The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Net Clinical Benefit Analysis of RTOG 0525: A Phase III Trial Comparing Conventional Adjuvant Temozolomide with Dose-Intensive Temozolomide in Patients with Newly Diagnosed Glioblastoma

Armstrong, et al

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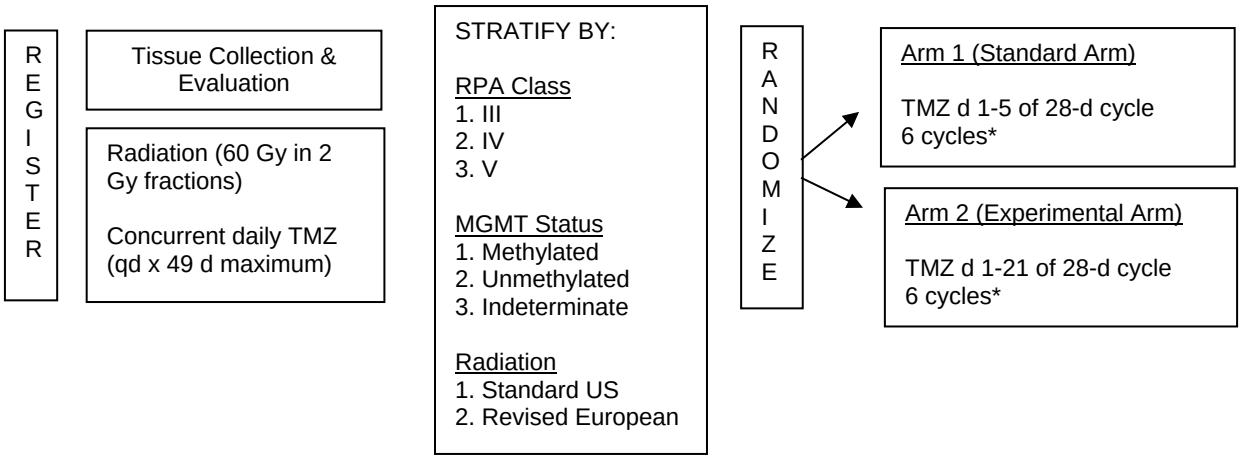

2.0 OBJECTIVES

2.1 Primary

To determine if dose-intensifying (increasing the "dose-density") the adjuvant temozolomide component of the chemoradiation treatment enhances treatment efficacy as measured by overall survival.

2.2 Secondary (6/12/06)

2.2.1 To determine if dose-intensifying the adjuvant temozolomide component of the chemoradiation treatment enhances treatment efficacy as measured by progression-free survival.

2.2.2 To determine in patients with unmethylated MGMT if dose-intensifying the adjuvant temozolomide component of the chemoradiation treatment enhances treatment efficacy (overall and progression-free survival) compared with patients receiving conventional temozolomide dosing.

2.2.3 To determine in patients with methylated MGMT if dose-intensifying the adjuvant temozolomide component of the chemoradiation treatment enhances treatment efficacy (overall and progression-free survival) compared with patients receiving conventional temozolomide dosing.

2.2.4 To determine if there is an association between tumor MGMT gene methylation status and treatment response.

2.2.5 To compare and record the toxicities of the conventional and dose-intense chemotherapy regimens.

2.2.6 To evaluate whether 6-month progression-free survival is associated with overall survival.

2.3 Net Clinical Benefit Objectives (5/16/07)

2.3.1 Primary

2.3.1.1 To compare between the two treatment arms the symptom burden, NCF, and HRQOL in patients who are without progression after 6 months of adjuvant therapy (6 month progression-free survival).

2.3.1.2 To evaluate midcycle differences in symptom burden and HRQOL in patients on the two arms at day 14 of course 1 and course 4.

2.3.2 Secondary

2.3.2.1 To evaluate longitudinal changes in HRQOL measures and determine the impact of dose-intense chemotherapy on these parameters.

2.3.2.2 To measure symptom burden and degree of interference over the course of therapy to evaluate differences between patients individual symptom severity, overall mean symptom severity, and difference in scores on the interference items between the two treatment arms.

2.3.2.3 To describe the association between quality of life as measured by the EORTC-QL30/BCM20 and mean symptom severity as measured by the MDASI-BT in patients

enrolled in this study.

2.3.2.4 To describe the variability of symptom severity across the epoch and follow-up period to compare differences between the two treatment arms.

2.3.2.5 To evaluate these instruments as a useful composite measurement of the impact of treatment and disease response in analysis of efficacy.

2.3.2.6 To evaluate differences in longitudinal changes on measures of NCF associated with dose-intense chemotherapy.

2.3.2.7 To evaluate the relationship between self-reported cognitive dysfunction and NCF testing.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (6/12/06)

3.1.1 Histopathologically proven diagnosis of glioblastoma. Since gliosarcoma is a variant of glioblastoma, gliosarcoma is also an eligible diagnosis.

3.1.2 Patients must have at least 1 block of tissue available for analysis of MGMT status; fresh frozen tumor tissue acquisition is encouraged.

3.1.3 Diagnosis must be established by open biopsy or tumor resection. Patients who have only had a stereotactic biopsy are not eligible..

3.1.4 The tumor must have a supratentorial component.

3.1.5 Patients must have recovered from the effects of surgery, postoperative infection, and other complications before study registration.

3.1.6 A diagnostic contrast-enhanced MRI or CT scan (if MRI is not available) of the brain must be performed preoperatively and postoperatively. The postoperative scan must be done within 28 days of registration and prior to the initiation of radiotherapy. Preoperative and postoperative scans must be the same type. If CT scans were performed perioperatively, a CT and an MRI should be performed before randomization.

3.1.6.1 Patients unable to undergo MR imaging because of non-compatible devices can be enrolled, provided pre- and post-operative contrast-enhanced CT scans are obtained and are of sufficient quality.

