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Phase II Trial of Low-Dose Whole Brain Radiotherapy with Concurrent Temozolomide and Adjuvant Temozolomide in Patients with Newly-Diagnosed Glioblastoma Multiforme

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TREATMENT SCHEMA

Weeks 1-6	**Adjuvant TMZ (4 weeks (+/- 3 days)) after the completion of RT)**
Concurrent RT+TMZ TMZ 75 mg/m2 / day RT = 2.0 Gy/day (5 days/week) x 30 fractions, total 60 Gy as follows: RT 0.15 Gy/day Whole Brain + RT 1.85 Gy/day Partial Brain Optional PCP prophylaxis	Standard Adjuvant TMZ (28 day cycle) TMZ 150 mg/m2 / day, Days 1-5, Cycle # 1 TMZ 200 mg/m2 / day, Days 1-5, Starting Cycle # 2 TMZ total of 6-12 cycles or until disease progression Optional Tumor Treating Fields Optional PCP prophylaxis

- TMZ = Temozolomide; RT = Radiation Therapy; Partial Brain = Planning Target Volume (PTV); PCP = pneumocystis carinii (jirovecii) pneumonia.

- Both the whole and partial brain RT will be given per day, giving the standard of care total of 2 Gy per day to the tumor, 5 days per week for a total of 60 Gy over 6 weeks.

- All Patients will receive the standard TMZ (Stupp regimen) during and after the completion of RT.

- RT/TMZ are to commence 3-6 weeks after surgery (can be biopsy only). If multiple surgeries are required (resection, abscess drainage, etc), then RT should commence not before 3 weeks, but no later than 6 weeks after the last surgical procedure.

1.0 INTRODUCTION

1.1 Background

Glioblastoma multiforme (GBM) is the most common of all adult malignant primary brain tumors and portends a very poor prognosis. Glioblastomas (World Health Organization [WHO] grade IV astrocytomas) comprise approximately 15% of all primary brain tumors, and the incidence is 2-3 new cases per 100,000 people per year.[1-2] In adults, GBM is almost always located in the cerebral hemispheres; though, rarely tumors may affect the brainstem or spinal cord.[1] Lower-grade astrocytomas (WHO grades II or III) can progress to GBM, but in the majority of cases (60%) glioblastomas develop de novo.[1] In cases of primary GBM, symptoms typically appear less than 3 months prior to diagnosis.[1] Common symptoms include headaches, nausea/vomiting, fatigue, personality changes, memory loss, and the development of neurological deficits. The pivotal Stupp trial, which set the current standard of care, demonstrated median, 2-year, and 5-year survivals of 14.6 months, 27%, and 10% respectively.[3-4] There are almost no long-term survivors.

Radiotherapy (RT) has been integral in the treatment of GBM since the 1970s when Walker et al. showed that post-operative whole brain radiotherapy (WBRT) offered significant improvements in median survival time, and even more so when given with concomitant BCNU chemotherapy.[5] Ensuing dose escalation studies found the optimal dose to be 60 Gy.[6] Patients could not tolerate escalation to higher doses than 60 Gy with WBRT due to unacceptable toxicity. Even with WBRT of 60 Gy, a huge volume of healthy brain tissue was unnecessarily treated with high-dose radiation; recurrences with WBRT remained overwhelmingly local.[7] Hochberg and Pruitt (1980) found that after WBRT only 3% of recurrences were outside 2 cm of the margins of the primary tumor.[8] With the rise of the CT scan in the 1980s and the MRI in the 1990s, along with subsequent improvements in three-dimensional conformal radiation, partial brain RT (PBRT) became practical since tumor margins could be visualized and irradiated more accurately.[9-10] Subsequently, WBRT was shown to provide no survival benefit over PBRT at the same dosage;[11-12] thus, the latter took over as the standard of care.

1.2 Role of Temozolomide

Until 2005, the standard of care was surgical resection, with post-operative RT alone or in combination with BCNU chemotherapy. Recurrences with PBRT still occurred almost exclusively within the field of the RT.[13-14] In fact, Chan et al. (2002) found that despite RT dose escalation to 90 Gy, failure patterns remained local.[10] Patients were not living long enough for distant failures to develop; median survival was still approximately less than one year after diagnosis.[15,16,17]

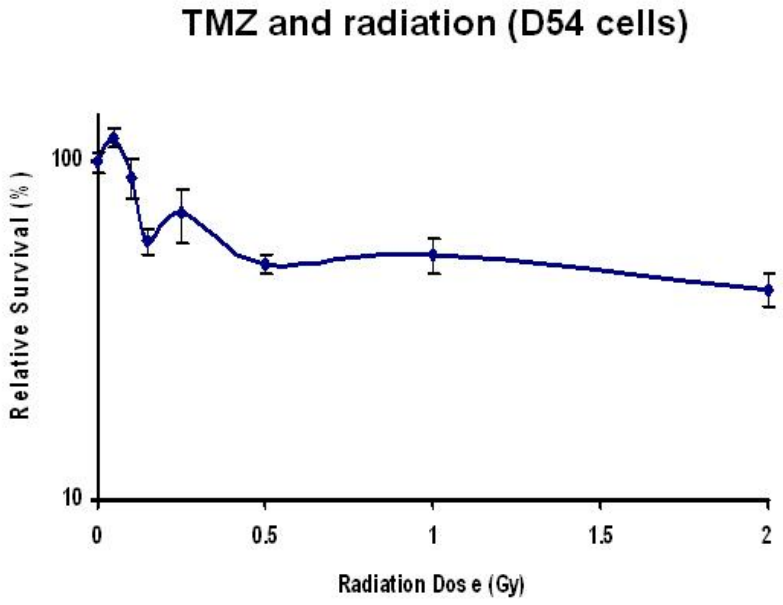
After the chemotherapy drug temozolomide (TMZ), an oral alkylating agent of the imidazotetrazine derivatives, demonstrated antitumor activity as a single agent, and then concomitantly with RT in a phase II trial,[18] the European Organisation

