NCIC CLINICAL TRIALS GROUP (NCIC CTG)

A RANDOMIZED PHASE III STUDY OF TEMOZOLOMIDE AND SHORT-COURSE RADIATION VERSUS SHORT-COURSE RADIATION ALONE IN THE TREATMENT OF NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME IN ELDERLY PATIENTS

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NCIC CTG STUDY CHAIRS: NORMAND LAPERRIERE
JAMES PERRY
RADIATION THERAPY QA CHAIR: WILSON ROA
EORTC BRAIN TUMOUR GROUP CHAIRS: ALBA A. BRANDES
JOHAN MENTEN
TROG BRAIN TUMOUR GROUP CHAIRS: CLAIRE PHILLIPS
MIKE FAY
SAITAMA MEDICAL UNIVERSITY GROUP CHAIR: RYO NISHIKAWA
NCIC CTG TRIAL COMMITTEE: GREG CAIRNCROSS
WARREN MASON
PROJECT COORDINATOR: CHRIS O'CALLAGHAN
BIOSTATISTICIAN: KEYUE DING
QUALITY OF LIFE COORDINATOR: DAVID OSOBA
STUDY COORDINATOR: CHAD WINCH
SPONSOR CANADA: NCIC CTG
SPONSOR EUROPE: EORTC
SPONSOR AUSTRALASIA: TROG
SPONSOR JAPAN: SAITAMA MEDICAL UNIVERSITY
SUPPORTED BY: SCHERING

(For contact information of study personnel see Final Page.)
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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Schering.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel.

I will provide copies of the protocol and access to all information furnished by NCIC CTG and Schering to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I will provide protocol information to my Research Ethics Board [REB], Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of Schering and NCIC CTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Schering and NCIC CTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to NCIC CTG. The study may be terminated at any time by NCIC CTG or Schering with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Schering and NCIC CTG and must be kept in confidence in the same manner as the contents of this protocol.

__________________________________________________________________________
Investigator Date
(printed name and signature)

Protocol Number: NCIC CTG CE.6

CENTRE: ________________________________
TREATMENT SCHEMA

Patients ≥ 65 years of age, with newly diagnosed, histopathologically confirmed, glioblastoma multiforme (GBM, WHO grade IV) who have had prior surgery/biopsy at diagnosis and who are not deemed suitable by their treating physician to receive the standard radiotherapy regimen (60Gy/30 fractions over 6 weeks) in combination with temozolomide

Stratification
(centre; age 65-70 years vs. 71-75 years vs. ≥76 years; ECOG performance status 0 or 1 vs. 2; extent of resection at surgery, biopsy only vs. complete/incomplete resection)

Randomization

ARM 1
Radiation Therapy
(40 Gy/15 fractions over 3 weeks)

Disease evaluation at 4 weeks after the end of radiotherapy.

Disease evaluation every 3 months until disease progression.

Follow-up every 3 months until death.

Planned Sample Size: 560

ARM 2
Radiation Therapy
(40 Gy/15 fractions over 3 weeks)
and Concurrent Temozolomide
(75 mg/m², daily, from the first to the last day of radiotherapy to a maximum of 28 days)

Disease evaluation at 4 weeks after the end of radiotherapy.

Adjuvant Temozolomide
until progressive disease or a maximum of 12 months
(daily, for the first 5 days of each 28-day cycle; 150 mg/m² on cycle 1, increase to 200 mg/m² in cycles 2 onwards in the absence of significant adverse events)

Disease evaluation every 3 months until disease progression.
1.0 OBJECTIVES

1.1 Primary Objective

To compare the overall survival (OS) rates between short-course radiation therapy alone and short-course radiation therapy given together with concurrent and adjuvant temozolomide, in elderly (≥65 years of age) patients with newly diagnosed glioblastoma multiforme (GBM, WHO grade IV), who have had prior surgery/biopsy at diagnosis and who are not deemed suitable by their treating physician to receive the standard radiotherapy regimen (60Gy/30 fractions over 6 weeks) in combination with temozolomide.

1.2 Secondary Objectives

• To compare progression-free survival (PFS) between the two arms.
• To compare the nature, severity, and frequency of adverse events between the two arms.
• To compare the quality of life between the two arms using the EORTC QLQ-C30 and the EORTC Brain Cancer Module (QLQ-BN20).
• To conduct molecular correlative studies, as follows:
  − Mandatory - To collect tumour samples obtained at the time of disease diagnosis in order to determine the methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) promoter.
  − Optional - To bank tumour samples obtained at the time of disease diagnosis for future studies aiming to correlate outcomes and response to treatment to the expression levels or genetic alterations at diagnosis of other scientifically justified markers, as considered appropriate.
2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is a uniformly fatal illness associated with a median survival of about 1 year [Laperriere 2002]. Post-operative radiotherapy (RT) has been the mainstay of therapy as the only treatment to significantly prolong survival following surgery [Laperriere 2002]. Most prior chemotherapy studies have demonstrated either no or a modest improvement in median survival [Fine 1993]. A recently completed randomized study of RT alone or RT with concurrent and adjuvant temozolomide has demonstrated a significant improvement in median survival from 12.1 to 14.6 months, and an improvement in 2 year survival from 10% to 26%, respectively [Stupp 2005]. The RT dose used in this trial was 60 Gy/30 and the patient population was 18 to 71 years old.

2.2 Rationale for This Study

Evidence suggests that the single most powerful predictor of outcome in GBM is age. A recent population based survey of 3298 patients with GBM in Ontario, Canada from 1982-1994 demonstrated a marked decrease in median survival with increasing decade of age, and in particular showed a median survival of 4-5 months in patients older than age 70 [Paszat 2001]. In addition, exploratory sub-group analysis of the results from the recent phase III study of radiation therapy and concurrent and adjuvant temozolomide in patients age 71 or less [Stupp 2005, unpublished data] revealed diminishing hazard ratios with increasing decade of age. For patients less than 50 years of age a hazard ratio of 0.50 (p=0.001) was observed, compared to a hazard ratio of 0.63 for the age group 50-60 (p<0.05), a hazard ratio of 0.72 for the age group 60-65 (p=0.0957) and a hazard ratio of 0.80 for the age group 65-71 (p=0.340). Despite these observations, a prospective sequential series of patients with GBM and age > 65 treated with radiotherapy (RT) only, RT plus PCV (Procarbazine, CCNU [Lomustine] and Vincristine), and RT with temozolomide (adjuvant only) demonstrated increasing median survivals of 11.2, 12.7, and 14.9 months, respectively [Brandes 2003], suggesting that addition of temozolomide to radiation therapy might still be beneficial to elderly patients.

Elderly patients tolerate high dose radiotherapy less well than younger patients with a significant incidence of somnolence and fatigue. There have been recent publications of shorter course radiation therapy in the 30 Gy/10 dose range in GBM patients older than age 60 with reasonable or poorer performance status which have been associated with median survivals of approximately 6 months [Bauman 1994, Ford 1997, Hoegler 1997, Slotman 1996, Thomas 1994]. In addition, a recently published randomized study of 40 Gy/15 versus 60 Gy/30 in 100 patients with age > 60 revealed no difference in survival between the two doses with a median survival of 5 months [Roa 2004].

In view of the recent phase III results [Stupp 2005] which show an advantage in combining temozolomide with RT in GBM, but leaves doubts as to whether this advantage extends to an elderly patient population, there is a need to study the combination of temozolomide and RT versus RT alone in this population. In addition, given recent results demonstrating no differences in survival in elderly GBM patients treated with a 40 Gy/15 versus a 60 Gy/30 dose of RT [Roa 2004], and the lower tolerance of this patient population to RT, the 40 Gy/15 (short-course) dose will be employed in this trial.
2.3 Quality of Life

Quality of life measurement is of particular relevance in patients with incurable disease. Despite the use of surgery and RT, median survival in elderly patients with GBM remains dismal, at about 5-6 months. In addition, GBM is symptomatic, associated with headaches, progressive weakness, speech, visual and motor disturbances and significant deterioration of overall neurological function. The large majority of patients who recur after surgery and RT cannot benefit any more from these treatments. The rationale for treatment with chemotherapeutic agents, such as temozolomide, is that any gain in the local control of the disease might translate into stabilization of neurological symptoms and maintenance of the quality of life. In addition, in a disease which is almost uniformly fatal, an improvement in quality of life due to temozolomide would be considered important.

Analysis from a phase III randomized study of RT alone or RT with concurrent and adjuvant temozolomide in GBM patients up to 71 years of age showed that the addition of temozolomide did not have a negative effect on quality of life [Taphoorn 2005]. More specifically, out of 13 different quality of life scales (5 functional, 3 symptom, 4 disease-specific and 1 global) and 13 single items tested, the two arms differed significantly only with respect to social functioning (favouring the RT only arm) and this difference was seen only in one of the six time points evaluated (the second assessment after the end of RT). In the present study we intend to build on the experience of this phase III study by measuring the effects of RT with or without concurrent and adjuvant temozolomide on the quality of life of an elderly (≥ 65) GBM population.

Quality of life is a multidimensional construct, which can be defined as a state of general well being reflecting physical, psychological, and social well being and the control of disease and/or treatment related symptoms. The aspects of quality of life that are most likely to be affected in this study are treatment related symptoms and overall quality of life.

Quality of life will be evaluated in all patients entered in the study. Assessments will consist of a self-administered questionnaire. In this study the EORTC core questionnaire QLQ-C30 in conjunction with the brain module QLQ-BN20 will be used. The QLQ-C30 consists of 30 questions which form 5 functional scales, 3 symptom scales, and a global health/quality of life scale. The remaining single items assess additional symptoms commonly reported by cancer patients. The disease-specific brain cancer module QLQ-BN20 was especially developed and tested in patients with brain cancer. It consists of 20 additional questions measuring 4 scales (visual disorder, motor disturbances, communication deficits, and uncertainty about the future), and 7 single items.

2.4 Correlative Studies

Molecular characterization of glioblastoma and correlation with survival and response to treatment is of interest. Thus, GBM tumour samples obtained at the time of disease diagnosis will be banked for consenting patients in order to facilitate future correlative studies.

Recent studies have shown that de novo or primary GBMs are more likely to carry 10q loss, EGFR amplification and CDKN2A/p16 deletions [Louis 2001]. The presently available data do not allow the substitution of the histological grading by a genetic typing, but there is evidence that the observed chromosomal abnormalities are of prognostic significance. The presence of LOH 10 or lesions at the MMAC/PTEN region has been found to be a prognostic unfavourable parameter [Schmidt 2002]. In other studies a better response to RT was observed in p53 mutant tumours and in tumours carrying 1p lesions (despite a non-oligodendrogial histology) [Schmidt 2002]. These data need confirmation, and none of the previous studies has been validated in a prospective clinical trial. They suggest though that genetic lesions may be related to the prognosis of patients, and that the combination of clinical, histologic and genetic analysis may have a role in the future management of patients.
Many of the reported genetic alterations can be investigated by in situ hybridization with locus specific probes on formalin fixed, paraffin embedded material. Therefore, as a part of this study fluorescence in-situ hybridization (FISH) analysis may be carried out in order to investigate genetic alterations of scientifically justified markers, as considered appropriate. Because fresh frozen material will not be available for the majority of patients, a FISH analysis will be performed on paraffin embedded material. The results of this will be correlated with the clinical characteristics and survival of patients. For the FISH analysis, a block of paraffin embedded tumour material (or if unavailable 20 unstained APES coated slides) are required.

The presence or absence of a methylated MGMT promoter significantly influenced survival in the recently completed randomized study of concurrent and adjuvant temozolomide [Hegi 2005]. Therefore the methylation status of the MGMT promoter will also be determined for patients in the present study using methylation-specific polymerase-chain-reaction (PCR) analysis.
3.0 BACKGROUND THERAPEUTIC INFORMATION

The following section is meant to provide only general information about temozolomide. For more details please refer to the Temozolomide Product Monograph.