3.1.7 Therapy must begin $\leq$ 5 weeks after the most recent brain tumor surgery.

3.1.8 History/physical examination within 14 days prior to study registration.

3.1.9 Neurologic examination within 14 days prior to study registration.

3.1.10 Documentation of steroid doses within 14 days prior to study registration and stable or decreasing steroid dose within 5 days prior to registration.

3.1.11 Karnofsky performance status of ≥ 60.

3.1.12 Age ≥ 18 years.

3.1.13 CBC/differential obtained within 14 days prior to study registration, with adequate bone marrow function as defined below:

3.1.13.1 Absolute neutrophil count (ANC) ≥ 1500 cells/mm^3.

3.1.13.2 Platelets ≥ 100,000 cells/mm^3.

3.1.13.3 Hemoglobin ≥ 10 g/dl. (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10 g/dl is acceptable.)

3.1.14 Adequate renal function, as defined below:

3.1.14.1 BUN ≤ 25 mg/dl within 14 days prior to study registration

3.1.14.2 Creatinine ≤ 1.7 mg/dl within 14 days prior to study registration

3.1.15 Adequate hepatic function, as defined below:

3.1.15.1 Bilirubin ≤ 2.0 mg/dl within 14 days prior to study registration

3.1.15.2 ALT ≤ 3 x normal range within 14 days prior to study registration

3.1.15.3 AST ≤ 3 x normal range within 14 days prior to study registration

3.1.16 Patients must sign a study-specific informed consent prior to study registration. If the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the responsible family member.

3.1.17 For females of child-bearing potential, negative serum pregnancy test within 72 hours prior to starting temozolomide.

3.1.18 Women of childbearing potential and male participants must practice adequate

contraception.

3.2 Conditions for Patient Ineligibility (6/12/06, 5/16/07)

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 Recurrent or multifocal malignant gliomas

3.2.3 Metastases detected below the tentorium or beyond the cranial vault.

3.2.4 Prior chemotherapy or radiosensitizers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable. Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment are not permitted. See Section 3.2.1.

3.2.5 Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields.

3.2.6 Severe, active co-morbidity, defined as follows:

3.2.6.1 Unstable angina and/or congestive heart failure requiring hospitalization

3.2.6.2 Transmural myocardial infarction within the last 6 months

3.2.6.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

3.2.6.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration

3.2.6.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.

3.2.6.6 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 may be significantly immunosuppressive.

3.2.6.7 Major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy.

3.2.6.8 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.

3.2.7 Pregnancy or 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 treatment involved in this study may be significantly teratogenic.

3.2.8 Pregnant or lactating women, due to possible adverse effects on the developing fetus or infant due to study drug;

3.2.9 Prior allergic reaction to temozolomide.

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

3.2.11 No tissue provided for histopathologic central review and MGMT status.

3.2.12 Tissue provided by stereotactic biopsy method

6.0 RADIATION THERAPY (Note: Intensity Modulated RT (IMRT) Is Not Allowed)

6.1 Dose Specifications and Schedule

Radiotherapy must begin within ≤ 5 weeks of surgery. One treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy over 6 weeks. All portals shall be treated during each treatment session. Doses are specified as the target dose that shall be to the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

6.1.1 For two opposed coaxial equally weighted beams: On the central ray at mid-separation of beams

6.1.2 For an arrangement of two or more intersecting beams: At the intersection of the central ray of the beams

6.1.3 For complete rotation or arc therapy: In the plane of rotation at the center of rotation

6.1.4 Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.

6.1.5 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity; however, if this technique is utilized, the dose shall be specified at the center of the target volume.

6.1.6 Other or complex treatment arrangements: At the center of the target volume

6.2 Technical Factors

Treatment shall be delivered with megavoltage machines of a minimum energy of Cobalt 60. 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. Photon energies > 10 MV should be utilized only in dual energy beam arrangements using at least one beam with energy $\leq$ 10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Source sizes must be no more than 2 cm in Cobalt 60 machines. For Cobalt 60 machines, secondary collimation is required. Electron, particle, 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 that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility. Simulation may include a dedicated radiotherapy simulator or a virtual simulation using a treatment planning CT.

6.4 Treatment Planning/Target Volumes (6/12/06)

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. CT/MRI-guided treatment planning is necessary to assure accuracy in the selection of field arrangements. Inability to achieve field placement as defined by the protocol will result in variation scores at RTOG Headquarters reviews.

The gross target volume (GTV) for both the initial volume (GTV1) and the conedown volume (GTV2) shall be based on the postoperative CT/MRI (and preferably the MRI; the preoperative scans may be used if postoperative scans are not available). This initial target volume (GTV1) shall include the contrast-enhancing lesion (and should include the surgical resection cavity) and surrounding edema (if it exists) demonstrated on CT/MRI plus a 2.0-cm margin (this 2.0-cm margin-extended volume will be considered the initial planning target volume, or PTV1). If no surrounding edema is present, the initial planning target volume (PTV1) should include the contrast-enhancing lesion (and should include the surgical resection cavity) plus a 2.5-cm margin. The initial target volume will be treated to 46 Gy in 23 fractions. Please note that clinical judgment may be used to modify PTV1 to exclude sensitive structures such as the optic chiasm, non-cranial contents, or anatomic regions in the brain where natural barriers would likely preclude microscopic tumor extension, such as the cerebellum, the contralateral hemisphere, directly across from the tentorium cerebri, the ventricles, etc. After 46 Gy, the tumor volume (GTV2) for the conedown treatment should include the contrast-enhancing lesion (without edema) on the post-surgery CT/MRI scan plus a 2.5-cm margin (PTV2). The preoperative scan may used if postoperative scans are not available. This will be boosted to a total of 60 Gy, with seven additional fractions of 2 Gy each (14 Gy boost dose).