for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups (EORTC) and the National Cancer Institute of Canada (NCIC) commissioned a phase III trial to compare this regimen with RT alone in patients with newly diagnosed GBM. TMZ has modest single agent efficacy and acts as a radiosensitizer. In this phase III trial reported by Stupp et al, the median survival was 12.1 months with RT alone, and 14.6 months with RT plus TMZ, with minimal additional toxicity.[4] Furthermore, the two year-survival rate was 10.4% with RT alone, and 26.5% with RT plus TMZ ($p < 0.001$). In the follow-up study it was shown that the benefits and survival advantage of adding adjuvant TMZ to treatment lasted throughout 5 years of follow-up ($p < 0.0001$).[3] Thus, RT (60 Gy given in 2 Gy fractions) plus concomitant and adjuvant TMZ has become the standard of care.

1.3 Treatment Failure Patterns in the Temozolomide Era

With the advent of TMZ and RT, the overall survival has increased due to improved local control; consequently, distant failure outside of the RT field has greatly increased in frequency. Brandes et al (2009) found that with treatment of RT plus TMZ, 28% of recurrences were outside the high dose PBRT field.[19] Also, recurrences outside the RT field occurred after a longer period of time than recurrences inside the RT field. It is theorized that once local tumor control has been achieved, the malignant cells outside the RT field remain and are able to proliferate. Indeed, classic autopsy series have demonstrated malignant cells very distant from the edge of the dominant tumor.[20] So it is clear that now that as GBM patients are experiencing longer survivals, distant brain failures are becoming a more frequent.

1.4 Low-dose Radiation



Recent presented data from our institution (above figure, ASTRO 2011) suggest that the combination of TMZ with very low-dose RT (0.15 Gy) proves significantly

toxic to GBM cell lines (70% reduction in survival rates).[21] It is thought that such low-dose RT is able to damage cellular DNA and induce apoptosis without activating DNA repair mechanisms. TMZ acts as radiosensitizer when given concurrently with radiation therapy.

Again, WBRT at conventional doses (60 Gy in 2 Gy fractions) is not given with concurrent TMZ since the severe toxicity risk would be prohibitive. However, fractions of 0.15-0.5 Gy, an order of magnitude less than what is conventionally given to patients, should be very tolerable if WBRT is given. The randomized trials studying concurrent TMZ and whole brain RT (WBRT) in patients with brain metastasis did not demonstrate increased serious toxicities associated with TMZ.[22,23] These trials had 2 Gy fractions to 40 Gy [Antonadou, 2002] and 3 Gy fractions to 30 Gy [Verger, 2005]. All available information suggests no overlapping or problematic toxicities will result from the low-dose WBRT given with TMZ. It is highly doubtful that low-dose WBRT of 0.15 Gy per day will be toxic since it is a whole magnitude less than utilized in these randomized trials, but since no phase I data exist for this specific treatment combination, this study is intended to determine the safety and efficacy of low-dose WBRT given in combination with the standard of care TMZ.

In the current proposed trial the role of the low-dose WBRT (0.15 Gy) would be to safely treat the microscopic distant GBM cells outside of the high dose RT region and sensitize the gross tumor, while the focal radiation dose (1.85 Gy) to the gross tumor will bring the total tumor dose of 2 Gy per fraction which is the standard of care.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the safety and efficacy of low-dose whole brain RT (WBRT) when given concurrently to the standard TMZ and focal partial brain RT (efficacy will be measured by decreased distant disease recurrence rate).

2.2 Secondary Objectives

2.2.1 To determine the radiographic response with the combination therapy.
2.2.2 To determine the treatment failure patterns after the combination therapy.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologically proven diagnosis of glioblastoma or gliosarcoma (WHO grade IV).
3.1.2 Infratentorial are eligible.
3.1.3 History and physical with neurological examination, steroid documentation, height, and weight within 14 days of registration.

3.1.4 A diagnostic contrast-enhanced MRI of the brain must be performed preoperatively and postoperatively prior to the initiation of radiotherapy. The postoperative scan must be performed within 28 days prior to registration. (Please note: Contrast enhanced Brain CT is allowed if MRI is contraindicated.)
3.1.5 Karnofsky performance status ≥ 70 or ECOG performance status ≤ 2.
3.1.6 Age ≥ 18.
3.1.7 CBC with differential obtained within 14 days prior to registration, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3.
- Platelets ≥ 100,000 cells/mm^3.
- Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥10.0 g/dl is acceptable).

3.1.8 Adequate renal function within 14 days prior to registration, as defined below:

- BUN ≤ 30 mg/dl.
- Creatinine ≤ 1.7 mg/dl.

3.1.9 Adequate hepatic function within 14 days prior to registration, as defined below:

- Bilirubin ≤ 2.0 mg/dl.
- ALT/AST ≤ 3 x upper limit of normal (ULN).