3.1 Name and Chemical Information

Generic name: Temozolomide
Commercial name: Temodal®
Chemical name: Imidazo[5,1-d]-1,2,3,5-tetrazin-8-carboxamide,3,4-dihydro-3-methyl-4-oxo
Empirical Formula: C₆H₆N₆O₆
Molecular weight: 194.15
Appearance: White to light tan/light pink powder
Melting point: Does not have a true melting point; decomposes from about 182 to 200 °C

3.2 Chemical Structure

![Chemical structure of Temozolomide]

3.3 Mechanism of Action

Temozolomide is an imidazotetrazine DNA alkylating agent. Once in the body it undergoes rapid conversion to the active compound, MTIC (monomethyl triazeno imidazole carboxamide). MTIC is thought to act primarily by causing alkylation of guanine in the O6 and N7 positions, which in turn results in the creation of methyl adducts. The cellular machinery lacks the ability to repair such adducts adequately, with the end result being the appearance of cytotoxic lesions.

3.4 Experimental Antitumour Activity

The anti-tumour activity of temozolomide has been tested both in vitro in cell lines and in vivo in human xenograft models.

Among a panel of human tumour cell lines, the ones from CNS tumours, and in particular U373MG astrocytoma, U87MG glioblastoma, glioma and medulloblastoma cell lines were the most sensitive to temozolomide.

Mice implanted with human CNS tumours, both subcutaneously and intracranially, and treated with temozolomide, either showed substantial tumour growth delays or were long term, tumour-free survivors. In particular, studies with subcutaneously implanted astrocytomomas showed a dose-dependent anti-tumour activity with 60-100% of mice being tumour-free 54 days after the start of temozolomide treatment. All 57 mice with U251 glioblastoma xenografts who survived treatment with temozolomide had complete tumour regressions.
3.5 Animal Toxicology

Acute toxicity studies (oral and intraperitoneal administration) in mice and rats resulted in observations of hypoactivity, hunched posture, partial closure of the eyes, tremors, prostration, ataxia, poor appetite, thin appearance, few or abnormal feces, anorexia, swollen heads and dyspnea. At necropsy, dark red areas were observed in the stomach, brain, reproductive organs, lymph nodes, pancreas, cecum, subcutaneous tissue, small intestine, lymph nodes and lung. In dogs, emesis, hypoactivity, ataxia, polyneia, mydriasis, discoloured mucoid feces, salivation, and abnormal or few feces were seen. At necropsy dogs were found to have dark red areas in the stomach, gastrointestinal tract, lymph nodes, cecum, heart, urinary bladder and subcutaneous tissue.

The main findings of multiple-dose, single-, three- and six-cycle toxicity studies conducted in rats, with doses equivalent or lower compared to the maximum recommended daily dose in humans, were hypoactivity, hunched posture, thin appearance, few feces, low hematologic counts (erythrocytes, leukocytes, platelets, lymphocytes and segmented neutrophils) and alopecia. In dogs, emesis, hypoactivity, dehydration, anorexia, abnormal feces and low hematologic counts (erythrocytes, and leukocytes mainly) were seen. Necropsy findings revealed red-dark areas in several organs of both dogs and rats, similar to what was seen in the acute toxicity studies.

Standard carcinogenicity studies of temozolomide have not been conducted. However, rats treated with a dose equivalent to the human maximum daily dose, in a schedule of 5 consecutive days every 28 days for 3 cycles, developed mammary carcinomas (both males and females). With 6 cycles of treatment and doses not exceeding one half of the human maximum daily dose equivalent, mammary carcinoma as well as many other carcinomas, fibrosarcomas and adenomas were observed. In addition, temozolomide was found to be mutagenic in vitro in bacteria (Ames assay) and clastogenic in vitro in mammalian cells (human peripheral blood lymphocyte assays).

While standard reproductive function studies have not been conducted with temozolomide, testicular toxicity was seen in both dogs and rats treated with temozolomide in multi-cycle toxicity studies with doses equivalent to 5/8 or less of the human maximum daily dose.

3.6 Phase II Trials

Temozolomide was tested in a number of phase II trials of patients with recurrent GBM and anaplastic astrocytoma and in one trial of patients with recurrent high grade glioma. In all cases, the results were consistent with achieving clinically meaningful efficacy and improved quality of life benefits compared to historic controls.

3.7 Phase III Trials

In a recently conducted phase III clinical trial radiotherapy plus concomitant and adjuvant temozolomide conferred a survival advantage to patients aged 18 to 70 with newly diagnosed GBM compared to radiotherapy alone [Stupp 2005]. A total of 573 patients from Europe and Canada were randomized to receive radiotherapy at a dose of 60 Gy/30 fractions for 6 weeks or radiotherapy with concurrent temozolomide (75 mg/m² daily for 6 weeks) followed by adjuvant temozolomide (6, 28-day-long cycles; temozolomide was given in a 5-day every 28 days schedule at a dose of 150 mg/m² in cycle 1 and 150 or 200 mg/m² in cycles 2-6, depending on whether significant toxicity had developed at the end of cycle 1). The median survival was 14.6 months in the radiotherapy plus temozolomide arm compared to 12.1 months in the radiotherapy alone arm. Two year survival rates were 26.5% versus 10.4%, respectively. The unadjusted hazard ratio was 0.63 (p<0.001). Grade 3 or 4 hematologic adverse events were seen in 7% of patients in the radiation plus temozolomide arm.
3.8 Pharmacokinetics

Temozolomide is rapidly and completely absorbed after oral administration. At physiological pH it is hydrolysed to 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC), which then breaks down into a reactive methyl-diazonium cation and an intermediate of the biosynthetic pathway to purines, called 5-amino-imidazole-4-carboxamide (AIC). AIC is believed to be the active alkylating species. Peak plasma concentrations are achieved 1 hour after ingestion. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and Tmax increased 2-fold when temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins.

3.9 Pharmaceutical Data

**Supplied:**

Temozolomide will be available in 5, 20, 100 and 250 mg capsules. Capsules will be supplied in Type 1 amber glass bottles.

**Stability and Storage:**

Temozolomide should be stored between 15°C and 30 ºC, and should be protected from moisture. Temozolomide must be stored in a secure, limited access location under the storage conditions specified on the drug supply label.

**Route of Administration:**

Oral.
4.0 **TRIAL DESIGN**

4.1 **Stratification**

Patients will be stratified by:
- Centre
- Age (65-70 years versus 71-75 years versus ≥ 76 years)
- Performance status (ECOG 0,1 versus 2)
- Extent of the resection at surgery (biopsy only versus complete/incomplete resection)

4.2 **Randomization**

Patients will be randomized to receive one of the two following treatments, to a planned sample size of 560:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Duration/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Radiotherapy</td>
<td>40 Gy/15 fractions</td>
<td>-</td>
<td>3 weeks (5 fractions per week)</td>
</tr>
<tr>
<td>2</td>
<td>Temozolomide (adjuvant; to start 4 weeks after the end of radiation)</td>
<td>150 mg/m² in cycle 1; escalate to 200 mg/m² in cycles 2 onwards in the absence of significant adverse events</td>
<td>PO</td>
<td>in 28-day long cycles (once a day, daily, for the first 5 days within each cycle), until progressive disease (PD) or unacceptable adverse events to a maximum of 12 months.</td>
</tr>
<tr>
<td></td>
<td>Temozolomide (concurrent with radiation)</td>
<td>75 mg/m²</td>
<td>PO</td>
<td>once a day, daily, from the first day to the last day of radiotherapy*</td>
</tr>
</tbody>
</table>

* If radiotherapy is interrupted due to radiation-attributable adverse events or for technical or medical reasons unrelated to temozolomide, daily treatment with temozolomide should continue during the days of radiation therapy interruption, but total temozolomide treatment should not exceed 28 consecutive days. If radiotherapy is discontinued then treatment with daily concurrent temozolomide should also be discontinued.
5.0 STUDY POPULATION

Patients 65 years of age or older, with newly diagnosed, histopathologically confirmed, glioblastoma multiforme (WHO grade IV) who have had prior surgery or biopsy at diagnosis and who are not deemed suitable by their treating physician to receive the standard radiotherapy regimen (60Gy/30 fractions over 6 weeks) in combination with temozolomide.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed PRIOR to randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Histopathologically confirmed newly diagnosed glioblastoma multiforme (GBM, WHO grade IV). The histological diagnosis must have been made after biopsy or neurosurgical tumour resection.

5.1.2 Protocol treatment must begin within 6 weeks of initial surgery/biopsy at diagnosis, and no greater than 2 weeks post-randomization.

5.1.3 Patient’s age is ≥ 65 years.

5.1.4 Patient is not deemed suitable by the treating physician to receive the standard radiotherapy regimen (60Gy/30 fractions over 6 weeks) in combination with temozolomide.

5.1.5 ECOG performance status of 0, 1 or 2 (See Appendix II).

5.1.6 Patient may have received and continue to receive corticosteroids, but s/he have to be on a stable or decreasing dose for at least 14 days prior to randomization.

5.1.7 Patient has not received prior chemotherapy or radiotherapy.

5.1.8 Adequate hematological, renal and hepatic functions as defined by the following required laboratory values obtained within 14 days prior to randomization:

\[
\begin{align*}
\text{Absolute granulocyte count (AGC)} & \geq 1.5 \times 10^9/L \ (1,500 \text{ cells/mm}^3) \\
\text{Platelet count} & \geq 100 \times 10^9/L \ (100,000 \text{ cells/mm}^3) \\
\text{Serum creatinine} & \leq 1.5 \text{ times the upper limit of normal} \\
\text{Total serum bilirubin} & \leq 1.5 \text{ times the upper limit of normal} \\
\text{ALT (SGPT)} & \leq 2.5 \text{ times the upper limit of normal} \\
\text{and/or AST (SGOT)} & \leq 2.5 \text{ times the upper limit of normal}
\end{align*}
\]
5.1.9 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires in either English or French or any other official language into which the questionnaire is required to be translated. The baseline assessment must have already been completed. Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

5.1.10 Patient consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements. Because of differing requirements, a standard consent form for the trial will not be provided but a sample form is provided. The patient must sign the consent form prior to randomization. Please note that the consent form for this study must contain a statement which gives permission for the NCIC CTG and monitoring agencies to review patient records (see section 16.4 for further details).

Canadian centres only: It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the NCIC CTG Study Coordinator that such clearance has been obtained, before the trial can commence in that centre. A copy of the initial full board REB approval and approved consent form must be sent to the central office.

5.1.11 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

5.1.12 All other investigations (physical exam, biochemistry and hematology tests etc.) as listed in section 6.0 have been performed prior to randomization (with the exception of requests for diagnostic tissue blocks/slides to be used for central pathology review and correlative studies which will be done after randomization).

5.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

5.2.1 Patients with a history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥ 5 years.

5.2.2 Patients with a serious active infection (such as a wound infection requiring parenteral antibiotics) at the time of randomization or other serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment.

5.2.3 Patients with any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol.

5.2.4 Patients with known hypersensitivity to temozolomide or compounds with similar chemical composition to temozolomide.

5.2.5 Patients who have had treatment with any investigational cancer drug prior to randomization.
### 6.0 PRE-TREATMENT EVALUATION

(See also Appendix I)

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History and Physical Exam including:</strong></td>
<td>within 14 days prior to randomization*</td>
</tr>
<tr>
<td>• Prior therapy, history, corticosteroid use 2 weeks prior to randomization</td>
<td></td>
</tr>
<tr>
<td>• Physical examination (including neurological evaluation)</td>
<td></td>
</tr>
<tr>
<td>• Height, weight, ECOG Performance Status</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, WBC with differential (granulocytes, lymphocytes), platelet count</td>
<td></td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, ALT (SGPT) and/or AST (SGOT), alkaline phosphatase, serum creatinine, serum total protein, random glucose</td>
<td></td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td></td>
</tr>
<tr>
<td>Gadolinium-enhanced MRI or contrast CT scan of the brain**</td>
<td>After surgery but prior to the start of treatment***</td>
</tr>
<tr>
<td><strong>Other Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental Status (see Appendix VII)</td>
<td>within 14 days prior to randomization*</td>
</tr>
<tr>
<td><strong>Adverse Events♦</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline adverse event evaluation (to document baseline symptoms and any residual adverse events from previous surgery)</td>
<td>within 14 days prior to randomization*</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td></td>
</tr>
<tr>
<td>Quality of Life Questionnaire: EORTC QLQ-C30 and QLQ-BN20 (see Appendix VI)</td>
<td>within 7 days prior to randomization*</td>
</tr>
<tr>
<td><strong>Tissue Collection</strong></td>
<td></td>
</tr>
<tr>
<td>Tissue blocks/slides for central pathology review, MGMT promoter methylation analysis and optional tumour banking</td>
<td>material already collected at the time of disease diagnosis will be requested directly from the corresponding departments of pathology after randomization</td>
</tr>
</tbody>
</table>

* To be performed prior to randomization, but after the surgical procedure leading to GBM diagnosis.