Isodose distributions for the initial target volume (PTV1) and the conedown target volume (PTV2) are required on all patients, including those treated with parallel opposed fields. A composite plan is required showing the respective target volumes. The following composite isodose lines should be included: 66 Gy (when 66 Gy dose

regions exist in the tumor), 60 Gy, 57 Gy, 48 Gy, 44 Gy and 40 Gy. The inhomogeneity within the target volume shall be kept to ≤ 10%.

The minimum dose to the target volume should be kept within 10% of the dose at the center of the volume. The use of vertex fields requires either a diagram or a photograph of the treatment position to be submitted to RTOG Headquarters.

6.5 Dose Limitation to Critical Structures

The lens and cervical spine must be shielded from the direct beam at all times. When possible to do so without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 54 Gy, the retina of at least one eye (but preferably both) to 50 Gy, and the brain stem to 60 Gy. When the optic chiasm must be included in the full dose, then there may be a finite risk of developing blindness.

6.6 Radiation Toxicity

6.6.1 Acute

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness. Reactions in the ear canals and on the ear should be observed and treated symptomatically; these reactions could result in short-term hearing impairment. Dry mouth or altered taste have been occasionally reported.

6.6.2 Early Delayed

Possible early delayed radiation effects include lethargy and transient worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.

6.6.3 Late Delayed

Possible late delayed effects of radiotherapy include radiation necrosis, endocrine dysfunction, and radiation-induced neoplasms. In addition, neurocognitive deficits, which could lead to mental slowing and behavioral change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

6.7 Treatment Delays

Radiation will be delayed or interrupted if the platelet count is < 20,000. Radiation will not begin or resume until the platelet count is ≥ 20,000. Hematologic toxicities should be rated on a scale of 0-5 as defined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

6.8 Documentation Requirements

At completion of treatment, the following should be forwarded to RTOG Headquarters: daily treatment record, all isodose distributions (in color), all treatment calculations, simulation/DRRs, and portal films of the large and conedown fields, and the radiotherapy summary per Section 12.1.

6.9 RT Quality Assurance Reviews

6.9.1 A random sample of cases will undergo RT Quality Assurance Review by the Radiation Oncology Co-Chair, Minesh Mehta, MD. After complete data for 200 cases enrolled have been received at RTOG Headquarters, a sample of 20% of those cases will be randomly selected for review. Likewise, 20% random samples will be selected of cases 201-400, 401-600, 601-800, and 800 to the final sample size . These reviews will be ongoing and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

6.10 Radiation Adverse Event Reporting — RTOG AE TELEPHONE LINE (215) 717-2762

See Sections 7.10 and 7.11.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Quality Control guidelines states in the RTOG Procedures Manual.

7.1. Temozolomide During Concomitant Radiation Therapy

7.1.1 Temozolomide will be administered continuously from day 1 of radiotherapy to the last day of radiation at a daily oral dose of 75 mg/m^2 for a maximum of 49 days. The drug will be administered orally 1 hour before each session of radiotherapy during weekdays (Monday through Friday). During weekends without radiotherapy (Saturday and Sunday), the drug will be taken in the morning.

7.1.2 The dose will be determined using the body surface area (BSA) calculated at the beginning of the concomitant treatment. The BSA will be calculated from the height obtained at the pretreatment visit and the weight obtained at the visit immediately before the first day of treatment. Capsules of temozolomide are available in 5, 20, 100, and 250 mg. The daily dose will be rounded to the nearest 5 mg.

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 on an empty stomach, therefore a minimum of 2 hours after a meal and with no food ingestion for 1 hour after temozolomide administration.

7.1.4 Antiemetic prophylaxis is usually not required for the continuous daily dosing schedule. However, prophylaxis with a 5-HT$_3$ antagonist is recommended prior to administration of the first few temozolomide doses and should be administered orally 30 to 60 minutes before temozolomide treatment.

7.2. Post-Radiation Temozolomide [*NOTE: If significant toxicity from concomitant treatment persists over 4 weeks, the patient should be removed from protocol treatment.*]

Patients will be randomized to receive one of two regimens. 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) after the first daily dose of temozolomide of the preceding cycle.

7.2.1 *Standard Arm*

7.2.1.1 Temozolomide 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/m^2/day, with a single dose escalation to 200 mg/m^2/day in subsequent cycles if no adverse events > grade 2 are noted.

7.2.1.2 The dose will be determined using the body surface area (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 immediately before each cycle. Capsules of temozolomide are available in 5, 20, 100, and 250 mg. The daily dose will be rounded to the nearest 10 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.

7.2.1.3 Prior to each treatment cycle with temozolomide a complete blood count (CBC) will be obtained (within 72 hours prior to dosing). 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) after the first daily dose of temozolomide of the preceding cycle.

7.2.1.4 Patients will be instructed to fast at least 2 hours before and 1 hour after temozolomide administration. Water is allowed during the fast period. Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them.

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

7.2.1.6 Antiemetic prophylaxis with a 5-HT$_3$ antagonist is strongly recommended and should be administered 30 to 60 minutes before temozolomide administration.

7.2.1.7 Duration of treatment

Patients will be treated with post-radiation temozolomide for 6 cycles unless there is evidence of tumor progression (defined in Section 11.4.5) or treatment-related toxicity

(defined in Section 7.5.1). 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 is met:

- Serial MR studies show continued tumor response as evidenced by reduction 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

7.2.2 *Experimental Arm*

7.2.2.1 Temozolomide will be administered orally once per day for 21 consecutive days (days 1-21) of a 28-day cycle. The starting dose for the first cycle will be 75 mg/m^2/day, with a single dose escalation to 100 mg/m^2/day in subsequent cycles if no adverse events > grade 2 are noted.

7.2.2.2 The dose will be determined using the body surface area (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 immediately before each cycle. Capsules of temozolomide are available in 5, 20, 100, and 250 mg. The daily dose will be rounded to the nearest 5 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.