Please note that if the liver function tests are abnormal, the decision to initiate temozolomide treatment should carefully consider the benefits and risks to the individual patient.
3.1.10 Systolic blood pressure ≤ 160 mg Hg or diastolic pressure ≤ 90 mg Hg within 14 days prior to registration.
3.1.11 Patient must provide study specific informed consent prior to study entry.
3.1.12 For women of child-bearing potential, negative serum pregnancy test within 14 days prior to registration.
3.1.13 Women of childbearing potential and male participants must practice adequate contraception.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior invasive malignancy (except for non-melanomatous skin cancer) unless disease free for ≥ 3 years. For example, carcinoma in situ of the breast, oral cavity, and cervix are all permissible.
3.2.2 Metastases beyond the cranial vault.
3.2.3 Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment is not permitted.
3.2.4 Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in significant overlap of radiation fields.
3.2.5 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure within the last 6 months.
- Transmural myocardial infarction within the last 6 months.
- New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to registration.

- History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months.
- Serious and inadequately controlled cardiac arrhythmia.
- Significant vascular disease (e.g., aortic aneurysm, history of aortic dissection) or clinically significant peripheral vascular disease.
- Evidence of bleeding diathesis or coagulopathy.
- Serious or non-healing wound, ulcer, or bone fracture or history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess, major surgical procedure or significant traumatic injury within 28 days prior to registration, with the exception of the craniotomy for tumor resection or follow-on craniotomies to manage complications of brain tumor management such as hemorrhage or infection.
- Bacterial or fungal infection requiring intravenous antibiotics at the time of registration.
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy 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.
- 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 necessary because the treatments involved in this protocol are significantly immunosuppressive.
- 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.
- Any other major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy.
- Cognitive impairment that precludes a patient from acting as his or her own agent to provide informed consent.

3.2.6 Women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the chemotherapeutic treatment involved in this study is significantly teratogenic.

3.2.7 Pregnant or lactating women, due to possible adverse effects on the developing fetus or infant due to study treatment.

3.2.8 Patients treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study.

3.2.9 Multi-focal tumors are ineligible

4.0 PATIENT TREATMENT EVALUATIONS

4.1 Within 14 days of registration:

4.1.1 History and Physical with neurological exam and steroid documentation.
4.1.2 Complete Blood Count (CBC) with differential.
4.1.3 Comprehensive metabolic panel (CMP) including Liver Function Tests.

4.2 Within 28 days of registration:
4.2.1 Post-operative, contrast-enhanced MRI of the brain (contrast enhanced Brain CT is allowed if MRI is contraindicated).

4.3 During TMZ and RT:
4.3.1 CBC with differential and CMP including Liver Function Tests will be done every 2 weeks.
4.3.2 Weekly patient evaluation with toxicity assessment.

4.4 During Adjuvant TMZ:
4.4.1 History and physical with neurological exam, steroid documentation, and toxicity assessment within 7 days prior to starting each cycle.
4.4.2 CBC with differential and CMP including Liver Function Tests will be done within 7 days prior to starting new cycle.
4.4.3 Brain MRI with contrast (contrast enhanced Brain CT is allowed if MRI is contraindicated) prior to cycle 1 and then every 2-3 months till the end of Adjuvant TMZ.

4.5 Standard of Care Follow-Up Assessments (to begin after completion of Adjuvant TMZ):

4.5.1 Follow-up schedule:
- Every 1-3 months for the first 2 years (years 1-2).
- Every 3-6 months for the next 2 years (years 3-4).
- Annually starting at year 5.

4.5.2 At each follow-up visit:
- History and physical with neurological exam and toxicity assessment.
- MRI of the brain with contrast (contrast enhanced Brain CT if MRI is contraindicated):
  - Usually, every 2-3 months for first 2 years. However, the frequency is at the discretion of the physician and, thus, it may be performed more frequently if medically necessary.
  - MRI perfusion and spectroscopic examinations are allowed at any time, if clinically indicated.
- Any other test deemed medically necessary.

4.6 If the patient progresses at any time during treatment, the patient will be considered off protocol. Any treatment and follow-up after that time will be at the discretion of the treating physician.

5.0 STUDY DESIGN AND TREATMENT SUMMARY

TREATMENT SCHEMA

Weeks 1-6	Adjuvant TMZ (4 weeks (+/- 3 days)) after the completion of RT)
Concurrent RT+TMZ TMZ 75 mg/m2 / day RT = 2.0 Gy/day (5 days/week) x 30 fractions, total 60 Gy as follows: RT 0.15 Gy/day Whole Brain + RT 1.85 Gy/day Partial Brain Optional PCP prophylaxis	Standard Adjuvant TMZ (28 day cycle) TMZ 150 mg/m2 / day, Days 1-5, Cycle # 1 TMZ 200 mg/m2 / day, Days 1-5, Starting Cycle # 2 TMZ total of 6-12 cycles or until disease progression Optional PCP prophylaxis

- TMZ = Temozolomide; RT = Radiation Therapy; Partial Brain = Planning Target Volume (PTV); PCP = pneumocystis carinii (jirovecii) pneumonia.
- Both the whole and partial brain RT will be given per day, giving the standard of care total of 2 Gy per day to the tumor, 5 days per week for a total of 60 Gy over 6 weeks.
- All Patients will receive the standard TMZ (Stupp regimen) during and after the completion of RT.
- RT/TMZ are to commence 3-6 weeks after surgery (can be biopsy only). If multiple surgeries are required (resection, abscess drainage, etc), then RT should commence not before 3 weeks, but no later than 6 weeks after the last surgical procedure.

Patients can only be enrolled after all eligibility criteria are met. The date of registration/enrollment is considered to be the day the Eligibility Checklist is signed by the verifying physician. Once a patient is enrolled, a unique case number will be assigned to the patient.