** To ensure comparability of disease status, brain imaging at time points subsequent to baseline must be performed using the exact same imaging techniques employed at baseline i.e. the same type of modality (MRI or CT), scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner.

*** Note that an MRI/CT also needs be done for radiation planning purposes - see section 8.1. Depending on institutional policy and local practice the diagnostic and radiation planning scans can be performed concurrently (i.e. a single scan) or separately (i.e. two separate scans), as long as they are done after surgery and prior to the first day of protocol treatment. Where possible, use of MRI is encouraged for both diagnostic and radiation planning purposes.

♦ Adverse events will be graded and recorded according to the NCI Common Terminology Criteria for Adverse Events Version 3.0 (Appendix V).
7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations will be done by the NCIC CTG by means of a web-based, password-operated electronic system. Complete details regarding obtaining a password, accessing the system and carrying out randomizations will be provided at the time of study activation and will also be included in the "Randomization and Data Management Guidebook", posted on the CE.6 area of the NCIC CTG web-site. If sites experience difficulties accessing the system and/or performing randomizations the CE.6 Study Coordinator should be contacted (see last page of this protocol for contact details).

The following information will be required at the time of randomization:

- trial code (NCIC CTG CE.6)
- treatment centre, centre code and investigator
- date of REB approval* for study at participating centre – Canadian centres only
- version of the informed consent that the patient signed – Canadian centres only
- patient's initials and hospital number (if permitted by the local REB)
- confirmation of the requirements listed in section 5.0, including dates of essential tests and actual laboratory values
- stratification parameters
- height and weight
- exception number – IF granted
* Initial approval of all studies must be Full Board.

7.2 BSA Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight.

7.3 Stratification

The randomization procedure will minimize the imbalance between treatment arms within each of the following stratification factors:

- Centre
- Age (65-70 years versus 71-75 years versus > 76 years)
- Performance Status (ECOG 0, 1 versus 2)
- Extent of resection at surgery (biopsy only versus complete/incomplete resection)

7.4 Randomization

Randomization will be performed electronically. Complete details will be provided at the time of study activation.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient’s data be withdrawn prior to final analysis, except on disclosure of initial ineligibility.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death. The follow-up requirement for ineligible patients is minimal follow-up using a Form 5S.
8.0 TREATMENT PLAN

Although the NCIC Clinical Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

Protocol treatment is to begin within 2 weeks of patient randomization.

8.1 High Precision Radiation Treatment Plan (Arms 1 and 2)

8.1.1 Positioning, Immobilization and Simulation

8.1.1.1 Positioning
The patient shall be treated in the supine position. A prone position would be acceptable for a posterior lesion.

8.1.1.2 Immobilization
The patient shall be treated in an immobilization device, such as a thermoplastic head mask that is transparent to x-rays. The device will ensure adequate immobilization during therapy and treatment reproducibility.

8.1.1.3 Simulation
Post-operative MRI or CT is required in delineation of treatment volume and organs at risk on the treatment planning simulation. The treatment planning CT shall be acquired with the patient in the same position and using the same immobilization device as for treatment. Pre-operative MRI or CT can be used for reference in case of gross tumour resection (8.1.3.3).

8.1.2 Equipment
Treatment shall be delivered with megavoltage equipment.

8.1.2.1 Photon Energy
Linear accelerator with minimal nominal energy of 4 MV shall be used. Selection of the appropriate photon energy should be based on optimizing the radiation therapy dose distribution within the target volume and minimizing dose to the normal tissue. $^{60}\text{Co}$, electrons, particles, implants or stereotactic radiotherapy are not permissible in this protocol.

8.1.2.2 Physical Factors
Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 100 cm. The minimum dose rate at the prescription point should not be less than 0.5 Gy per minute.

8.1.3 Volumes
Only one volume will be considered throughout radiotherapy, and no cone-down or boost volume is allowed.

8.1.3.1 Gross Target Volume (GTV)
The Gross Target Volume (GTV) is defined as the entire contrast-enhanced tumour (by CT or MRI obtained post-operatively). If the tumour has been completely resected, the GTV will be the surgical defect plus any contrast-enhanced abnormality surrounding the surgical defect. In case of post-operative bleeding and/or tumour bed shifting, the definition of volume is left to the best judgment of local investigators making reference to the pre-operative CT or MRI.
8.1.3.2 *Clinical Target Volume (CTV)*

The Clinical Target Volume (CTV) is defined as the GTV plus a 15 mm, with no expansion outside of any natural barriers to tumour growth (e.g., skull and tentorium). For non-uniform margin expansion at anatomical barrier such as skull, a minimum margin on the GTV would be 0 mm.

8.1.3.3 *Planning Target Volume (PTV)*

The Planning Target Volume (PTV) is defined as the CTV plus 5 mm in all directions. In case of complete surgical removal, the position of the tumour bed is sometimes shifted as compared to pre-operative CT/MRI. In this case, the definition of the tumour bed is left to the best judgment of local investigators, still with a CTV and PTV as described above.

8.1.3.4 *Planning Target Volume for Dose Evaluation (PTV_{EVAL})*

The Planning Target Volume for Dose Evaluation (PTV_{EVAL}) is defined as the portion of PTV that is collapsed to inside natural barriers for dose evaluation, and limited to 5 mm from the skin surface. This ensures that surface dose inaccuracies of the treatment planning computers are not included, and field margins stay large enough with adequate target coverage when random set-up errors happen on treatment.

8.1.3.5 *Organs at Risk (OAR)*

The organs at risk (OARs) are defined as the optic nerves, optic chiasm, eye globes (including lens and retinas), and brain stem (including mid brain,pons and medulla oblongata). Every attempt should be made to shield the contoured OARs during radiotherapy planning to minimize their dose after satisfying planning requirements for the PTV_{EVAL}.

8.1.4 *Treatment Planning*

Three-dimensional (3D) treatment planning shall be used, with non-coplanar beam angles as indicated. The volume should be treated with a combination of the appropriate number of convergent fields, depending on tumour size, location and CT-planning. Treatment planning may include 2 fields, 3 fields, rotation or multiple field techniques. The use of three or multiple conformal fields is strongly encouraged to prevent irradiation of healthy tissue (see 8.1.6.1 and 8.1.6.2 for dose constraints).

8.1.4.1 *Beam Delivery*

Appropriate, customized and focused blocks or multi-leaf collimators designed to shield sensitive uninvolved structures are to be used for beam delivery.

8.1.4.2 *Beam Arrangement*

Treatment planning with beam’s eye views is necessary to ensure accuracy in the selection of beam arrangements. Eye globes should not receive any direct radiation beams.

8.1.5 *Dose Specification*

8.1.5.1 *Dose*

A total dose of 40.05 Gy will be delivered in 15 daily fractions over 3 weeks. One treatment of 2.67 Gy will be given daily, five days per week, with no treatment for the weekends. All portals shall be treated during each treatment session. The dose is prescribed at the reference ICRU 50 point (i.e. the intersection of the central axis of the beams).
For the following portal arrangements, target dose will be specified as follows:

- For two opposed co-axial equally weighted beams: on the central ray at mid-separation of beams.
- For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.
- For complete rotation or arc therapy: in the plane of rotation or centre of rotation.
- For other or complex treatment arrangements, the target dose shall be at the center of the target volume.
- Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.
- The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and dose inhomogeneity.

IMRT is not permitted. The maximum and minimum doses to PTV_{EVAL} are 42 Gy and 38 Gy, respectively.

8.1.5.2 Dose Heterogeneity
The inhomogeneity across the target volume shall be kept to a minimum. The minimum dose to the PTV_{EVAL} should be kept within 5% of the dose at the center of the target volume. The maximum dose should be no higher than 5% of dose at the center of the volume. Filters or other compensating devices should be used to improve the dose distribution as indicated.

8.1.5.3 Dose Deviation
See section 8.1.12.

8.1.5.4 Fractionation
See section 8.1.5.1.

8.1.5.5 Corrections for Interruption
Interruption in radiotherapy may be necessitated by skin reaction, brain edema, or other acute complication. If the sum total of such interruptions exceed five normally-scheduled treatment days, the treatment may be considered in major deviation of protocol. Radiation therapy will be continued as soon as possible after interruptions without dose correction.

8.1.6 Dose Limits to Normal Tissues
Whenever possible, without under-dosing PTV_{EVAL} (< 95% of the prescribed dose), attempts should be made to minimize the dose to normal tissues.

8.1.6.1 Organs at Risk
Organs at risk (i.e. eye globes, optic nerves, optic chiasm, and brain stem including mid-brain, pons, and medulla oblongata) should not be allowed to receive more than 100% of the prescribed dose. Dose to lens should be less than 4 Gy. Unacceptable deviations from the protocol are defined in section 8.1.12. Calculation of biological effective dose is shown in Appendix IX.

8.1.6.2 Non Specified Normal Tissue Dose Limits
The maximal dose to non-specified normal tissues, such as skin and any uninvolved brain hemisphere, is 105% of the prescription dose. Unacceptable deviations from the protocol are defined in section 8.1.12.
8.1.7 Planning Priorities

The protocol priorities are:
1. PTV\textsubscript{EVAL} coverage
2. Organs at risk
3. Normal brain and other non-specified normal tissues.

8.1.8 Verification

Treatment isocenter position of the target shall be compared on day 1 orthogonal images to orthogonal digital reconstructed radiographs (DRRs) or simulation films. Port films of each field should be taken weekly and compared with the simulation or DRR images. Non MV portal images are permitted for verification. For all offsets more than 5 mm, re-positioning and re-imaging will be required that day only. A higher frequency of re-imaging at the treating physician’s discretion is allowed to optimally correct for systemic errors. Use as low a number of MUs as possible to achieve an acceptable quality image. Dose from portal images should be accounted for in the distribution.

8.1.9 Concurrent Therapy

8.1.9.1 Agents

Patients in arm 1 will receive no therapy concurrently with radiation.

Patients in Arm 2 will receive an oral daily dose of 75 mg/m\textsuperscript{2} of temozolomide concurrently with radiation therapy. Temozolomide will start on the first day and end on the last day of radiation treatment. In case of radiation interruption, daily treatment with temozolomide will continue while radiation therapy is on hold to a maximum of 28 consecutive days. See section 8.2.1 below for more details.

8.1.9.2 Scheduling

Patients in arm 2 receiving concurrent temozolomide and RT should take temozolomide one hour before each session of radiotherapy. On days of no radiotherapy (i.e. weekends) temozolomide will be taken as per institutional policy.

8.1.10 Documentation Requirements

8.1.10.1 Volumes

The volumes of all GTV, CTV, PTV, and OAR must be documented. All PTV\textsubscript{EVAL}s are to be displayed on the planning CT axial cuts with a maximum slice thickness of 5 mm. Orthogonal images through the isocenter of GTVs are to be documented. Orthogonal cuts through the plan hotspots with contours and designated isodose lines are recommended. CT/MRI documentation for the definition of targets as well as a maximum dose grid resolution of 3 mm is required.

8.1.10.2 Dose Summary Statistics

The minimum dose, mean dose and maximum dose must be reported for every GTV, CTV, and PTV\textsubscript{EVAL}, and for the OAR of eye globes, optic nerves, chiasm, and brain stem. Dose volume histograms (DVHs) are required for all target volumes and listed organs at risk.