7.2.2.3 Prior to each treatment cycle with temozolomide a complete blood count (CBC) will be obtained (within 72 hours prior to dosing). The start of the first cycle will be scheduled 28 days ± 3 day after the last day of radiotherapy. The start of all subsequent cycles (2-12) will be scheduled every 4 weeks (28 days) after the first daily dose of temozolomide of the preceding cycle.

7.2.2.4 Patients will be instructed to fast at least 2 hours before and 1 hour after temozolomide administration. Water is allowed during the fast period. 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.

7.2.2.5 Antiemetic prophylaxis with a 5-HT_3 antagonist is strongly recommended and should administered 30 to 60 minutes before temozolomide administration.

7.2.2.6 Duration of treatment

Patients will be treated with post-radiation temozolomide for 6 cycles unless there is evidence of tumor progression (defined in Section 11.4.5) or treatment-related toxicity (defined in Section 7.5.2). 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 are met:

- Serial MR studies show continued tumor response as evidenced by reduction 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

7.4 Dosing Modifications for Temozolomide During Concomitant Radiation Therapy (6/12/06)

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

If the administration of temozolomide has to be interrupted, the radiotherapy will proceed normally. Missed doses of temozolomide will not be made up at the end of radiotherapy. The total number of days and total dose of temozolomide will be recorded on the Treatment Summary Form (TF).

If one or more of the following are observed:

- ANC < 1.0 x 10^9/ L
- Platelet count < 50 x 10^9/L
- Grade 3 non-hematologic AE (except alopecia, nausea and vomiting while on maximal antiemetic therapy, and fatigue)

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

- ANC ≥ 1.0 x 10^9/L
- Platelet count ≥ 50 x 10^9/L
- Grade ≤ 1 non-hematologic AE (except alopecia, nausea and vomiting, and fatigue)

In case of hematologic AE as defined above, a complete blood count (CBC) should be performed at least twice weekly. In case of non-hematologic AE, the patient should be assessed at least weekly with relevant laboratory test(s). As soon as all of the above conditions are met, the administration of temozolomide 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 < 10 x 10^9/L (Grade 4)
- Grade 3 or 4 non-hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy, and fatigue)

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

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

Summary of Temozolomide Delay or Discontinuation During Concomitant Radiation Therapy

AE	Value	Grade	Action
ANC	≥ 0.5 and < 1.0 x 10^9/L	2, 3	**Delay** temozolomide until: ---ANC > 1.0 x 10^9/L ---Platelet > 50 x 10^9/L ---Non-hem AE ≤ 1
Platelet count	≥ 10 and < 50 x 10^9/L	2, 3	
Non-hematologic (except alopecia, nausea/vomiting unless on maximal antiemetic therapy)	NA	3	
ANC	< 0.5 x 10^9/L	4	**Stop** concomitant temozolomide
Platelet count	< 10 x 10^9/L	4	
Non-hematologic (except alopecia, nausea/vomiting)	NA	4	

7.4.1 Concomitant temozolomide, if radiotherapy is interrupted

If radiotherapy has to be temporarily interrupted for technical or medical reasons unrelated to the temozolomide administration, then treatment with daily temozolomide should continue. If radiotherapy has to be permanently interrupted then treatment with daily temozolomide should stop.

7.5 Dosing Modifications for Post-Radiation Temozolomide (DATE)

7.5.1 *Standard Arm*

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

First cycle
Temozolomide will be started at a dose of 150 mg/m^2/day.

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

Delay
On day 1 of each cycle (within the prior 72 hours), ANC ≥ 1.5 x 10/L, platelet count ≥ 100 x 10/L and all grade 3 or 4 non-hematologic AEs (except alopecia, nausea, and vomiting) must have resolved (to grade ≤ 1).
If AEs persists, treatment should be delayed by 1 week for up to 3 consecutive weeks. If, after 4 weeks of delay, all AEs have still not resolved: then any further adjuvant treatment with temozolomide should be stopped.

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 temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 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).

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

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

Subsequent cycles (3-12): Any dose reductions of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as

(2) (2) the nadir (lowest/worst) ANC and platelet counts observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied.

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

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

Summary of Dose Modification or Discontinuation During Post-Radiation Temozolomide

Worst Non-Hematologic AE (except alopecia, nausea and vomiting) 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 and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable. No further escalation is possible. If the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then stop.
4	Stop (except alopecia, nausea and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable.

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

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

Hematologic AE on Day 1 of Each Cycle (within 72 hours before)	
AE	**Delay**
ANC< 1.5 x 10^9/L and/or Platelet count < 100 x 10^9/L	Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

Non-Hematological AE (except for alopecia, nausea and vomiting) on Day 1 of Each Cycle (within 72 hours before)	
Grade	**Delay**
2-3	Delay up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks, then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

7.5.2 *Experimental Arm*

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	Dose mg/m^2	Remarks
- 2	35	Reduction if prior AE
-1	50	Reduction if prior AE
0	75	Starting dose for cycle 1, increase to 100 mg/m^2 for cycle 2 and beyond if no toxicity ≥ grade 3
+1	100	Highest possible dose level (adjuvant)

First cycle

Temozolomide will be started at a dose of 75 mg/m^2/day.

Second cycle

The dose of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the worst ANC and platelet counts.

Delay

On day 1 of each cycle (within the prior 72 hours), ANC ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L and all grade 3 or 4 non-hematologic AEs (except for alopecia, nausea and vomiting) 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 temozolomide should be stopped.

Dose reductions

If, during the first cycle, all non-hematologic AEs observed were grade ≤ 2 (except alopecia, nausea and vomiting) and with platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x10^9/L: then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 temozolomide 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).

Dose reductions

If any non-hematologic AE observed was grade > 2 (except alopecia, nausea and vomiting) 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. Patients who require more than two dose reductions will have treatment stopped.

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

Subsequent cycles (3-12): Any dose reductions of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the lowest ANC and platelets observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied. *Important:* If the dose was reduced or delayed for AEs, there will be no dose escalation.

