (i.e. one of the two groups has < 15% of patients), this analysis will not occur. A general linear model using maximum likelihood estimation will be built for CTB COMP and each individual test score over time including baseline score, treatment arm, time, treatment*time interaction (if significant), stratification factors, and chemotherapy use. If chemotherapy use is significant, it will be considered for inclusion in the primary endpoint model.

Assuming the sample sizes of each group (completed per protocol vs. those who did not) are sufficient, subgroup analyses will be conducted comparing treatment arms within each subgroup. Each neurocognitive test, HVLT-R, TMT Part A & B, and COWA, will be analyzed along with the CTB COMP score. The decline at each follow-up time point, as defined by the RCI criteria, will be compared between treatment arms using a chi-square test (or Fisher's exact if the cell sizes are < 5). Given the 2:1 randomization, statistical tests will only be performed if the sample size in the control arm is sufficient for testing.

Dosimetric Outcomes

The dose-response relationship between cognition, using the CTB COMP and each individual test score, and neuro-anatomic dosimetry, including the hippocampus and whole brain, will be assessed. The decline, as calculated using the RCI, will be used to determine neurocognitive impairment. The dose-response curve will be modeled using a non-linear model.

Tumor Molecular Status

1p19q will be determined by the institution. Cognition, using the CTB COMP and each individual test score, will be compared by 1p19q status. A general linear model using maximum likelihood estimation will be built for CTB COMP and each individual test

score over time including baseline test score, 1p19q status, treatment arm, and stratification factors.

Radiation Delivery Type
Radiation delivery type is categorized as scanning beam proton therapy, passive scatter proton therapy or intensity modulated photon therapy. If one of these groups has < 15% of patients, then this analysis will not occur. Cox models will also be built to assess the effect of radiation delivery type on patterns of failure while adjusting for stratification factors. Patterns of failure refer to local failure (within high dose), marginal failure (at edge of treatment field) or distant failure (outside radiation volume). The association of pseudoprogression, a yes/no variable, and radiation delivery type at each follow-up time point will be assessed using a Chi-square test or Fisher's exact test if the cell size is < 5. Pseudoprogression by treatment arm at each follow-up time point will also be assessed using a Chi-square test or Fisher's exact test if the cell size is < 5.

Efficacy Endpoints by Tumor Grade
Local control PFS, and OS are defined in Section 14.6.2. OS and PFS will be estimated using the Kaplan-Meier method and compared between tumor grades, ignoring treatment arm, using the log rank test (Kaplan 1958; Mantel 1966). Cox proportional hazards models will be used for OS and PFS adjusting for treatment arm and stratification factors (Cox 1972). Local control will be estimated using cumulative incidence, treating death prior to an event as a competing risk. Gray's test will be used to compare local control rates between tumor grade ignoring treatment arm (Gray 1988). Cause-specific Cox proportional hazards models will be used for local control, adjusting for grade, treatment arm and stratification factors. A two-sided significance level of 0.05 will be used for comparisons between groups.

Work and Activity Participation
The WPAI will be used to measure work productivity and activity participation. The WPAI will be collected prior to the start of treatment, at the end of RT, 6 months, 1 and 2 years from the end of radiation. The WPAI has 4 outcome variables: absenteeism (work time missed), presenteesism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment=absenteeism + presenteeism), and activity impairment. If sample sizes are large enough, subset analyses will be conducted by occupation (managerial or professional specialty, sales/technical/administrative support, service, operatory/fabricator/laborer, arts/media/athletics, other).

The distributions of each item and outcome measure of the WPAI will be tabulated at each time point. Absenteeism, presenteeism, and work productivity loss will be limited to those patients working outside of the home while activity impairment will be for all employed patients (inside and outside the home). The association between each of the four WPAI outcomes and NCF, as measured by the CTB COMP score and each NCF test separately, and symptoms, as measured by the MDASI-BT total symptom burden score and total interference score, will be assessed using Pearson correlation coefficients at each time point. If the MDASI-BT scores are significant at the 0.05 level, then further exploration using the individual items making up the significant score(s) will be assessed.

General linear models with maximum likelihood estimation for each of the 4 WPAI outcomes will be built to determine the effect the CTB COMP score and the MDASI-BT total symptom burden score and affective sub-dimension score on each of the WPAI outcomes while adjusting for KPS. Separate models will be built for CTB COMP and symptoms (total symptom burden score and total interference score) due to the different collection times (NCF is not collected at the end of RT) resulting in two models for each of the 4 WPAI outcomes.

14.8 Gender/Ethnicity/Race Distribution

Although this trial is open to all NRG Oncology members, there are few international sites with proton centers that will be able to enroll English speaking patients. Therefore, international enrollment is expected to be minimal on this trial (5%). No differences across patient subsets are anticipated.

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	1	0	0	2
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	4	4	1	1	10
White	32	38	8	19	97
More Than One Race	0	0	0	0	0
Total	39	46	9	20	114

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	0
Asian	1	2	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	2	1	0	0	3
More Than One Race	0	0	0	0	0
Total	3	3	0	0	6

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