5.1 Safety and efficacy

It is highly doubtful that low-dose WBRT of 0.15 Gy per day will have any significant side-effects. However, since no study has been performed to test this regimen, this study will test the safety and efficacy of low-dose WBRT with concurrent TMZ. A total of 47 patients will be enrolled on this study, with a mandatory interim review after the first 6 patients. A dose-limiting toxicity (DLT) will be assessed from the first day of treatment with TMZ (the night prior to starting RT or TMZ can be started within 24 hours of first RT treatment) to 1 month after the completion of RT. Thus, the 7th patient cannot be enrolled until all 6 patients have been assessed for 1 month after the completion of RT. Low-dose WBRT will be deemed safe and effective if no more than 1 out of 6 patients'

experiences a DLT as defined below. If 2 or more patients experience a DLT, then low-dose WBRT at this dose of 0.15 Gy will be deemed unsafe, and the trial will close.

5.2 Definition of Dose-Limiting Toxicity (DLT)

Toxicities will be graded according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If multiple toxicities are seen, the presence of DLT should be based on the most severe toxicity experienced. DLT will be defined as any of the following events occurring during treatment with TMZ and RT, and attributable (probably related) to the study regimen:

- Any grade 4 thrombocytopenia, grade 4 anemia, or grade 4 neutropenia with fever (> 100.4°F) or grade 4 neutropenia lasting more than 7 days.
- Any non-hematologic grade 3 or greater toxicity (excluding alopecia) maintained despite maximal medical therapy 72 hours after maximal medical therapy is instituted; except infection, seizure, deep venous thrombosis (DVT) or pulmonary embolism (PE). The reason for this exclusion is that seizures, DVT and/or PE are very common in the glioblastoma multiforme population, are conventionally treated without interruption of the primary brain tumor treatment, and their existence does not influence the decision to go forward with completion of chemoradiation to otherwise qualifying patients. Management of DVT with or without PE conventionally involves insertion of a Greenfield filter and consideration of anticoagulation to a dose and degree that is dependent on a consideration of individual comorbidities and individualized for each patient. Thus the occurrence of DVT or PE will not influence a consideration of the feasibility of adding low-dose WBRT. Management of seizures conventionally can involve consultation with neurology and the regimen employed likewise does not influence completion of chemoradiation. Management of infection occurs via the standard of care unless due to accompanying grade 4 neutropenia as described above.

Please Note: non-hematologic toxicities such as rash, nausea, vomiting, diarrhea, mucositis, hypophosphatemia, and hypertension will only be considered DLTs if they remain grade 3 or greater despite maximal medical therapy 72 hours after maximal medical therapy is instituted.

5.3 Temozolomide

This will follow the standard Stupp regimen with optional PCP prophylaxis. The decision to start and the choice PCP prophylaxis is up to the discretion of the treating physician

5.3.1 During RT: TMZ 75 mg/m^2 / day from the evening before the first dose of RT to the last day of RT. Please note that TMZ can be started within 24 hours of first fraction of Radiation Treatment (± 1 day of RT).

5.3.2 Adjuvant treatment:

- Cycle #1: TMZ 150 mg/m^2 / day on days 1-5 of a 28 day cycle.
- Cycle #2 (and all subsequent cycles): TMZ 200 mg/m^2 / day on days 1-5 of a 28 day cycle.
- TMZ regimen can be switched to TMZ 75 mg/m^2 / day on days 1-21 of a 28 day cycle at the treating physician's discretion.

5.4 Radiation Therapy

The radiation dose will remain the same for all patients and is to begin 3-6 weeks after the last craniotomy (i.e., if multiple procedures). All patients will receive 0.15 Gy of WBRT, followed by a partial brain boost dose of 1.85 Gy, bringing the standard of care total dose of 2.0 Gy to the tumor each day, 5 days per week to a total dose of 60 Gy.

5.5 Distant Failure Definition

Definition per Brandes et al[19]: 80% or more of the volume of recurrent/progressive tumor must be outside of the 95% isodose line; or any volume non-contiguous tumor (separate nodule) occurring outside of the 95% isodose line.

6.0 RADIATION THERAPY

6.1 Timing of Radiation Therapy

RT will begin no earlier than 3 weeks and no later than 6 weeks after surgery. If multiple procedures (e.g., resection, abscess draining, etc) are required, then the timing of RT will begin after the final procedure.

6.2 Technical Factors

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

6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device and a mouth piece to ensure adequate immobilization during therapy and ensure reproducibility are strongly recommended. A treatment planning CT is mandatory. The entire cranial contents down to the lower cervical spine should be scanned in 1-3 mm slice thickness. Intravenous contrast while permitted is usually not necessary since post-operative MRI fusion will be utilized for planning. Daily image guidance (e.g., MV, KV, CT imaging) for localization is strongly recommended.

6.4 Treatment Planning/Target Volumes

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. Intensity-modulated Radiation Therapy (IMRT) is permitted. Any of the methods of IMRT may be used. CT-based treatment planning is necessary to assure accuracy in the selection of field arrangements. MRI-fusion for accurate target delineation is strongly recommended. RT will begin no earlier than 3 weeks and no later than 6 weeks after craniotomy (after the last surgery if multiple procedures).