Summary of Dose Modifications or Discontinuation During Post-Radiation Temozolomide

Worst Treatment-Related Non-Hematological AE (except for alopecia, nausea and vomiting) During the Previous Cycles	
Grade	**Dose Modification**
0-2	No dose modifications for non-hematologic AEs. Dose reductions based on ANC and platelet counts are applicable.
3	Reduce by one dose level (except alopecia, nausea and vomiting).
4	Stop (except alopecia, nausea and vomiting). Dose modifications based on ANC and platelet counts are not applicable.

Worst Treatment-Related Hematologic AE During the Previous Cycle

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

Note: A complete blood count must be performed on days 14, 21 and 28 (± 48 hours) after the first daily dose of each adjuvant treatment cycle.

Hematological AE on Day 1 of Each Cycle (within the prior 72 hours before Day 1)	
AE	**Delay**
ANC< 1.5 x 10^9/L and/or Platelet count < 100 x 10^9/L	Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

Non-Hematologic AE (except for alopecia, nausea and vomiting) On the day 1 of Each Cycle (within the prior 72 hours)

Grade	Delay
2-3	Delay up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AE then no escalation is possible.

7.8 Criteria for Removal From Protocol Treatment

Patients will be removed from the study for the following reasons:

- Progression of disease;
- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and RTOG Headquarters data management must be notified;
- A delay in chemotherapy > 4 weeks as described in detail above in Sections 7.5.1 and 7.5.2.

The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (6/12/06, 5/16/07)

Assessment	Prior to Therapy	During Chemo-RT	Post RT-Exper. Dose TMZ	Post RT-Standard Dose TMZ	After Therapy Completion	
Neurological Exam	X[a]		X[c]	X[c]	X[h]	
History and Physical	X[a]		X[c]	X[c]		
Steroid Dose Documentation	X[a]		X[f]	X[f]		
CBC with Differential, Platelet Count	X[a]	Monthly	X[d]	X[e]		
Serum Creatinine, BUN, Bilirubin, ALT/AST	X[a]	Monthly	X[f]	X[f]		
Contrast-enhanced Brain CT or MRI	X[b]		X[c]	X[c]	X[h]	
AE Evaluation		Weekly	X[f]	X[f]		
Serum Pregnancy Test	X[g]					
CD4			X[i]	X[i]		
EORTC QLC3/BCM 20	X		X[j]	X[j]		X
MDASI-BT	X		X[j]	X[j]		X
NCF Battery (See Appendix VI for details) ▪ Hopkins Verbal Learning Test–Revised ▪ Controlled Oral Word Association ▪ Trail Making Test Part A ▪ Trail Making Test Part B	X		X[k]	X[k]		X

a. Within 14 days prior to study registration.
b. Within 28 days prior to study registration; both preoperatively and postoperatively prior to

radiotherapy.

c. Before the initiation of cycle 1, 4, 7 (if administered), 10 (if administered) within 72 hours prior to day 1 and 1 month after the completion of the final cycle.
d. Immediately after completing radiotherapy, then on days 14, 21, 28 of each cycle (± 3 days).
e. Immediately after completing radiotherapy; then on days 21 and 28 of each cycle (± 3 days).
f. Day 28 of each treatment cycle (± 3 days).
g. Within 72 hours prior to starting temozolomide.
h. Every 3 months for 1 year, then every 4 months for 1 year, then every 6 months.
i. If lymphocyte count is < 500 mm^3. j. Before the initiation of cycles 1, 2, 3, 5, 6, 9 (if administered or 3 months after completing cycle 6), cycle 12 (if administered or 6 months after completing cycle 6) within 72 hours prior to day 1. In addition, during cycle 1 and cycle 4, testing should occur on day 14 ± 3 days.
k. Every 3 months for a maximum of 4 assessments.

NOTE: It is mandatory that patients be followed with the same study (CT vs. MRI) as the pre- and post-operative diagnostic studies (for further details, see Section 3.1.6).

13.0 STATISTICAL CONSIDERATIONS

13.1 Study endpoints (6/12/06, 5/16/07)

13.1.1 *Primary endpoint*

13.1.1.1 To determine if dose-intensifying (increasing the "dose-density") the adjuvant temozolomide component of the chemoradiation treatment enhances treatment efficacy as measured by overall survival.

13.1.2 *Secondary endpoints*

13.1.2.1 To determine if dose-intensifying the adjuvant temozolomide component of the chemoradiation treatment enhances treatment efficacy as measured by progression-free survival.

13.1.2.2 To determine in patients with unmethylated MGMT if dose-intensifying the adjuvant temozolomide component of the chemoradiation treatment enhances treatment efficacy (overall and progression-free survival) compared with patients receiving conventional temozolomide dosing.

13.1.2.3 To determine in patients with methylated MGMT if dose-intensifying the adjuvant temozolomide component of the chemoradiation treatment enhances treatment efficacy (overall and progression-free survival) compared with patients receiving conventional temozolomide dosing.

13.1.2.4 To determine if there is an association between tumor MGMT gene methylation status and treatment response.

13.1.2.5 To compare and record the toxicities of the conventional and dose-intense chemotherapy regimens.

13.1.2.6 To evaluate whether 6-month progression-free survival is associated with overall survival.

13.1.3 *Net clinical benefit*

13.1.3.1 To compare between the two treatment arms the symptom burden, NCF, and HRQOL in patients who are without progression after 6 months of adjuvant therapy (6 month progression-free survival.

13.1.3.2 To evaluate midcycle differences in symptom burden and HRQOL in patients on the two arms at day 14 of course 1 and course 4.

13.1.3.3 To evaluate longitudinal changes in HRQOL measures and determine the impact of dose-intense chemotherapy on these parameters.

13.1.3.4 To measure symptom burden and degree of interference over the course of therapy to evaluate differences between patients individual symptom severity, overall mean symptom severity, and difference in scores on the interference items between the two

treatment arms.