8.1.10.3 Dosimetry

Dosimeties through orthogonal planes at the isocenter and through the maximum dose are required, with a minimum of dose displayed on every 2 cm axial slices through the treatment fields. Isodose distributions for the target volume are required on all patients, including those treated with parallel-opposed fields.
8.1.11 Radiation Therapy Quality Assurance

The radiation therapy quality assurance procedure for this study will constitute of a single dry-run case from each centre. The dry-run will be reviewed centrally by the CE.6 Radiation Therapy Quality Assurance Chair to ensure that institutions can plan patients according to the protocol.

Each centre will be asked to plan one case of its choice of 3D radiotherapy using an anonymous CT data set. The first randomized case of a participating centre is permissible to the dry run. CT/MR fusion images, structure and volume delineation on CT/MR images, $PTV_{EVAL}$ and OAR coverage as displayed on DVH, and the dose distribution on orthogonal slices through $PTV_{EVAL}$ will be reviewed. The dry-run should be saved on a CD and sent to the CE.6 Radiation Therapy Quality Assurance Chair by courier. Details of the software/electronic format to be used and the address where the CD should be sent will be provided at the time of centre activation.

Centre activation to this study will not be contingent on the completion of the RT dry-run. However, this run must be completed and submitted for review prior to the randomization of the 5th patient at each participating centre. Failure to do so will result in halting of randomization at the centre until such time as the dry-run has been submitted, reviewed and been found to be satisfactory.

In the event that the dry-run of a centre is deemed unsatisfactory, with concerns such as erroneous target definition or major radiotherapy planning deviation (8.1.12) upon review, accrual at that centre will be suspended. Accrual will be reinstated once the centre makes the necessary amendment to satisfy the specifically identified requirements.

8.1.12 Radiation Therapy Deviation Definition

Minor deviations may be identified and reported to the investigator. Major deviations are not permitted. If a major deviation is identified on the dry-run, an amendment of the treatment plan will be required.

$PTV_{EVAL}$ minor deviation = failure to meet $PTV_{EVAL}$ criteria, where $PTV_{EVAL}$ receives 90-95% and/or 105-110% of the prescription dose, but not a major deviation.

$PTV_{EVAL}$ major deviation = failure to meet $PTV_{EVAL}$ criteria, where $PTV_{EVAL}$ receives less than 90% and/or higher than 110% of the prescription dose.

OAR major violation = failure to meet OAR criteria, where any OAR receives higher than 100% of the prescription dose.

Any non-specified normal tissue receiving higher than 105% of the prescription dose will be accounted for as a major deviation.

8.1.13 Interruption of Radiotherapy due to Adverse Events

Acute adverse events to radiotherapy are anticipated to be mild. Expected side-effects include fatigue, alopecia, skin reaction, mucositis (if nasopharynx included) and temporary hearing loss (if ear canal included).
Depending on the tumour location and the region to be irradiated, several tissues or organs are potentially at risk for late damage, such as the brain hemispheres, brain stem, chiasm and ear (mid or internal). All efforts should be made during planning to minimize the dose to critical structures.

Both acute and late occurring adverse events to radiation treatment will be graded according to NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) and will be recorded on the CRFs.

With the type and site of radiotherapy in this protocol, interruption of radiotherapy due to acute adverse events is extremely unlikely. Individual cases, such as major worsening of neurological or mental status or any other medical conditions/symptoms attributable to radiotherapy (for e.g. grade 3 CNS toxicity or ototoxicity) that could cause interruption or discontinuation of radiotherapy, will be considered on an individual basis by the local investigator.

If radiation therapy is interrupted or delayed for any reason, attempts should be made to ensure the patient receives the full dose of radiotherapy as stipulated in the protocol. Missed radiotherapy doses should be delivered in daily fractions at the end of the three week period to ensure the total dose is received. The total duration of radiation therapy as well as any interruptions or early termination will be recorded on the CRF.

8.2 Temozolomide Treatment Plan (Arm 2)

8.2.1 Temozolomide Given Concurrently With Radiation

Concurrent temozolomide treatment should begin at the same day as radiation therapy and within 2 weeks of randomization. Temozolomide will be given orally, once a day, daily, at a dose of 75 mg/m² until the last day of radiotherapy. If radiotherapy is interrupted due to radiation-attributable adverse events or for technical or medical reasons unrelated to temozolomide, daily treatment with temozolomide should continue during the days of radiation therapy interruption, but total temozolomide treatment should not exceed 28 consecutive days. If radiotherapy is discontinued then treatment with daily concurrent temozolomide should also be discontinued. These statements are summarized in the table below:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Temozolomide (concurrent with radiation)</td>
<td>75 mg/m²</td>
<td>PO</td>
<td>3 weeks</td>
<td>once a day, daily, from the first day to the last day of radiotherapy, but for no longer than 28 days</td>
</tr>
</tbody>
</table>

8.2.1.1 Premedication – Concurrent Temozolomide

Antiemetic prophylaxis (with a 5-HT3-antagonist or metoclopramide) is optional and may be used at the discretion of the investigator.

Continuous temozolomide therapy as well as corticosteroids (expected to be used for most patients in this trial) induce lymphocytopenia. Patients receiving any of these drugs alone or both concomitantly are at an increased risk for opportunistic infections, most notably *P. carinii* pneumonia. The temozolomide product monograph lists *P. carinii* prophylaxis as a requirement for patients (regardless of age) receiving a 42-day-long regimen of radiotherapy/temozolomide. In this study the radiotherapy/temozolomide interval is shorter (21 days), but patients are elderly and may be at a higher risk of infection. Therefore, *P. carinii* prophylaxis for patients receiving concomitant daily temozolomide during radiotherapy in this protocol will be at the discretion of the investigator. If *P. carinii* prophylaxis is used then one of the following treatments is recommended:
Pentamidine inhalations, given once prior to the start and once after the completion of concomitant temozolomide treatment

Trimethoprim-sulfamethoxazole (Bactrim forte®), 1 tablet, 3 times a week

If prophylaxis is given it should continue until patients have fully recovered from any lymphocytopenia (grade < 1).

8.2.1.2 Drug Administration – Concurrent Temozolomide

Dose will be based on body surface area (BSA). The BSA will be calculated from the height and weight obtained immediately before the first day of treatment.

Capsules of temozolomide are available in 5, 20 and 100, 250 mg strengths. The daily dose will be rounded to the nearest 5 or 10 mg, whichever minimizes the number of capsules the patient needs to take per day. Each daily dose should be given with the least number of capsules.

Temozolomide should be taken one hour before each session of radiotherapy during weekdays (5/7 days). During weekends, when no radiotherapy is to be given (2/7 days), temozolomide should be taken as per institutional policy.

To reduce the possibility of nausea and vomiting and because absorption is affected by food, temozolomide should be taken on an empty stomach (i.e. at least 1 hour before or 1 hour after the ingestion of any food). Patients should be told to swallow the whole capsules in rapid succession without chewing them.

If vomiting occurs shortly after the temozolomide capsules are swallowed, the dose should not be repeated. The next dose should be taken the following day, as per schedule. Missed doses should be skipped.

8.2.1.3 Dose Interruptions/Discontinuation – Concurrent Temozolomide

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 (see Appendix V)

The major adverse effects of temozolomide are nausea, vomiting and myelosuppression (neutropenia and/or thrombocytopenia). Other adverse events frequently observed include anemia, anorexia and constipation.

There will be no dose reductions. In case of temozolomide-attributable adverse events, drug administration should either be interrupted or discontinued based on the guidelines in sections A and B below.

If temozolomide is interrupted due to adverse events, radiotherapy should continue. When treatment with temozolomide resumes, daily doses should be taken until the last day of radiotherapy as per the original schedule, i.e. missed doses of temozolomide will not be replaced or restored.
A: Hematologic Adverse Events- Concurrent Temozolomide

### Hematologic Counts

<table>
<thead>
<tr>
<th>Absolute Granulocytes (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose of Temozolomide Given Concurrently with Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 x 10^9/L and ≥ 100 x 10^9/L</td>
<td>75 mg/m²</td>
<td></td>
</tr>
<tr>
<td>≥ 0.5 to &lt; 1.5 x 10^9/L and/or ≥ 25 and &lt; 100 x 10^9/L</td>
<td>Hold until recovery* then resume daily dosing at 75 mg/m²</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5 x 10^9/L and/or &lt; 25 x 10^9/L</td>
<td>Stop</td>
<td></td>
</tr>
</tbody>
</table>

* absolute granulocytes ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L.

B: Non-hematologic Adverse Events - Concurrent Temozolomide

Concurrent temozolomide should be interrupted/discontinued for non-hematologic adverse events as follows:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Dose of Temozolomide Given Concurrently with Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>any</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td>Nausea or Vomiting</td>
<td>1, 2</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Hold until recovery to ≤ grade 2 and then resume daily treatment at 75 mg/m²</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Stop</td>
</tr>
<tr>
<td>All other, temozolomide-related, non-hematologic adverse events</td>
<td>1</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td></td>
<td>2,3</td>
<td>Hold until recovery to ≤ grade 1 and then resume daily treatment at 75 mg/m²</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Stop</td>
</tr>
</tbody>
</table>

8.2.1.4 Patient Compliance - Concurrent Temozolomide

Compliance with daily temozolomide while the patient is receiving radiotherapy is important to the conclusions of this study. Study site pharmacy staff will make tablet counts either weekly or at the end of treatment with concurrent temozolomide. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the CRF.
8.2.2 *Temozolomide Given as Adjuvant Treatment*

Adjuvant temozolomide treatment should begin 28 days (four weeks) after the end of radiation treatment.

Temozolomide will be taken orally, once a day, daily, for the first 5 days of each 28-day cycle. Cycles should continue until progressive disease to a maximum of 12 months of treatment. The starting dose of the first cycle will be 150 mg/m²/day. The dose of temozolomide will be escalated to 200 mg/m²/day in cycle 2 providing that ALL FOUR of the following conditions have been met:

- **During cycle 1**, the absolute granulocyte count was ≥ 1.5 x 10⁹/L and the platelet count was ≥ 100 x 10⁹/L.
- **During cycle 1**, the worse toxicity grade for nausea and vomiting was ≤ 3 and the worse toxicity grade for all other non-hematologic adverse events was ≤ 2.
- **On day 1 of cycle 2**, the absolute granulocyte count is ≥ 1.5 x 10⁹/L and the platelet count is ≥ 100 x 10⁹/L.
- **On day 1 of cycle 2**, the worse toxicity grade for nausea and vomiting is < 3 and the worse toxicity grade for all other non-hematologic adverse events is < 2.

If escalated to 200 mg/m² in cycle 2, this dose will also be the starting dose for subsequent cycles, provided that none of the dose reduction/interruption/discontinuation guidelines described in section 8.2.2.3 below are met. If no escalation occurs in cycle 2 then the dose cannot be escalated in subsequent cycles. These statements are summarized in the table below:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent(s)</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Temozolomide (adjuvant)</td>
<td>150 mg/m² in cycle 1*; escalate to 200 mg/m² in cycles 2 onwards in the absence of significant adverse events</td>
<td>PO</td>
<td>28-day long cycles, starting 4 weeks after the end of radiotherapy and continuing until progressive disease to a maximum of 12 months</td>
<td>once a day, daily, for the first 5 days of each 28-day cycle</td>
</tr>
</tbody>
</table>

* The dose of the first adjuvant temozolomide cycle may be reduced from 150 mg/m² (in accordance with section 8.2.2.3 of the protocol) as a result of adverse events experienced during the 4 week follow up period post radiation therapy

8.2.2.1 *Premedication – Adjuvant Temozolomide*

Antiemetic prophylaxis with a 5-HT₃-antagonist or metoclopramide is required.

8.2.2.2 *Drug Administration – Adjuvant Temozolomide*

Dosage will be based on body surface area (BSA). 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 and 100 and 250 mg strengths. The daily dose will be rounded to the nearest 5 or 10 mg, whichever minimizes the number of capsules the patient needs to take per day. Each daily dose should be given with the least number of capsules.
Temozolomide should be taken as per institutional policy. To reduce the possibility of nausea and vomiting and because absorption is affected by food, temozolomide should be taken on an empty stomach (i.e. at least 1 hour before or 1 hour after the ingestion of any food). An overnight fast is preferred with subsequent administration of temozolomide early the next morning in the fasted state. Water is allowed during the fast period. Patients should be told to swallow the whole capsules in rapid succession without chewing them.