6.4.1 Initial Target Volume (PTV1): Target volumes will be based upon postoperative-enhanced MRI. Preoperative imaging should be used for correlation and improved identification. The initial gross tumor volume ($GTV1_T$) will be defined by either the T2 or the FLAIR abnormality on the postoperative MRI scan. This must also include all postoperative-enhanced MRI enhancement and the surgical cavity. The initial clinical target volume ($CTV1_T$) will be the $GTV1_T$ plus a margin of 1.5 cm. If no surrounding edema is present or if the edema is judged by the treating physician to be too large for safety delivery of radiation, the initial clinical target volume ($CTV1_T$) should include the contrast-enhancing lesion (and should include the surgical resection cavity) plus a 1.5 cm margin. The $CTV1_T$ margin may be reduced to as low 0 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the normal tissues, if necessary. The initial planning target volume ($PTV1_T$) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility. PTV margins account for variations in set-up and reproducibility. However, this may reduced to as low as 0 cm around natural barriers to tumor growth or to allow sparing of normal tissues.

The dose to $PTV1_T$ will be 1.85 Gy per day for 5 days per week. All patients will receive low-dose WBRT ($PTV1_W$). The standard WBRT will be utilized (inferior border being at C1/2 cervical space) using the opposed lateral technique. The dose to $PTV1_W$ will be 0.15 Gy per day for 5 days per week. Thus, a total dose (PTV1) will be the standard of care 2.0 Gy per day (1.85 Gy + 0.15 Gy) for 23 daily fractions for a total of 46 Gy.

Low-dose WBRT:	$PTV1_W$ = 0.15 Gy/day
Partial brain RT:	$PTV1_T$ = 1.85 Gy/day
Total:	PTV1 = 2.00 Gy/day x 23 = 46 Gy

6.4.2 Boost Target Volume (PTV2): The gross tumor volume ($GTV2_T$) will be defined by the T1 abnormality on the postoperative MRI scan. This must include all postoperative-enhanced MRI enhancement and the surgical cavity. The initial clinical target volume ($CTV2_T$) will be the $GTV2_T$ plus a margin of 1.5 cm. The $CTV2_T$ margin may be reduced to as low 0 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the normal tissues, if necessary. The initial planning target volume ($PTV2_T$) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility. PTV margins account for variations in set-up and reproducibility. However, this may reduced to as low as 0 cm around natural barriers to tumor growth or to allow sparing of normal tissues.

The dose to $PTV2_T$ will be 1.85 Gy per day for 5 days per week. All patients will receive low-dose WBRT ($PTV2_W$). The standard WBRT will be utilized (inferior border being at C1/2 cervical space) using the opposed lateral technique. The dose to $PTV2_W$ will be 0.15 Gy per day for 5 days per week. Thus, a total dose (PTV2) will be the standard of care 2.0 Gy per day (1.85 Gy + 0.15 Gy) for 7 daily fractions for a total of 14 Gy.

Low-dose WBRT:	$PTV2_W$ = 0.15 Gy/day
Partial brain RT:	$PTV2_T$ = 1.85 Gy/day
Total:	PTV2 = 2.00 Gy/day x 7 = 14 Gy

In summary:

PTV1: 2 Gy x 23 = 46 Gy
PTV2: 2 Gy x 7 = 14 Gy
Total: = 60 Gy

6.5 Dose Limitation to Critical Structures

In addition to the above defined GTVs, CTVs and PTVs, the lenses of both eyes, both retinae (as outlined as the whole globe), both lacrimal glands, both optic nerves, the optic chiasm, and the brainstem must be defined. The maximum point (defined as a volume greater than 0.03 cc) doses (and mean dose for lacrimal glands) permissible to the structures are listed in the table below.

Critical Structure	Maximum Dose (> 0.03 cc)
Lenses	7 Gy
Retinae	50 Gy
Optic Nerves	55 Gy
Optic Chiasm	56 Gy
Brainstem	60 Gy
Lacrimal Glands	26 Gy (mean dose)

6.6 Treatment Planning Goals

6.6.1 100% of the PTV volume should be covered by the 95% isodose line.

6.6.2 The maximal dose (hotspot) should be less than 105% of the dose.

6.6.3 Acceptable deviation (e.g., to meet the critical organ constraints) will be if the 90-95% isodose line covers the 100% of the PTV volume or if 95% isodose line covers 95% of the PTV volume.

6.6.4 It may be impossible to account for all anatomic tumor to normal structure configurations and scenarios. There may be scenarios in which normal structure constraints cannot be achieved (for example edema or gross tumor that contacts these structures like medial temporal tumors). As per standard of care guidelines, all attempts to spare normal structures (for example decrease CTV/PTV) should be attempted.

7.0 DRUG THERAPY

Treatment must begin ≥ 3 weeks and ≤ 6 weeks after (the last) surgery. This will follow the standard Stupp regimen with optional PCP prophylaxis. These are guidelines for the standard concurrent and adjuvant temozolomide. The decision and timing of temozolomide dose maintenance, escalation and/or reduction will be at the discretion of the treating physician since this is not a study related question.

7.1 TMZ During Concomitant RT

7.1.1 TMZ will be administered continuously starting the night before the first day to the last day of radiation at a daily oral dose of 75 mg/m2 for a maximum of 49 days. The drug will be administered orally at night. Please note TMZ can be started within 24 hours of first fraction of Radiation Treatment (± 1 day of RT).

7.1.2 The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The BSA will be calculated from the height and weight obtained at the pretreatment history and physical. Capsules of TMZ are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be delivered within ± 10% of target dose determined by BSA.

7.1.3 Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The capsules should be taken at least two hours after last food consumption with no food consumption for at least 1 hour after TMZ administration. Nightly administration just before bedtime is conventionally recommended, starting on the night prior to initiating RT. Any dose that is missed will not be made up.