13.1.3.5 To describe the association between quality of life as measured by the EORTC-QL30/BCM20 and mean symptom severity as measured by the MDASI-BT in patients enrolled in this study.

13.1.3.6 To describe the variability of symptom severity across the epoch and follow-up period to compare differences between the two treatment arms.

13.1.3.7 To evaluate these instruments as a useful composite measurement of the impact of treatment and disease response in analysis of efficacy.

13.1.3.8 To evaluate differences in longitudinal changes on measures of NCF associated with dose-intense chemotherapy.

13.1.3.9 To evaluate the relationship between self-reported cognitive dysfunction and NCF testing.

13.2 Sample Size (6/12/06, 5/16/07, DATE)

13.2.1 *Stratification*: Stratification will take place following a patient's completion of concurrent chemotherapy and radiation therapy. The RTOG has previously performed a recursive partitioning analysis of patients with glioblastoma and has identified four distinct prognostic groups based upon age, performance status, extent of pretreatment surgery, neurological function, and mental status.[35] Patients on this study will be classified either as class III (age <50 and KPS 90-100), class IV (age <50 and KPS <90 **OR** age ≥ 50 and partially or total resected with no worse than minor neurofunction impairment), or class V (age ≥ 50 and partially or totally resected with worse than minor neurofunction impairment, **OR** age ≥ 50 and having been biopsied only, **OR** age ≥ 50, KPS ≥ 60, and normal mental status). In addition to RPA class, patients will be stratified by MGMT methylation status (methylated vs. unmethylated vs. indeterminate) as well as by whether radiation was planned to be delivered according to the standard criteria in Section 6 of the protocol or by the criteria defined in Appendix IX. The treatment allocation scheme described by Zelen[36] will be used because it balances patient factors other than institution.

13.2.2 *Sample Size Derivation*: The sample size calculations will address the specific primary hypothesis that a dose-intensive adjuvant temozolomide schedule will improve overall survival in patients with GBMs. The EORTC/NCIC study reported a median survival of 14.6 months in patients treated with temozolomide, with a patient population of 27% RPA class III, 63% RPA class IV, and 10% RPA class V. The RTOG experience in recent trials of GBM patients has seen a distribution of 15% class III, 57% class IV, and 28% class V. For this study the null hypothesis is that both arms under study will have a median survival time (MST) of 14 months. The alternative hypothesis is that the patients receiving the dose-intensive temozolomide with have an MST of at least 17.5 months, a 25% relative improvement in MST corresponding to a 0.80 hazard ratio. Using a one-sided test with alpha of 0.025 and five planned analyses of the data (four interim and one final), a sample size of 750 patients will have at least 80% power of detecting the hypothesized difference. Based upon the analysis of the first 313 patients entered, the rate of patients not being randomized was very much underestimated (30% vs. originally projected 10%). All but 9 of the 313 patients came from RTOG institutions and the nonrandomized rate of 30% may change when more patients are entered from EORTC and NCCTG. So a slightly higher nonrandomized rate of 35% was adopted to re-calculate the targeted sample size for the study. With that rate 1153 patients would have to be entered in order to have 750 patients randomized.

13.2.3 *Power justifications of secondary endpoints*

13.2.3.1 *Progression-free survival:* This outcome will be tested using a one-sided test with alpha of 0.025. The EORTC/NCIC study reported a median progression-free survival of 7.2 months in patients treated with chemoradiation followed by adjuvant temozolomide. Adjusting for the expected distribution of cases by RPA on this study, it is hypothesized that patients treated with the standard adjuvant dose of temozolomide will have a median progression-free survival of 6.7 months. With 750 analyzable patients, we would have at least 90% power of detecting a 2 month increase in progression-free survival for patients treated with dose-intense adjuvant temozolomide.

13.2.3.2 *Treatment efficacy in patients with unmethylated MGMT:* This outcome will be tested using a

one-sided test with alpha of 0.025. It is expected that approximately 50%-55% of patients on this study that can be assessed for MGMT status will have unmethylated MGMT. The two-year overall survival rate of these patients treated with standard therapy is estimated at 13.8%. With 350 unmethylated cases we should have at least 84% power to detect a hazard ratio of 0.70 (corresponding to a two-year survival rate of 25% in patients receiving dose-dense temozolomide) and at least 94% power to detect a hazard ratio of 0.65 (corresponding to a two-year survival rate of 27.6% in patients receiving dose-dense temozolomide). Based upon the June 2007 RTOG meeting summary report, 59% of patients randomized had unmethylated MGMT. If that rate continues for the rest of the study, there will be 442 unmethylated cases for the treatment comparison. With that sample size, there will be at least 91% power to detect a hazard ratio of 0.70 and 97% to detect a hazard ratio of 0.65.

13.2.3.3 *Treatment efficacy in patients with methylated MGMT:* This outcome will be tested using a one-sided test with alpha of 0.025. It is expected that approximately 45%-50% of patients on this study that can be assessed for MGMT status will have methylated MGMT. The two-year-overall survival rate such patients receiving standard dose temozolomide is estimated as 46%. With 350 analyzable patients with methylated MGMT, we would have at least 77% power to detect a hazard ratio of 0.65 (corresponding to a two-year rate of 60% in patients receiving dose-dense temozolomide) and at least 88% power to detect a hazard ratio of 0.60 (corresponding to a two-year rate of 63% in patients receiving dose-dense temozolomide). Based upon the June 2007 RTOG meeting summary report, 35% of patients randomized had methylated MGMT. If that rate continues for the rest of the study, there will be 262 methylated cases for the treatment comparison. With that sample size, there will be at least 65% power to detect a hazard ratio of 0.65 and 77% to detect a hazard ratio of 0.60.