If vomiting occurs shortly after the temozolomide capsules are swallowed, the dose should not be repeated. The next dose should be taken the following day or on day 1 of the next cycle, as per schedule. Missed doses should be skipped.

8.2.2.3 Dose Adjustments – Adjuvant Temozolomide

Doses will be adjusted for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 (see Appendix V).

The major adverse effects of temozolomide which limit dose are nausea, vomiting and myelosuppression (neutropenia and/or thrombocytopenia). Other adverse events frequently observed include anemia, anorexia and constipation. The guidelines in sections C and D below outline dose adjustments for several of these adverse effects. If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

The dose of temozolomide for cycle 1 will be 150 mg/m². The dose for cycle 2 will be 200 mg/m² if ALL FOUR conditions outlined in section 8.2.2 above are met. Otherwise the cycle 2 dose will either be 150 mg/m² or lower based on the guidelines described in sections C and D below. In subsequent cycles the starting dose of temozolomide will be the same as for cycle 2 unless dose reductions are warranted based on the guidelines shown in the sections C and D below.

In general the dose of temozolomide for a given cycle will be determined based on two things:
1. the worst severity of adverse events experienced during the previous cycle, and
2. the severity of adverse events seen on the first day of the current cycle

**IMPORTANT:** Hematologic and non-hematologic adverse events should be considered together, so that a patient who fulfils the criteria for a dose reduction/delay in one of the categories/types of adverse events must have his/her dose reduced/delayed even if he/she qualifies for no dose reductions/delays by the rest of the criteria.

The adjuvant temozolomide dose reduction levels are:

<table>
<thead>
<tr>
<th>Cycles 2 onwards if dose reduced in cycle 1</th>
<th>Starting Dose (mg/m²/day)</th>
<th>1st Reduction (mg/m²/day)</th>
<th>2nd Reduction (mg/m²/day)</th>
<th>3rd Reduction (mg/m²/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles 2 onwards if no dose escalation in cycle 2</td>
<td>150</td>
<td>100</td>
<td>discontinue temozolomide</td>
<td>-</td>
</tr>
<tr>
<td>Cycles 2 onwards if dose escalated in cycle 2</td>
<td>200</td>
<td>150</td>
<td>100</td>
<td>discontinue temozolomide</td>
</tr>
</tbody>
</table>

Once the dose of adjuvant temozolomide has been reduced due to adverse events it may not be escalated again.
C: Hematologic Adverse Events- Adjuvant Temozolomide

### Hematologic Counts on DAY 1 of Cycle

<table>
<thead>
<tr>
<th>Absolute Granulocytes (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Temozolomide Dose This Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 x 10^9/L and ≥ 100 x 10^9/L</td>
<td>Treat on time, no dose modification</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.5 x 10^9/L and/or &lt; 100 x 10^9/L</td>
<td>Delay start of cycle by 1 week intervals, to a maximum of 3 weeks,* until recovery, then treat with same dose as day 1 of previous cycle</td>
<td></td>
</tr>
</tbody>
</table>

* If the counts have not recovered after 3 weeks then adjuvant temozolomide should be stopped.

### Worst Hematologic Counts during the PREVIOUS cycle*

<table>
<thead>
<tr>
<th>Absolute Granulocytes (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Temozolomide Dose This Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0 x 10^9/L and ≥ 50 x 10^9/L</td>
<td>Treat on time, no dose modification</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0 x 10^9/L and/or &lt; 50 x 10^9/L</td>
<td>Treat on time, reduce by one dose level</td>
<td></td>
</tr>
</tbody>
</table>

* The previous cycle for the first adjuvant cycle of temozolomide refers to the 4 week post radiation therapy follow up period.

D: Non-hematologic Adverse Events - Adjuvant Temozolomide

### Non-hematologic Adverse Events on DAY 1 of Cycle

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Temozolomide Dose This Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>Any</td>
<td>Treat on time, no dose modification</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>1,2</td>
<td>Treat on time, no dose modification</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Delay start of cycle by 1 week intervals, to a maximum of 3 weeks,* until recovery to ≤ grade 2, then treat with same dose as day 1 of previous cycle</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Stop</td>
</tr>
<tr>
<td>All other temozolomide-related non-hematologic adverse events</td>
<td>1</td>
<td>Treat on time, no dose modification</td>
</tr>
<tr>
<td></td>
<td>2,3</td>
<td>Delay start of cycle by 1 week intervals, to a maximum of 3 weeks,* until recovery to ≤ grade 1, then treat with same dose as day 1 of previous cycle</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Stop</td>
</tr>
</tbody>
</table>

* If not recovered after 3 weeks then adjuvant temozolomide should be stopped.
<table>
<thead>
<tr>
<th>Worst Grade of Non-hematologic Adverse Events during the PREVIOUS cycle</th>
<th>Adverse Event</th>
<th>Grade</th>
<th>Temozolomide Dose This Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>Any</td>
<td>Treat on time, no dose modification</td>
<td></td>
</tr>
<tr>
<td>All other temozolomide-related non-hematologic adverse events</td>
<td>1, 2</td>
<td>Treat on time, no dose modification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Treat on time, reduce by one dose level*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Stop</td>
<td></td>
</tr>
</tbody>
</table>

* if the same non-hematologic adverse event recurs with a grade 3 severity then temozolomide should be **stopped**

8.2.2.4 Duration of Therapy - Adjuvant Temozolomide

Unless unmanageable adverse events occur, treatment with adjuvant temozolomide will continue until progressive disease or to a maximum of 12 months.

8.2.2.5 Patient Compliance – Adjuvant Temozolomide

Compliance with adjuvant temozolomide treatment is important to the conclusions of this study. Study site pharmacy staff will make pill counts at the beginning of every cycle. Patients will be instructed to notify study site personnel of missed doses. Dates of missed, held or reduced doses will be recorded on the CRF.

8.3 Concomitant Therapy

8.3.1 Permitted

- Prophylactic antiemetics.

- Corticosteroids may be administered at the discretion of the treating physician.

- Agents (such as pentamidine and trimethoprim-sulfamethoxazole (Bactrim forte®)) for *Pneumocystis carinii* prophylaxis (see also section 8.2.1.1)

- Patients should receive full supportive and palliative care (e.g. pain control) as clinically indicated during the trial (including transfusion of blood products and analgesics) when appropriate.

8.3.2 Not permitted

- Growth factors should not be used to induce elevations in neutrophil count for the purposes of administration of temozolomide on the scheduled dosing interval or to allow treatment with temozolomide at a higher dose or to avoid interruption of the treatment during concomitant radiotherapy. Erythropoietin may not be used.

- No other investigational drugs.

- Surgical procedures for tumour debulking, other types of chemotherapy, 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 have to come off protocol therapy.
9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

Note: One of the possible effects seen early after radiotherapy is that CT/MRI contrast uptake may be enhanced. For this reason, if radiological evidence of disease progression is observed on its own (i.e. unaccompanied by clinical worsening) shortly after the end of radiotherapy it may not be proof of disease progression. See also section 10.0

9.1 Evaluation During Protocol Treatment

9.1.1 Evaluation During Protocol Treatment - ARM 1 (RT only)

Patients receiving radiotherapy will be seen weekly by their physician, as part of standard practice. A formal evaluation for the purposes of this trial is required one week after the end of radiotherapy. Details are as follows (see also Appendix I):

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam including:</td>
<td></td>
</tr>
<tr>
<td>Physical examination (including neurological evaluation)</td>
<td>Weekly up until and including 1 week after the last fraction of radiotherapy*</td>
</tr>
<tr>
<td>Weight, ECOG Performance Status</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, WBC with differential (granulocytes, lymphocytes), platelet count</td>
<td>1 week after the last fraction of radiotherapy</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, ALT (SGPT) and/or AST (SGOT), alkaline phosphatase, serum creatinine, serum total protein, random glucose</td>
<td></td>
</tr>
<tr>
<td>Other Investigations</td>
<td></td>
</tr>
<tr>
<td>Mini-Mental Status (see Appendix VII)</td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
</tr>
<tr>
<td>Recorded and graded according to the NCI Common Terminology Criteria for Adverse Events Version 3.0 (Appendix V)</td>
<td>Weekly up until and including 1 week after the last fraction of radiotherapy**</td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
</tr>
<tr>
<td>Quality of life questionnaire: EORTC QLQ-C30 and QLQ-BN20 (see Appendix VI)</td>
<td>Weekly up until and including 1 week after the last fraction of radiotherapy**</td>
</tr>
</tbody>
</table>

* Evaluations on: day 1 of weeks 1, 2 and 3 of radiotherapy; then 1 week after the last fraction of radiotherapy.
** Questionnaires should be completed prior to the patient receiving his/her daily radiation treatment on the days of the 5th, 10th and 15th fraction of radiotherapy; then 1 week after the last fraction of radiotherapy.
9.1.2 Evaluation During Protocol Treatment - ARM 2 (RT plus Temozolomide)

While on radiotherapy and concomitant temozolomide and for the four weeks after the end of radiotherapy, patients in arm 2 should be evaluated weekly. Patients will also be assessed on days 1 and 21 of each cycle of adjuvant temozolomide treatment and at the end of the last cycle of adjuvant temozolomide. Details are as follows (see also Appendix I):

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Exam including:</strong></td>
<td>Weekly until the last fraction of radiotherapy, and at 1 week and 4 weeks after the last fraction of radiotherapy (and as clinically indicated in the interim)();) day 1 of each cycle** of adjuvant temozolomide; at the end of the last cycle of adjuvant temozolomide</td>
</tr>
<tr>
<td>* Physical examination (including neurological evaluation)</td>
<td></td>
</tr>
<tr>
<td>* Weight, ECOG Performance Status</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td>Weekly up until and including 4 weeks after the last fraction of radiotherapy(*; ) days 1 and 21 of each cycle of adjuvant temozolomide</td>
</tr>
<tr>
<td>Hemoglobin, WBC with differential (granulocytes, lymphocytes), platelet count</td>
<td></td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td>1 week after the last fraction of radiotherapy; 4 weeks after the last fraction of radiotherapy; day 1 of each cycle** of adjuvant temozolomide; at the end of the last cycle of adjuvant temozolomide</td>
</tr>
<tr>
<td>Total bilirubin, ALT (SGPT) and/or AST (SGOT), alkaline phosphatase, serum creatinine, serum total protein, random glucose</td>
<td></td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td>4 weeks after the last fraction of radiotherapy**; at the end of every 3 cycles of adjuvant temozolomide</td>
</tr>
<tr>
<td>Gadolinium-enhanced MRI or contrast CT scan of the brain*</td>
<td></td>
</tr>
<tr>
<td><strong>Other Investigations</strong></td>
<td>1 week after the last fraction of radiotherapy; 4 weeks after the last fraction of radiotherapy; at the end of every 3 cycles of adjuvant temozolomide</td>
</tr>
<tr>
<td>Mini-Mental Status (see Appendix VII)</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td>Weekly until the last fraction of radiotherapy and at 1 week and 4 weeks after the last fraction of radiotherapy (and as clinically indicated in the interim)(*; ) day 1 of each cycle** of adjuvant temozolomide</td>
</tr>
<tr>
<td>Recorded and graded according to the NCI Common Terminology Criteria for Adverse Events Version 3.0 (Appendix V)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>Weekly up until and including 1 week after the last fraction of radiotherapy***; 4 weeks after the last fraction of radiotherapy; day 1 of cycles 4, 7 and 10 of adjuvant temozolomide*; day 28 of cycle 12 of adjuvant temozolomide</td>
</tr>
<tr>
<td>Quality of life questionnaire: EORTC QLQ-C30 and QLQ-BN20 (see Appendix VI)</td>
<td></td>
</tr>
</tbody>
</table>

\* Evaluations on: day 1 of weeks 1, 2 and 3 of radiotherapy; then 1 week and 4 weeks after the last fraction of radiotherapy (as well as in the interim if clinically indicated). Hematology must also be done at 2 and 3 weeks after the last fraction of radiotherapy, but results can be provided by an outside lab (and faxed to the investigator for data entry).