7.1.4 During treatment with RT and TMZ a CBC with differential and a CMP including Liver Function Tests will be obtained every 2 weeks. The patient will also be evaluated for toxicities weekly.

7.1.5 Prophylaxis with a 5-HT3 antagonist is recommended prior to administration of TMZ doses and should be administered orally 30 to 60 minutes before TMZ treatment. In the unusual event that a 5-HT3 antagonist is not adequate to control nausea, additional use of Compazine, Phenergan, or metoclopramide may be utilized at the discretion of the treating physician.

7.1.6 Pneumocystis carinii prophylaxis is optional during the radiation phase.

7.1.7 If significant toxicity from concomitant treatment persists over 8 weeks from the time of completion of the radiation, the patient will be removed from protocol treatment.

7.2 Post-Radiation TMZ

7.2.1 TMZ will be administered orally once per day for 5 consecutive days (days 1-5) of a 28 day cycle. The starting dose for the first cycle will be 150 mg/m2 / day, with a single dose escalation to 200 mg/m2 / day in subsequent cycles if no treatment-related adverse events > grade 2 are noted. (TMZ regimen can be switched to TMZ 75 mg/m^2 / day on days 1-21 of a 28 day cycle at the treating physician's discretion.)

7.2.2 The start of the first cycle will be scheduled 28 days ± 3 days after the last day of radiotherapy. The start of all subsequent cycles (2-12) will be scheduled every 4 weeks (28 days ± 3 days) after the first daily dose of TMZ of the preceding cycle.

7.2.3 The dose will be determined using the BSA calculated at the beginning of each treatment cycle. The BSA will be calculated from the height obtained at the pretreatment visit and from the weight obtained at the visit prior to each cycle start. Capsules of TMZ are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be delivered within ± 10% of target dose determined by BSA. The exact dose administered should be recorded. Each daily dose should be given with the least number of capsules.

7.2.4 Patients will be instructed to fast at least 2 hours before and 1 hour after TMZ administration. Water is allowed during the fast period. Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. Treatment should be given at night. Any dose that is missed will not be made up.

7.2.5 Prior to each treatment cycle with TMZ a complete blood count (CBC) with differential and CMP including Liver Function Tests, a history and physical with neurological exam, steroid documentation, and toxicity assessment is to be done within 7 days prior to start of each cycle. Prior to cycle 1 and then every 2-3 months until the end of Adjuvant TMZ a brain MRI with contrast (or brain CT with contrast, if MRI is contraindicated) will be obtained.

7.2.6 If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

7.2.7 Antiemetic prophylaxis with a 5-HT3 antagonist is strongly recommended and should be administered 30 to 60 minutes before TMZ administration. See Section 7.1.5.

7.2.8 Pneumocystis carinii prophylaxis is optional during the adjuvant phase.

7.2.9 Duration of Treatment

Patients will be treated with post-radiation TMZ for 6 cycles unless there is evidence of tumor progression or treatment-related toxicity. At the completion of 6 cycles, patients may receive up to an additional 6 cycles of treatment (therefore, a maximum of 12 cycles) if treatment has been well tolerated and at least one of the following criteria demonstrating continued benefit is met:

- Serial MRI studies show continued tumor response as evidenced by no increase in tumor size.
- The patient demonstrates progressive improvement in overall performance status.
- The patient demonstrates clinical improvement by improvement in neurologic function.
- The patient demonstrates ongoing treatment benefit by a decreasing requirement of corticosteroids.

7.2.10 Tumor Treating Fields can be used after radiation therapy at the discretion of the treating physician.

7.3 TMZ Agent Information (Temozolomide, Temodar, Temodal)

Please refer to the package insert for comprehensive information.

7.3.1 Formulation

Other Names: methazolastone; TMZ is supplied in white opaque, preservative-free, two-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lautyl sulfate NF.

7.3.2 Mode of Action

Alkylating agent of imidazotetrazinone class.

7.3.3 Storage and Stability

The capsules are packaged in amber glass bottles and should be stored at 25°C. Temperature excursions between 15 and 30°C are permissible. Refer to the commercially labeled bottles for expiration dating.

7.3.4 Pharmacokinetics

TMZ is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of TMZ absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and Tmax increased 2-fold (from 1.1 to 2.25 hours) when TMZ was administered after a modified high-fat breakfast.

TMZ is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. TMZ has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

7.3.5 Metabolism and Elimination

TMZ is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to TMZ acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of TMZ and MTIC. Relative to the AUC of TMZ, the exposure to MTIC and ACI is 2.4% and 23%, respectively. About 38% of the administered TMZ total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged TMZ (5.6%), AIC (12%), TMZ acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of TMZ is about 5.5 L/hr/m2.

7.3.6 Special Populations

7.3.6.1 Creatinine Clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m2 has no effect on the clearance of TMZ after oral administration. The pharmacokinetics of TMZ have not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/m2). Caution should be

exercised when TMZ is administered to patients with severe renal impairment. TMZ has not been studied in patients on dialysis.

7.3.6.2 Hepatically Impaired Patients: In a pharmacokinetic study, the pharmacokinetics of TMZ in patients with mild to moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when TMZ is administered to patients with severe hepatic impairment.

7.3.6.3 Gender: Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for TMZ than men. Women have higher incidences of grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.

7.3.6.4 Age: Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of TMZ. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of grade 4 neutropenia and grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age. In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older.