13.2.3.4 Net Clinical Benefit Power Analysis: Given that the primary endpoint is survival in the original RTOG 0525 protocol where the required sample size has been increased to 1153 but nearly 500 patients have already been accrued, these power analyses section calculate the magnitude of effect sizes that can be detected in assessing symptom burden, NCF, and HRQOL for the given sample sizes. Two sample sizes were considered, a total of 120 patients with 60 per group and another total of 240 patients. Since the RTOG 0525 protocol is now accruing 60 patients per month, when we start patient accrual for this study during year 2 of the RTOG 0525 protocol, we anticipate accrual of the total 240 patients by the end of the second year of accrual the RTOG 0525 protocol. Briefly, with a sample size of 120 (n=60 in each arm) we would be able to detect an effect size difference of 0.52, .4, and 0.37 in the selected scores/subscales of the MDASI-BT, EORTC-QLQ30/BN20, and NCF, respectively. With 240 subjects, detectable effect sizes is 0.36, .3, and 0.26. Power analysis for effect size for each measure is provided below. All analyses were performed using the assumption of a two-tailed test at the 0.05 level of significance and with 80% power.

MDASI-BT: For this part of the study, the object of the study is to determine whether the dose-intense temozolomide arm has higher symptom severity specific to brain tumor patients than the conventional adjuvant temozolomide arm by examining change scores in certain items of the MDASI-BT items from baseline to Day 14 of the first cycle of treatment. From our pilot data of brain tumor patients undergoing active treatment, the five top symptoms were reported to be fatigue, sleep disturbance, dry mouth, drowsiness, and distress. Two other symptoms, lack of appetite and constipation, were deemed to be important when comparing the effect of the treatments under study. The standard deviation of the average of these seven symptom items was 1.78.

With a sample size of 120 (n=60 in each arm) we would be able to detect a mean difference of 0.92 (on a 0-10 scale) between the dose-intense temozolomide and the conventional adjuvant temozolomide or equivalently an effect size of 0.52. Using 240 subjects (n=120 per arm), we would be able to detect an effect size of 0.36 or a mean difference of 0.64 (on a 0-10 scale).

EORTC QLQ30/BN20: The EORTC QLQ30/BN20 has several subscales and individual

items from which scores can be calculated.

With a sample size of 120 (n=60 in each arm), we would be able to detect a change of 10 points in any of the scales of the EORTC QLQ-C30 or the BCM20 questionnaires. Using 240 subjects (n=120 per arm), we would be able to detect a change of 7.5. Effect sizes are .4/SD and .3/SD respectively for 120 and 240 total patient samples.

NCF: The effect sizes were determined on the basis of changes in standardized scores (utilizing normative data that is corrected for patient age and education) on the HVLT and Trail Making Test Part B.

With a sample size of 120 (n=60 in each arm), we would be able to detect an effect size difference of 0.37. Using 240 subjects (n=120 per arm), we would be able to detect an effect size difference of 0.26.

13.4 Analysis Plan (5/16/07,

13.4.1 *Statistical Methods*: Overall and progression-free survival rates will be estimated using the Kaplan-Meier method,[37] and differences between treatment groups will be testing using the log rank test.[38] Differences in treatment response rates and observed severities of toxicities between groups will be tested using a chi square test. Multivariate testing of treatment and stratification variables will be made using the Cox proportional hazard model.[39] Assuming a sufficient number of patients on the trial will have been entered from European institutions, the covariate of North American versus European treating institution will also be included in the multivariate model.

13.4.1.2 *Statistical methods for net clinical benefit*

13.4.1.2.1 Analysis plan. Descriptive statistics will be used to describe how patients rate symptom severity and interference with function at each time point. Error bar graphs for each of the symptoms will be constructed at each time point. Proportions of patients rating their symptoms to be 7 or greater (on a 0-10 scale) will also be reported, as ratings of 7 or higher of both pain and fatigue have been shown to correlate with a decrease in functional status.[40,41] Patient profile plots and prognostic plots will be constructed to describe our data.[42] Individual patient profiles for each of the selected symptoms will be constructed to describe the individual patient's patterns of change over time. Multilevel modeling will be used to analyze our repeated measures data in addition to the traditional univariate repeated measures approach. In analyzing the clinical trial data, we will use the 'intent to treat' principle. This principle states that we include all randomized patients in the analysis regardless of losses after randomization or losses before the outcome is measured due to dropout or noncompliance.

13.4.1.2.2 Analytical strategies to address the hypotheses. We will calculate the area under the curve using severity of symptoms as the ordinate and time as the abscissa. This approach is similar to the method used by Lydick et al[43] in examining pain from herpes zoster patients. We will calculate the mean core symptom severity, mean severity of the MDASI-BT, and mean symptom interference at the day 14 measurements on the first and sixth cycles and compare the dose-intense temozolomide arm to the standard adjuvant temozolomide arm using t-test. If the parametric assumptions are not met, then the Mann-Whitney test will be used. T- tests or its nonparametric counterpart will be used in comparing the dose-intense temozolomide arm and the standard adjuvant temozolomide arm at the same measurements on specific symptoms such as fatigue, nausea, and changes in bowel function. A t-test or its nonparametric counterpart will be used to comparing the mean MDASI-BT score and mean symptom interference score between the dose-intense treatment arm and the standard adjuvant temozolomide arm at day 14 of the 4th cycle as compared to baseline. To assess the association of MDASI-BT scores with the 6-month progression-free survival, a Cox proportional hazards model adjusting for treatment arm and stratification and other prognostic covariates will be completed. Various models, including the Cox proportional hazards model and mixed and hierarchical linear models, will be used. Finally, a Cox's proportional hazards model for overall survival will be developed using baseline HRQOL ratings on scales of

cognitive function, physical function, and fatigue as candidate predictors and adjusting for treatment stratification and other prognostic covariates.