\** Excluding cycle 1 - the "4 weeks after the last fraction of radiotherapy" evaluation to count towards "day 1 of cycle 1" as well.

\* To ensure comparability of disease status, brain imaging at time points subsequent to baseline must be performed using the exact same imaging techniques employed at baseline i.e. the same type of modality (MRI or CT), scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner.

\** Because CT/MRI contrast uptake enhancement is one of the possible early side-effects of radiotherapy, radiological evidence of disease progression on its own (i.e. unaccompanied by clinical worsening) 4 weeks after the end of radiotherapy should not be considered proof of disease progression.

\*** Questionnaires should be completed prior to the patient receiving his/her daily radiation treatment on the days of the 5th, 10th and 15th fraction of radiotherapy; then 1 week after the last fraction of radiotherapy.

\*\* Questionnaires should be completed prior to the patient taking his/her day 1 dose of temozolomide.
9.2 Evaluation After Protocol Treatment

9.2.1 Evaluation After Protocol Treatment - ARM 1 (RT only)

Patients in arm 1 will be assessed 4 weeks after the end of radiotherapy and thereafter every 3 months until death. After disease progression occurs, patients will only be required to undergo physical exam and adverse event evaluation. Details are as follows (see also Appendix I):

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Exam including:</strong></td>
<td></td>
</tr>
<tr>
<td>• Physical examination (including neurological evaluation)</td>
<td>4 weeks after the last fraction of radiotherapy and then every 3 months until death</td>
</tr>
<tr>
<td>• Weight, ECOG Performance Status</td>
<td>4 weeks after the last fraction of radiotherapy and then every 3 months until progression</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, WBC with differential (granulocytes, lymphocytes), platelet count</td>
<td>4 weeks after the last fraction of radiotherapy</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, ALT (SGPT) and/or AST (SGOT), alkaline phosphatase, serum creatinine, serum total protein, random glucose</td>
<td>4 weeks after the last fraction of radiotherapy</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td></td>
</tr>
<tr>
<td>Gadolinium-enhanced MRI or contrast CT scan of the brain*</td>
<td>4 weeks after the last fraction of radiotherapy** and then every 3 months until progression</td>
</tr>
<tr>
<td><strong>Other Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental Status (see Appendix VII)</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) (Appendix V).</td>
<td>4 weeks after the last fraction of radiotherapy and then every 3 months until death</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td></td>
</tr>
<tr>
<td>Quality of life questionnaire: EORTC QLQ-C30 and QLQ-BN20 (see Appendix VI)</td>
<td>4 weeks after the last fraction of radiotherapy, every 3 months until progression and at the time of progression*</td>
</tr>
</tbody>
</table>

* To ensure comparability of disease status, brain imaging at time points subsequent to baseline must be performed using the exact same imaging techniques employed at baseline i.e. the same type of modality (MRI or CT), scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner.

** Because CT/MRI contrast uptake enhancement is one of the possible early side-effects of radiotherapy, radiological evidence of disease progression on its own (i.e. unaccompanied by clinical worsening) at 4 weeks after the end of radiotherapy should not be considered proof of disease progression.

♦ If the patient goes off treatment for disease progression, and the QoL was already completed within 2 weeks of date of progression, questionnaire need not be completed again.
9.2.2 **Evaluation After Protocol Treatment - ARM 2 (RT plus Temozolomide)**

After discontinuation of adjuvant temozolomide patients in arm 2 will be assessed every 3 months until death. Once disease progression occurs, patients will only be required to undergo physical exam and adverse event evaluation. Details are as follows (see also Appendix I):

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam including:</td>
<td></td>
</tr>
<tr>
<td>• Physical examination (including</td>
<td>Every 3 months until death</td>
</tr>
<tr>
<td>neurological evaluation)</td>
<td></td>
</tr>
<tr>
<td>• Weight, ECOG Performance Status</td>
<td>Every 3 months until progression</td>
</tr>
<tr>
<td>Radiology</td>
<td></td>
</tr>
<tr>
<td>Gadolinium-enhanced MRI or contrast</td>
<td></td>
</tr>
<tr>
<td>CT scan of the brain*</td>
<td>Every 3 months until progression</td>
</tr>
<tr>
<td>Other Investigations</td>
<td></td>
</tr>
<tr>
<td>Mini-Mental Status (see Appendix</td>
<td></td>
</tr>
<tr>
<td>VII)</td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
</tr>
<tr>
<td>Adverse events will be recorded</td>
<td>Every 3 months until death</td>
</tr>
<tr>
<td>and graded according to the NCI</td>
<td></td>
</tr>
<tr>
<td>Common Terminology Criteria for Ad-</td>
<td></td>
</tr>
<tr>
<td>verse Events Version 3.0 (CTCAE)</td>
<td></td>
</tr>
<tr>
<td>(Appendix V).</td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
</tr>
<tr>
<td>Quality of life questionnaire:</td>
<td>Every 3 months until progression and</td>
</tr>
<tr>
<td>EORTC QLQ-C30 and QLQ-BN20 (see</td>
<td>at the time of progression**</td>
</tr>
<tr>
<td>Appendix VI)</td>
<td></td>
</tr>
</tbody>
</table>

* To ensure comparability of disease status, brain imaging at time points subsequent to baseline must be performed using the exact same imaging techniques employed at baseline i.e. the same type of modality (MRI or CT), scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner.

** If the patient goes off treatment for disease progression, and the QoL was already completed within 2 weeks of date of progression, questionnaire need not be completed again.
10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1 Overall Survival

All randomized patients will be included in the analysis of overall survival, which is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive.

10.1.2 Progression Free Survival

Progression free survival is defined as the time interval between the date of randomization and the date of disease progression or death, whichever comes first. If neither event has been observed, then the patient will be censored at the date of the last disease assessment.

Disease progression is defined as objective (radiological) progression. In the event that objective (radiological) progression cannot be determined (if, for example, a patient cannot be subjected to brain imaging) disease progression is defined as symptomatic (neurological/clinical) progression. The following definitions should be used:

Objective (Radiological) Progression:
For patients with complete resections at the time of study entry, objective progression is defined as the recurrence of tumour as detected by MRI or CT. For patients with incomplete resections or biopsy only at entry, objective progression is defined as the appearance of new lesions and/or an increase of contrast uptake on MRI or CT of > 25%, as measured by the product of two perpendicular tumour diameters compared to the smallest product of measurements ever recorded post-operatively by the same technique.

Note: Because CT/MRI contrast uptake enhancement is one of the possible early side-effects of radiotherapy, radiological evidence of disease progression on its own (i.e. unaccompanied by clinical worsening) 4 weeks after the end of radiotherapy should not be considered proof of disease progression. Please consult Appendix X about pseudoprogression for more information.

Symptomatic (Clinical/Neurological) Progression:
Symptomatic Progression is defined as general deterioration of health, in the absence of both (i) objective (radiological) evidence of disease progression and (ii) clinical explanation(s) other than tumour progression. The criteria constituting "general deterioration of health" are at the investigator's discretion and may include some or all of the following three conditions:

• clinical deterioration of performance status;
• deterioration of neurological functions;
• increase in corticosteroid dosage by 50%;

It is strongly recommended to perform, whenever possible, a radiological confirmation of the clinical suspicion, of tumour progression. Symptomatic progression should only be declared where it is not possible to document objective disease progression.
The date of disease progression is defined as the date when the criteria for objective progression are first met. In the case when no brain imaging is possible, the date of disease progression is defined as the date when, in the investigator's opinion, the patient first achieved symptomatic progression.

It is important to note that the results of subsequent brain imaging will always supersede any prior declaration of symptomatic disease progression. For patients who are first declared to have symptomatic progression and are then radiologically confirmed to have progressed objectively, the documented date of progression will be the date of the objective disease progression. Conversely, patients whose clinical declaration of tumour progression is not confirmed objectively upon subsequent brain imaging will be considered to not have progressed at all.

10.1.3 *Evaluable for Adverse Events*

All patients who have received at least one dose of study treatment (radiotherapy alone or radiotherapy in combination with temozolomide) will be considered evaluable for adverse events.

10.1.4 *Evaluable for Quality Of Life Assessment*

All patients who have completed the quality of life questionnaire are evaluable for quality of life.
11.0 SERIOUS ADVERSE EVENT REPORTING

Note: This section provides SAE Reporting instructions for Canadian centres and also describes the process of SAE reporting and flow between the NCIC CTG central office, Schering and the EORTC data centre. For SAE reporting instructions specific to International centres please consult the appropriate Group Specific Appendix.

This protocol does not contain investigational agent(s), and adverse events occurring as a result of this commercially available treatment (temozolomide) should be reported to NCIC CTG in the manner described below. In addition, your local Research Ethics Board (REB) should be notified.

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 3.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all “reportable” serious adverse events are subject to expedited reporting using the NCIC CTG SAE form. The term ‘reportable SAE’ is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to NCIC CTG.

11.1 Definition of a Reportable Serious Adverse Event

• All serious adverse events which are unexpected and related to temozolomide treatment must be reported in an expedited manner (see Section 11.2 for reporting instructions).
• Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the temozolomide product monograph (Temodal Product Monograph).
• Adverse events considered related to temozolomide treatment are those for which a relationship to temozolomide cannot reasonably be ruled out.
• A serious adverse event (SAE) is any adverse event that at any dose:
  – results in death
  – is life-threatening
  – requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  – results in persistent or significant disability or incapacity
  – is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether an event can be deemed “serious” in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events occurring during temozolomide treatment and within 30 days of the last temozolomide dose, must be reported as follows:
Within 24 hours: Report event by telephone and/or fax to:

Chad Winch or Dr. Chris O’Callaghan
NCIC Clinical Trials Group
Phone: +613-533-6430
Fax: +613-533-2941

Within 10 days: Mail completed Serious Adverse Event form to the NCIC CTG central office.

All reportable serious adverse events must ALSO be recorded on the corresponding treatment/ follow-up form(s) within the CE.6 Electronic Data Capture web-based system.

11.3 Reporting Secondary Malignancies or Myeloid Dysplasia

Secondary malignancies or myeloid dysplasia should only be reported in writing on a Serious Adverse Event Form within 15 working days of when diagnosis is known to the investigator if thought to be possibly, probably or definitely related to protocol therapy AND unexpected (not consistent with information contained in the temozolomide product monograph).

11.4 NCIC CTG Responsibility for Reporting Serious Adverse Events to Health Canada (Clinical Trials Division and to Marketed Health Products Directorate [MHPD])

The NCIC CTG will provide expedited reports of SAEs to Health Canada (Clinical Trials Division and to Marketed Health Products Directorate [MHPD]) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to temozolomide (or for which a causal relationship with temozolomide can not be ruled out).

The NCIC CTG will be responsible for deciding which reportable serious adverse events (as defined in section 11.1) meet the requirements for expedited reporting to regulatory authorities and for preparing event summaries.

11.5 NCIC CTG Reporting Responsibilities to Schering Canada

Schering will be notified by NCIC CTG of all reportable serious adverse events (as defined in section 11.1) within 1 working day of receipt.

For events that have been deemed by NCIC CTG to be reportable to regulators (see section 11.4), the NCIC CTG will be responsible for providing event summaries to Schering within 2-4 days prior to the event's due date to regulatory authorities.

11.6 Schering Reporting Responsibilities

Schering will be responsible for providing NCIC CTG with CIOMS reports for reportable events, no later than 1 working day before they are due to regulators, so that NCIC-CTG can report them to Health Canada (according to section 11.4) within Health Canada’s timelines.

Schering will notify NCIC CTG of all Safety Letters / Safety Updates and International Safety Letters from other studies with temozolomide already reported to regulatory authorities (including Health Canada) by Schering.
11.7 **EORTC Data Centre Reporting Responsibilities**

The EORTC Data Centre will be responsible for notifying the NCIC CTG, within 1 working day of receipt, of all CE.6 events from European centres which meet the reportable definition described in section 11.1, that is events that are serious, unexpected and related to temozolomide treatment.