7.3.7 Drug-Drug Interactions

In a multiple dose study, administration of TMZ with ranitidine did not change the Cmax or AUC values for TMZ or MTIC. Population analysis indicates that administration of valproic acid decreases the clearance of TMZ by about 5%. The clinical implication of this effect is not known. Population analysis failed to demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2-receptor antagonists, or phenobarbital on the clearance of orally administered TMZ.

7.3.8 TMZ is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered.

7.3.9 Contraindications

TMZ is contraindicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.

7.3.10 Pregnancy Category D

TMZ may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TMZ.

Treatment of a man with TMZ may increase the risk of birth defects if he causes a woman to become pregnant while he is taking TMZ. Men treated with TMZ may have difficulty causing a woman to become pregnant after their treatment is

completed. Men receiving TMZ should be directed to use effective contraception while they are being treated. There is insufficient data to know what the risk of subsequent problems with fertility will be. Similarly, women who are treated with TMZ may have difficulty becoming pregnant in the future and may at be at increased risk of having children with birth defects. There is insufficient evidence to determine what the risk of these complications will be.

7.3.11 Supply

Commercially available.

7.4 Dose Modifications

7.4.1 TMZ

7.4.1.1 TMZ During Concomitant RT

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

If the administration of TMZ has to be interrupted, the radiotherapy will proceed normally. Missed doses of TMZ will not be made up at the end of radiotherapy. The total number of days and total dose of TMZ will be recorded.

If one or more of the following are observed:

- ANC < 1.0 x 10^9/L
- Platelet count < 75 x 10^9/L
- Grade 3 non-hematologic AE (except alopecia, nausea and vomiting while on maximal antiemetic therapy, fatigue, DVT and PE)

Then treatment with concomitant TMZ will be withheld until all of the following conditions are met:

- ANC ≥ 1.0 x 10^9/L
- Platelet count ≥ 75 x 10^9/L
- Grade ≤ 1 non-hematologic AE (except alopecia, nausea and vomiting, fatigue, DVT and PE)

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

If one or more of the following are observed:

- ANC < 0.5 x 10^9/L (Grade 4)
- Platelet count < 25 x 10^9/L (Grade 4)

- Grade 4 non-hematologic AE (except alopecia, nausea and vomiting, unless the patient has failed maximal antiemetic therapy, fatigue, DVT and PE)

Then treatment with concomitant TMZ should be stopped.

AE	Value	Grade	Action
ANC	< 1.0 – 0.5 x 10^9/L	3	Delay TMZ until: - ANC ≥ 1.0 x 10^9/L - Platelet ≥ 75 x 10^9/L - Non-hem AE ≤ 1
Platelet Count	< 75 – 25 x 10^9/L	2, 3	
Non-hematologic (except alopecia, nausea/vomiting unless on maximal antiemetic therapy)	N/A	3	
ANC	< 0.5 x 10^9/L	4	**Stop** concomitant TMZ
Platelet count	< 25 x 10^9/L	4	
Non-hematologic (except alopecia, nausea/vomiting)	N/A	4	

7.4.1.1.1 Concomitant TMZ, if RT is interrupted

If radiotherapy has to be temporarily interrupted for technical or medical reasons unrelated to the TMZ administration, then treatment with daily TMZ should also stop. If radiotherapy has to be permanently interrupted then treatment with daily TMZ should stop. TMZ can resume with resumption of radiotherapy. TMZ can also resume with the initiation of the adjuvant phase of treatment.

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

7.4.1.2 Post-Radiation (Adjuvant) TMZ

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

Dose Level	TMZ Dose, mg/m^2 / day	Remarks
-2	100	Reduction if prior AE grade 3 event attributable as probably related to Temodar, persisting > 7 days despite optimal medical management, except DVT or PE
-1	125	Reduction if prior AE grade 3

		event attributable as probably related to Temodar, persisting > 7 days despite optimal medical management, except DVT or PE
0	150	Starting dose cycle 1 (adjuvant)
+1	200	Escalated dose at cycle 2, for cycles 2-12 in absence of AE

7.4.1.2.1 Delay

Within 7 days of the start of a new cycle, ANC ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L and all treatment-related grade 3 or 4 non-hematologic AEs (except alopecia, nausea, vomiting, fatigue, DVT and PE) must have resolved (to grade ≤ 1).

If AEs persists, treatment should be delayed by 1 week for up to 4 consecutive weeks. If, after 4 weeks of delay, all AEs have still not resolved: then any further adjuvant treatment with TMZ should be stopped.

7.4.1.2.2 Dose escalation

If, during the first cycle, all non-hematologic AEs observed were grade ≤ 2 (except alopecia, nausea and vomiting) and with platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x10^9/L: then the TMZ dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles (3-12).

7.4.1.2.3 Dose reduction

If any non-hematologic AE observed was grade > 2 (except alopecia, nausea, vomiting, fatigue, DVT and PE) and/or if platelets < 50 x 10^9/L and/or ANC < 1 x 10^9/L, then the dose should be reduced by one dose level. For patients who would require dose reductions to a dose level < 100 mg/m2 / day, TMZ will be stopped. Also, if any of the same non-hematologic grade 3 AE recurs (except alopecia, nausea, vomiting, and fatigue) after reduction for that AE, then TMZ will be stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except alopecia, nausea, vomiting, and fatigue) then adjuvant TMZ treatment should be stopped.

7.4.1.2.4 Subsequent cycles

Any dose reductions of TMZ will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the nadir (lowest/worst) ANC and platelet counts observed.

No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied.