Alternatively, multilevel modeling will be used to detect differences between the two groups on symptom severity over time. Specifically, we will construct a regression model with auto-correlated errors where the levels of symptom severity are modeled as polynomials over time and the independent variables are time, time squared, and other relevant covariates.[44]

13.4.1.2.3 Comparison between study arms. A similar approach will be used in the comparison of the dose-intense temozolomide arm and standard adjuvant temozolomide arm when the outcome of interest is either HRQOL or NCF. In addition, a mixed-model approach will be used to estimate HRQOL differences with a one-step autoregressive covariance structure on the intent-to-treat population. All eligible patients with at least one valid HRQOL form will be included in the analysis. All HRQOL data received after randomization will be used in the primary analyses. The longitudinal component may be slit into a piecewise model consisting of an on-treatment and post-treatment part as secondary analyses. By means of sensitivity analysis, performance status and type of surgery will be added as fixed-effects covariates to the specified model.

13.4.1.2.4 Missing data. We will compare possible differences between patients who dropped out of the study against those who remained in the study. A reasonable assumption is that patients who have very severe pain and related symptoms are more likely to drop out during treatment. We will compare data from the baseline assessment for this group (patients with severe symptoms who drop out) versus a similar group of patients (patients with severe symptoms) who remained in the study. In addition, the use of hierarchical linear modeling allows flexibility in analyzing data with missing responses. Given that missing data is a common problem in prior HRQOL studies, we will undertake sensitivity analyses to investigate reasons for missingness (e.g., by drop-out) of various clinical factors. We will calculate the number of missing observations (analyzed by logistic regression: completers vs noncompleters), and time until drop-out (Kaplan-meier method and log-rank test). Analysis of complete cases and last observation carried forward with missing observations (before death or progression) will be done to check robustness of the main results. Finally, received MDASI-BT and EORTCQLQ30/BN20 forms will be checked versus the timing schedule and considered as valid if they fall into an appropriate time window. Compliance rates will be calculated as the number of received valid forms over the number of expected forms. Differences between groups in compliance will be tested by use of Fisher's exact test at every time point.

13.4.1.2.5 Primary outcome of clinical benefit studies. The primary outcome measure of these studies is to determine the impact of therapy on the three measures and evaluate the relationship among measures. While it is true that there are items that overlap between the measures (e.g, symptom items in the MDASI-BT and EORTC QLQ-30/BN20), the EORTC QOL30/BN20 was also included because this instrument measures themes/constructs that are different than those measured by the MDASI-BT. The MDASI-BT is strictly a symptom assessment tool that measures symptom severity and its impact on functioning. The EORTC-QOL30 is generally regarded as a health-related quality of life questionnaire.

Because changes in symptom severity are usually associated with changes in quality of life, we are interested in assessing the relationship of symptom severity and symptom interference on health-related quality of life.

13.4.1.2.6 Clinical significance. For the EORTC QLQ30/BN20 differences of at least 10 points will be classified as the minimum clinically meaningful change in a HRQOL measure. For example, an increase of 10 points or more on a functional scale would mean a moderate improvement, whereas a decrease of 10 points or more would be interpreted as moderate worsening. Furthermore, a rise in a symptom score means deterioration. Changes of less than 10 points will be regarded as no change or as clinically irrelevant, and changes of more than 20 points will be considered large effects.[45] For the MDASI-BT, a change in symptom severity of one point will be classified as the minimum clinically meaningful change. Mean symptom severity and mean symptom interference will also be calculated and assessed for significance in relation to treatment. For the NCF battery, the inherent error in test scores is known for tests

with published test-retest reliability. A Reliable Change Index (RCI) may be calculated to determine changes in performance that are both clinically and statistically meaningful. The RCI is derived from the standard error of the measure for each test and represents the 90% confidence interval for the difference in scores from baseline to follow-up that is expected if no real change has occurred. A reliable change in test scores from baseline to follow-up is considered significant if it falls outside of the 90% confidence interval.

13.4.2 *Significance Testing for Early Termination and Reporting:* There will be four interim analyses conducted on the study, at which time only the primary endpoint will be analyzed. The analyses will be done on an intent-to-treat basis, with all eligible cases being included in the treatment arm to which they were randomized regardless what treatment the patients actually received. The looks will take place at the first meetings of the RTOG Data Monitoring committee after 130, 259, 389 and 518 events (deaths) have been observed among all patients on the study. The stopping rules are set using an O'Brien-Fleming boundary for early rejection of the null hypothesis. The significant levels for early stopping are as follows:

Events	*Critical Value (Z)*	*Significance Level*
130	*4.8769*	*<0.00001*
259	*3.357*	*0.0004*
389	*2.6803*	*0.0037*
518	*2.2898*	*0.011*

13.4.3 *Significance Testing for Final Analysis:* The final analysis will be done in an intent-to-treat basis such that all eligible cases on the study will be included in the arm to which they were randomized regardless of what treatment the patients actually received. It will occur at the next RTOG meeting after there have been at least 647 deaths reported. If the observed p-value at the time of the final analysis is ≤ 0.0211, we will reject the null hypothesis that the two treatments have a common survival.

13.4.4 *Interim Analysis to Monitor the Study Progress*: Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; rates of patient exclusion rates due to ineligibility and failure to be randomized following registration; compliance rate of treatment delivery with the distributions of important prognostic baseline variables including MGMT methylation status; and the frequencies and severity of treatment-related adverse events by treatment arm. The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints (overall survival, progression-free survival, treatment response). The RTOG DMC will review the accrual to the study and the rate of adverse events on the study at least twice a year until the initial results of the study have been presented to the scientific community.

13.4.5 *Interim Analysis of Efficacy Results*: As mentioned in Section 13.4.2, the efficacy results of this study will be reviewed by the RTOG DMC three times. At such times, the DMC will be presented with a report as in 13.4.4 with the addition of blinded comparison of overall survival. The study statistician will also make a recommendation to the committee based upon the observed results at the time of the analysis. If the boundary for rejecting the null hypothesis is crossed while the study is still open to patient accrual, the statistician will recommend immediately closing the study to accrual.

13.4.6 This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.