In the event that the EORTC Data Centre mandates that European centres follow a broader definition for reportable SAEs than Canadian centres (e.g. all serious events), the EORTC Data Centre will be responsible for processing the serious adverse events originating from Europe and only notifying the NCIC CTG of the events that are serious and unexpected and related.

The EORTC Data Centre will notify the European Regulatory Authorities and all European CE.6 Investigators of all SAEs from this trial which are deemed to be reportable, as reported to the EORTC Data Centre by the NCIC CTG (see section 11.8 below).

**Note:** For reporting responsibilities of other collaborating groups, please consult the appropriate Group Specific Appendix.

11.8 **NCIC CTG Reporting Responsibilities to the EORTC Data Centre**

The NCIC CTG will be responsible for notifying the EORTC Data Centre of all events from CE.6 which have been deemed to be reportable. The NCIC CTG will further be responsible for sending to the EORTC Data Centre the final CIOMS reports for submission to regulators, no later than 1 working day before these reports are due.

11.9 **Reporting Safety Reports to Local Research Ethics Boards**

NCIC CTG will notify all Canadian Investigators of all Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials that are reportable to regulatory authorities in Canada as reported to the NCIC CTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to temozolomide. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Product Monograph. The date of REB Submission for SAEs and SUs will need to be entered into the NCIC CTG trial CE.6 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.

For this purpose, the REB submission template letter provided by NCIC CTG should be used. Please note:

- this letter must be either printed on institutional letterhead or contain the centre identification/REB name;
- the date of REB submission must be provided;
- an individual on the approved Participants List for this trial must sign this form.

The submission of these events to your ethics board should be done as soon as possible. It is expected that these will be submitted for review within 30 days of the date of the letter to Investigator.
12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in section 8.0.
- Tumour progression or disease recurrence as defined in section 10.0.

**Note:** Because CT/MRI contrast uptake enhancement is one of the possible early side-effects of radiotherapy, radiological evidence of disease progression on its own (i.e. unaccompanied by clinical worsening) 4 weeks after the end of radiotherapy should not be considered proof of disease progression. Please consult Appendix X about pseudoprogression for more information.

- Request by the patient.
- Physician decision to discontinue treatment for any reason if he/she judges it to be in the best interest of the patient.

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 Therapy After Protocol Treatment is Stopped

- **Prior to Progression** patients may not receive any other anti-cancer treatment.
- **After Progression Occurs** further cancer therapy is at the discretion of the investigator. Patients on the radiotherapy alone arm may receive temozolomide as salvage chemotherapy, provided the drug is available for this indication on the market or on a compassionate use program. Study medication may not be used for these patients.

12.3 Follow-up Off Protocol Treatment

Patients completing protocol treatment in arms 1 (radiotherapy) and 2 (radiotherapy plus concurrent and adjuvant temozolomide) will be followed extensively (including radiological assessment of disease and quality of life) every 3 months until progression. After disease progression occurs, patients will only be required to undergo physical exam and adverse event evaluation every three months until death. Complete details are given in section 9. A final report (Form 6) will be required on all patients at the time of death (see Appendix IV - Documentation for Study).
13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Radiology Review

There will be no central review of CT scans or MRIs.

13.2 Central Pathology Review and Tissue Collection for MGMT Promoter Methylation Testing

Patients will be randomized to this study based on histological confirmation of GBM obtained locally, at each participating centre. However, histology will also be confirmed for all patients through central pathology review. This is a mandatory component of the study and it will take place retrospectively (i.e. at the end of the study). Central pathology review will be performed by neuro-pathologists Drs. John Rossiter and Samuel Ludwin of the Department of Pathology and Molecular Medicine at Queen’s University in Kingston, Ontario, Canada.

The methylation status of the MGMT promoter will be determined for all patients. This is a mandatory component of the study and it will take place retrospectively (i.e. at the end of the study). The MGMT methylation testing will be done by Oncomethylome Sciences (locations in Belgium, Netherlands and Durham, NC, USA) under the direction of the NCIC Clinical Trials Group. Patient tissue specimens will be identified to Oncomethylome Sciences only by a code in order to protect patient identity and privacy.

Diagnostic pathology reports will be received as part of the supporting documentation required for this trial. Receipt of pathology reports will initiate a request directly from the NCIC CTG central office to the corresponding pathology departments where diagnostic tissue is held. All details/requirements regarding sample submission will be specified within the letter of request sent by the NCIC CTG central office to the pathology departments.

13.3 Tissue Collection for Banking

The collection of a representative block of the diagnostic tumour tissue for banking is an important part of this trial. This is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Blocks will be carefully banked as part of the NCIC CTG tissue/tumour bank at Queen’s University in Kingston, Ontario, Canada. Tumour blocks will be the preferred material to collect, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

The tissue may be used by researchers now or in the future to better understand the nature of cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval. Patients will not be identified by name. The only identification of tissue will be by the patient study number assigned at the time of randomization to the trial, the surgical/histology number, patient initials and the tumour bank code. Material issued to researchers will be anonymized and only identified by a coded number.

For patients consenting to tissue banking, the Queen’s Department of Pathology will request a representative tumour block directly from the corresponding pathology department.
Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

13.4 Central Radiotherapy Review

Radiotherapy review will be included on this trial as a credentialing process prior to the enrollment of the 5th patient from each centre. No real-time or final review will be performed. Refer to section 8.1 for further information.
14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

The primary objective of this study is to assess the effect of the addition of concurrent and adjuvant temozolomide to short-course radiotherapy, in comparison with short-course radiotherapy alone, on the survival of elderly patients (≥ 65 years old) with newly diagnosed, histopathologically confirmed, glioblastoma multiforme (WHO grade IV) who have had prior surgery or biopsy and who are not deemed suitable by their treating physician to receive the standard radiotherapy regimen (60Gy/30 fractions over 6 weeks) in combination with temozolomide. Secondary objectives include comparisons of time to progression, quality of life, adverse events between the two treatment arms, and molecular correlative studies.

This is a multi-centre, prospective, randomized phase III trial. Patients will be randomized to receive either short-course radiotherapy plus concurrent and adjuvant temozolomide or short-course radiotherapy alone in a 1:1 ratio and will be stratified by centre, ECOG performance status (0 + 1 versus 2), age (65-70 years versus 71-75 years versus ≥ 76 years) and extent of resection at surgery (biopsy only versus complete/incomplete resection) by using the dynamic minimisation method.

14.2 Study Endpoints and Analysis

Overall survival, the primary endpoint of this study, is defined as the time from randomization to the time of death from any cause. Patients who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive. Patients will be analyzed in the arm to which they are randomized regardless of the treatment they received (intent-to-treat analysis). The survival experience of patients in both treatment groups will be described by the Kaplan-Meier method. A stratified log-rank test, adjusting for the stratification factors (except centre) plus MGMT promoter methylation status, will be used as the primary method to compare the overall survival between the two arms. An unadjusted analysis will also be performed. As an exploratory analysis, a Cox proportional hazards regression model will be used to adjust the observed treatment effect for the influence of various prognostic factors at study entry and identify factors significantly related to the survival. The final Cox model will be determined using a stepwise model building procedure.

Progression free survival (PFS) is defined as the time from randomization to the date of documented disease progression or death due to any cause. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last disease assessment. All analyses for survival will also be performed for PFS, using similar methodology.

All patients who have received at least one dose of study treatment will be included in the safety analysis. The incidence of adverse events will be summarized by type of adverse event and severity using the NCI Common Terminology Criteria for Adverse Events Version 3.0. A Fisher’s exact test will be used to compare adverse events between the two arms if needed.
14.3 Sample Size and Duration of Study

The median survival for the study patient population treated by radiotherapy alone is estimated to be 6 months. In order to have 90% power to detect a hazards ratio of 1.33 between the two treatment arms (an improvement of median survival from 6 to 8 months), using a two-sided 5% level test, a minimum of 520 deaths will be needed before the final analysis. Assuming an accrual rate of 150 patients per year, a total of 560 patients will be accrued in 3.7 years, and the required number of deaths (520) would be observed after following all randomized patients for an additional year. The total duration of this trial will be about 5 years.

14.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the NCIC CTG central office and their frequencies will be reported annually at investigators' meetings. The Data and Safety Monitoring Committee (DSMC) of the NCIC CTG will monitor safety data from this trial every 6 months.

14.5 Interim Analysis

A formal interim analysis for the comparison of the two arms with respect to the primary endpoint will be carried out. The interim analysis will be done at the time when 2/3 of the planned total number of patients has been accrued (i.e. when about 370 patients have been accrued and about 120 events have been observed). The results of this analysis will be presented to the DSMC. Termination of the study will be considered if, at the time of the interim analysis, there is very little evidence that the study treatment is effective. A two-stage stopping rule of Ellenberg and Eisenberge [Ellenberg 1985] will be used. An early termination will be considered by the DSMC if the estimated hazard ratio (radiotherapy plus concurrent and adjuvant temozolomide versus radiotherapy alone) is not less than 1 in the primary analysis of overall survival at the time of the planned interim analysis. At the final analysis, a one-sided 2.5% level will be used.

14.6 Quality of Life Analyses

Quality of life will be assessed using the EORTC QLQ-C30 and in conjunction with the brain module QLQ-BN20. No specific hypotheses about expected changes in quality of life scores are being tested.

All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales. Changes of the quality of life scores while on study versus baseline will be examined using descriptive statistics. The primary test to compare treatment arms will be a Wei-Lachin test [Wei 1984] for stochastic ordering, including all time points where QoL was measured. In addition, baseline scores will be compared using a Wilcoxon rank sum test, and a pattern mixture model [Little 1995] identifying drop-out patients as a special category will be performed to evaluate the effect of missing data. Additional analyses will be conducted using NCIC CTG standard analysis programs [Osoba 2005].
15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

• The first authors will generally be the chairs of the study.
• A limited number of the members of the NCIC Clinical Trials Group and EORTC may be credited as authors depending upon their level of involvement in the study.
• Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
• In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

"A study coordinated by the NCIC Clinical Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the study chairs to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the EORTC, the NCIC CTG physician, senior biostatistician and study coordinator, and approval of the study chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.
16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

Note: This section refers to Canadian regulatory requirements only. International centres please consult the appropriate Group Specific Appendix.

16.1 Institution Eligibility for Participation

All member centres in good standing of the NCIC CTG are eligible to participate in this study. Institutions which are not NCIC CTG members can either make application for membership or submit a single study agreement document. Any centre joining the NCIC CTG is required to sign a Participating Centre Study Agreement and have Standard Operating Procedures regarding the conduct of clinical trials.

16.2 Investigator Qualifications

For all investigators (principal investigators and co-investigators) the following documentation must be on file with the NCIC CTG:

- A current curriculum vitae, updated and submitted within two years prior to central activation of the trial.
- Documentation indicating completion of training in the protection of human research participants (e.g. NCI U.S. Completion Certificate).

16.3 REB (Research Ethics Board) Approval for Protocols

Each participating centre will have on file with the NCIC CTG central office, as part of its membership/agreement documents, a description of its ethics review process and composition of its REB.

This documentation must be received by the NCIC CTG central office before the centre can be locally activated.

Initial Approval

Member centres wishing to participate in a trial are required to obtain full board local ethics approval of the protocol and consent form (see below) by the appropriate REB. A completed NCIC CTG Confirmation of Initial Ethical Approval form must be submitted to document the REB was properly constituted and there were no conflicts of interest in the REB approval process.

Annual Re-Approvals

Annual re-approval is required for as long as the trial is open to patient accrual or patients are receiving protocol treatment or undergoing protocol mandated interventions.

Amendments/Administrative Updates

All amendments or administrative updates to the protocol must undergo review by local REBs. Amendments/administrative updates will be circulated to all participating sites in a standard format with clear instructions regarding REB review. If full board approval of an amendment is required it will be specified.

Serious Adverse Events, Safety Updates and Product Monograph Updates

During the course of the study serious adverse events, safety updates or product monograph updates may be sent to you for reporting to your REB. The date of REB submission for these documents will need to be entered into the NCIC CTG trial CE.6 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.
16.4 Informed Consent

_Informed Consent Document_

The REB of an institution must approve the consent form document which will be used at that centre prior to its local activation; changes to the consent form in the course of the study will also require REB approval.