7.4.1.2.5 Important

If the dose was reduced or delayed for adverse events, there will be no dose escalation. The reason(s) for the dose reduction and/or delay must be documented.

Summary of Dose Modification or Discontinuation During Post-Radiation TMZ

Hematologic AE on Day 1 of Each Cycle (within 7 days* before starting)	
AE	**Delay**
ANC < 1.5 x 10^9/L **and/or** **Platelet count < 100 x 10^9/L**	Delay in 1 week increments up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

* See Section 7.2.5 for timing of evaluations prior to starting each adjuvant cycle.

Non-Hematological AE (except for alopecia, nausea, vomiting,fatigue, DVT and PE) on Day 1 of Each Cycle (within 7 days* before starting)	
Grade	**Delay**
2-3	Delay in 1 week increments up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks, then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

* See Section 7.2.5 for timing of evaluations prior to starting each adjuvant cycle.

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

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

7.5 Data Safety Monitoring and Adverse Events

7.5.1 Data and Safety Monitoring / Quality Assurance Committee

This study will be governed by the UMGCC Data Safety Mointoring / Quality Assurance Committee (DSMQAC). The study will be sent to the DSMQAC for a mandatory interim review after the first 6 patients have been accrued. Once the DSMQAC has reviewed and approved the initial 6 patients on the study, 41 additional patients will be enrolled. The study will be reviewed by the DSMQAC on an annual basis and a report will be uploaded in the continuing review submitted to the Institutional Review Board (IRB).

7.5.2 Anticipated Toxicities

All anticipated toxicities are listed in the informed consent document.

7.5.3 Toxicity Reporting

The research team and the treating physicians/PI will review the toxicities and record them in Oncore. Attribution of toxicity to protocol and clinical relevance will be reviewed.

If a dose limiting toxicity or other significant medical event is unexpected and probably related to study treatment, then it will be submitted to the IRB via the Reportable New Information (RNI) guidelines. All AE's entered into Oncore will be submitted for review on an annual basis.

Patients that are withdrawn from protocol treatment will be followed for adverse events for 30 days after last dose of TMZ or Radiation Treatment.

7.5.4 Grading Toxicities

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

8.0 SURGERY AND OTHER THERAPY

8.1 Surgery

8.1.1 All patients require histological confirmed WHO grade IV tumor. Thus, at the minimum, a biopsy is required.

8.1.2 Decision for surgical resection is at the discretion of the treating surgeon since this is the standard of care. Multiple attempts at resection are allowed. Other procedures such as shunt placement, abscess drainage, wound repair, etc will be allowed at the discretion of the surgeon.

8.2 Permitted Supportive Therapy

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.

8.2.1 Anticonvulsants: Anticonvulsants may be used as clinically indicated. Doses at study entry and at specific time points of the treatment must be

recorded. The use of hepatic cytochrome p450 enzyme inducing anticonvulsants does NOT change dosing of TMZ.

8.2.2 Corticosteroids: Corticosteroids may be administered at the treating physician's discretion. Doses at study entry and at specific time points of the treatment must be recorded.

8.2.3 Antiemetics: Prophylactic antiemetics may be administered at the treating physician's discretion.

8.2.4 Pneumocystic Carinii Prophylaxis: Both corticosteroid therapy and continuous TMZ therapy induce lymphocytopenia. Patients receiving any of these drugs or both concomitantly are at an increased risk for opportunistic infections. Therefore, a prophylaxis against P. carinii pneumonia is required for all patients receiving TMZ during radiotherapy: 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). Prophylaxis is recommended to continue for the duration of radiotherapy, regardless of the lymphocyte count. After completion of the chemoradiation, patients with a lymphocyte count < 500/mm3 should have CD4 quantification. If the CD4 is < 200, then prophylaxis is recommended to continue and the CD4 should be quantified on a monthly basis. If the lymphocyte count is ≥ 500 or the CD4 is > 200, then prophylaxis can be stopped.

8.3 Non-Permitted Supportive Therapy

8.3.1 Growth factors are not permitted to induce elevations in neutrophil count for the purposes of: (1) administration of TMZ on the scheduled dosing interval; (2) allowing treatment with TMZ at a higher dose; or (3) avoiding interruption of the treatment during concomitant radiotherapy.

8.3.2 No other investigational drugs will be allowed during the trial.

8.3.3 Other types of chemotherapy, and immunotherapy or biologic therapy must not be used. Further, additional stereotactic boost radiotherapy is not allowed. If any of these treatments are required, the patient will be off protocol. All further therapy is at the treating physicians discretion, but should be recorded.

9.0 STATISTICAL CONSIDERATIONS

This study will enroll 47 patients total. After the first 6 patients have been enrolled a mandatory review will take place. Should the study be approved to proceed, 41 additional patients will be enrolled.

The primary endpoint for this trial and the one that is factored into the power analysis is the proportion of patients that have distant metastases at 1 year. The historical rate of distant metastases is 30% and we anticipate that this rate will be lowered to 10% among the patients accrued to this trial. We plan to accrue 37 patients to achieve 80% power to conclude that the rate is ≤ 10% given that the true rate doesn't exceed 16%. Given that 6 or fewer patients experience distant metastases during the first year, we

will accept the research hypothesis that the rate ≤ 10%. If 7 or more patients have distant metastases within the first year, we will instead not reject the null hypothesis that the experimental rate is no different from the historical rate; we will have 95% confidence to make this determination. To account for patients that fail to provide enough follow-up, or are withdrawn from the study, we plan to accrue 25% more patients that required for a total of 47 patients to be enrolled.

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