It is essential that the consent form contain a clear statement which gives permission for 1) information to be sent to and 2) source medical records to be reviewed by the NCIC CTG and other agencies as necessary. In addition, the consent form should include all NCIC CTG, Tri Council Policy Statement (TCPS), and ICH-GCP consent elements.

Informed consent forms that do not contain all required elements will require an amendment and will lead to the delay of local activation.

_Consent Process/Patient Eligibility_

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

16.5 Retention of Patient Records and Study Files

ICH Good Clinical Practice guidelines apply to NCIC CTG studies. It is the responsibility of NCIC CTG to inform the investigator/institution as to when trial related records no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

NCIC CTG will notify all the trial investigators/institutions and all the regulatory authorities if clinical development of an investigational product discontinues or when trial related records no longer need to be retained.

16.6 Centre Performance Monitoring

Ineligibility and timeliness of data submission are monitored for all centres and the results are reported in the Centre Performance Index. There are minimum standards for performance.

Forms are to be submitted according to the schedule in Appendix IV (Documentation for Study).

16.7 On-Site Monitoring/Auditing

In addition to the routine review of case report forms and supporting documents sent to the central office, NCIC CTG site monitoring will be conducted at participating centres in the course of the study as part of the overall quality assurance programme. The monitors/auditors will require access to patient medical records to verify the data, as well as essential document binders, standard operating procedures (including electronic information) and ethics documentation.
16.8 Case Report Forms (CRFs)

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except Quality of Life and SAE reporting. For details of accessing the EDC system and completing the online forms please refer to the "Randomization and Data Management Guidebook" posted on the CE.6 area of the NCIC CTG web-site (www.ctg.queensu.ca).

The following ELECTRONIC CRFs will be used for this trial:

- Initial Evaluation (Form 1)
- Radiation Therapy Report (Form 4)
- Systemic Therapy Report (Form 3)
- Follow-up Report (Form 5)
- Short Follow-up Report (Form 5s)
- Relapse/Progressive Disease Report (Form 9)
- Death Report (Form 6)

The following PAPER CRFs will be used for this trial:

- Pathology Information Form
- Quality of Life Questionnaire
- Serious Adverse Event (SAE) Report

Forms will capture information as follows:

- For all patients, trial entry information will be captured on a Form 1, details regarding the diagnostic tissue specimens will be captured on a Pathology Information Form, progressive disease information on a Form 9, follow-up information AFTER progressive disease has occurred on a Form 5s, Quality of Life information on the Quality of Life Questionnaire, death information on a Form 6 and serious adverse event information on a SAE Report.

- For patients in Arm 1 a Form 4 (specific to Arm 1) will be submitted after radiation therapy is completed and a Form 5 (specific to Arm 1) will be used for follow-up until progressive disease occurs.

- For patients in Arm 2 a Form 4 (specific to Arm 2) will be submitted after therapy with radiation and concurrent temozolomide is completed. A Form 3 will be used to capture all the information from the end of radiation therapy until treatment with adjuvant temozolomide is concluded. Patients who stop adjuvant temozolomide due to progressive disease will switch to a Form 5S for further follow-up, while patients who stop treatment due to other reasons or who complete the maximum amount of treatment allowed (12 months) will be followed with a Form 5 (specific to Arm 2) until progressive disease occurs.

A list of all forms (electronic or paper) that need to be completed together with expectation dates and details of required supporting documentation, is given in Appendix IV.
17.0 REFERENCES


### APPENDIX I - PATIENT EVALUATION FLOW SHEET

**ARM 1 – Radiation Therapy Alone**

<table>
<thead>
<tr>
<th>Required Investigations</th>
<th>Pre-Study</th>
<th>Treatment</th>
<th>Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekly until 1 week after the last fraction of RT</td>
<td>1 week after the last fraction of RT</td>
<td>4 wks. after the last fraction of RT</td>
</tr>
<tr>
<td>History and Physical Exam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination (including neurological evaluation)</td>
<td>✓</td>
<td>✓*</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, ECOG Performance Status</td>
<td>✓</td>
<td>✓*</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, WBC with differential (granulocytes, lymphocytes)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet Count</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, AST (SGOT) and/or ALT (SGPT), alkaline phosphatase, serum creatinine, total protein, random glucose</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadolinium-enhanced MRI or contrast CT scan of the brain**</td>
<td>✓</td>
<td></td>
<td>✓*</td>
</tr>
<tr>
<td>Other Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini mental status</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recorded and graded according to NCI CTCAE Version 3.0</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30 and QLQ-BN20</td>
<td>✓</td>
<td>✓**</td>
<td></td>
</tr>
</tbody>
</table>

♦  Evaluations on: day 1 of weeks 1, 2 and 3 of radiotherapy; then 1 week after the last fraction of radiotherapy

◆◆◆  Questionnaires should be completed prior to the patient receiving his/her daily radiation treatment on the days of the 5th, 10th and 15th fraction of radiotherapy; then 1 week after the last fraction of radiotherapy

◆◆◆◆  To ensure comparability of disease status, brain imaging at time points subsequent to baseline must be performed using the exact same imaging techniques employed at baseline i.e. the same type of modality (MRI or CT), scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner.

*  Because CT/MRI contrast uptake enhancement is one of the possible early side-effects of radiotherapy, radiological evidence of disease progression on its own (i.e. unaccompanied by clinical worsening) at 4 weeks after the end of radiotherapy should not be considered proof of disease progression.

**  QoL questionnaire to also be done at the time of progression unless already completed within 2 weeks of date of progression, in which case the questionnaire need not be completed again.
### ARM 2 – Radiation Therapy (RT) plus Concomitant and Adjuvant Temozolomide (TMZ)

#### Required Investigations

<table>
<thead>
<tr>
<th></th>
<th>Pre-Study</th>
<th>During Treatment</th>
<th>Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Weekly during RT 1 wk. after the last fraction of RT 4 wks. after the last fraction of RT Day 1 of each cycle of adjuvant TMZ Day 21 of each cycle of adjuvant TMZ At end of every 3 cycles of adjuvant TMZ treatment At end of adjuvant TMZ treatment Every 3 mo. until progression Every 3 mo. until death</td>
<td></td>
</tr>
<tr>
<td>History and Physical Exam</td>
<td></td>
<td>1 wk. after the last fraction of RT Day 1 of each cycle of adjuvant TMZ Day 21 of each cycle of adjuvant TMZ</td>
<td>/simple_text/At end of every 3 cycles of adjuvant TMZ treatment At end of adjuvant TMZ treatment Every 3 mo. until progression Every 3 mo. until death</td>
</tr>
<tr>
<td>Medical History</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Physical examination (including neurological evaluation)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Height</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, ECOG Performance Status</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Corticosteroids</td>
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</tr>
<tr>
<td>Hematology</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, WBC with differential (granulocytes, lymphocytes) Platelet Count</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, AST (SGOT) and/or ALT (SGPT), alkaline phosphatase, serum creatinine, total protein, random glucose</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Radiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadolinium-enhanced MRI or contrast CT scan of the brain**</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Other Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini mental status</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recorded and graded according to NCI CTC/CAE Version 3.0</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30 and QLQ-BN20</td>
<td>✓   ✓** ✓ ✓ ✓</td>
<td>✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓</td>
<td>✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓   ✓✓✓✓</td>
</tr>
</tbody>
</table>

** Evaluations on: day 1 of weeks 1, 2 and 3 of radiotherapy; then 1 week and 4 weeks after the last fraction of radiotherapy (as well as in the interim if clinically indicated). Hematology must also be done at 2 and 3 weeks after the last fraction of radiotherapy, but results can be provided by an outside lab (and faxed to the investigator for data entry).

** To ensure comparability of disease status, brain imaging at time points subsequent to baseline must be performed using the exact same imaging techniques employed at baseline i.e. the same type of modality (MRI or CT), scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and, preferably, the same scanner.

* Because CT/MRI contrast uptake enhancement is one of the possible early side-effects of radiotherapy, radiological evidence of disease progression on its own (i.e. unaccompanied by clinical worsening) at 4 weeks after the end of radiotherapy should not be considered proof of disease progression.

** Questionnaires should be completed prior to the patient receiving his/her daily radiation treatment on the days of the 5th, 10th and 15th fraction of radiotherapy.

*** Questionnaires should be completed on day 1 of cycles 4, 7 and 10 of adjuvant temozolomide (prior to the patient taking his/her dose of temozolomide) and on day 28 of cycle 12 of adjuvant temozolomide.

**** QoL questionnaire to also be done at the time of progression unless already completed within 2 weeks of date of progression, in which case the questionnaire need not be completed again.
## APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

### PERFORMANCE STATUS CRITERIA

*Karnofsky and Lansky performance scores are intended to be multiples of 10.*

<table>
<thead>
<tr>
<th>ECOG (Zubrod)</th>
<th>Karnofsky</th>
<th>Lansky*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Description</td>
<td>Score</td>
</tr>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
<td>100</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
<td>90</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.</td>
<td>80</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self, unable to carry on normal activity or do active work.</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care.</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled, hospitalization indicated. Death not imminent.</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>Moribund, fatal processes progressing rapidly.</td>
<td>10</td>
</tr>
</tbody>
</table>

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.
APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Note: The following section refers to drug distribution, supply and control for Canadian centres. International centres please consult the appropriate Group Specific Appendix.

General

Temozolomide will be provided as 5, 20, 100 and 250 mg capsules by Schering.

Temozolomide supplied for this study should be stored in a secure area according to local regulations and under the storage conditions stipulated on the product label. It is the responsibility of the Investigator at each site to ensure that the temozolomide supply designated for use on this study is only dispensed to study subjects. Study drug must be dispensed only from official study sites and by authorized personnel, according to local regulations.

Distribution

Schering will be responsible for distributing temozolomide to all Canadian centres. Start up supplies will be dispatched upon receipt at NCIC CTG of all required regulatory documentation including copies of REB approval and the REB-approved consent form. Full details regarding drug re-ordering will be provided at study initiation.

Drug Accountability

It is the responsibility of the Investigator to ensure that a current record of study product disposition is maintained at each site where study product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g. lost, wasted, broken).
- Amount returned to the Sponsor
- Amount destroyed at study site, if applicable.
- Retain samples sent to third party for bioavailability/bioequivalence, if applicable.

NCIC CTG will provide forms to facilitate inventory control on the CE.6 website. Accountability will be maintained by the site pharmacy staff and bottles will be treated as unit dose containers (i.e. bottles and or capsules will not be shared between patients).

The health care professional will determine the number of bottles and the appropriate bottle dosage strength of temozolomide to dispense to the patient at the beginning of each treatment period/cycle. The health care professional will instruct the patient that all dispensed bottles must be returned at each follow-up visit.
Return Reconciliation and Destruction

- Patients must return all unused study medication and empty containers to the investigator or pharmacist.
- At the end of the study, it must be possible to reconcile delivery records with records of usage/returned stock by completion of the study drug accountability forms. Any discrepancies must be accounted for. NCIC CTG will undertake final accountability and reconciliation of the study product through on-site audits.
- After accountability and reconciliation have been completed, all unused or returned study medication should be destroyed locally according to centre SOPs. Destruction of study medication or return to the pharmaceutical sponsor must not take place until drug accountability and reconciliation are concluded.
APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except Quality of Life and SAE reporting. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Randomization and Data Management Guidebook" posted on the CE.6 area of the NCIC CTG web-site (www.ctg.queensu.ca).

Please see section 16.8 for details of form flow by arm.

The ELECTRONIC CRFs to be used in this trial are as follows:

<table>
<thead>
<tr>
<th>Electronic Form</th>
<th>Timing</th>
<th>To be submitted electronically</th>
<th>Supporting Documentation to be sent by MAIL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Form 1) Initial Evaluation</td>
<td>Within 6 weeks of randomization</td>
<td></td>
<td>Copies of signed consent form and tissue banking consent (Canadian patients only), relevant pathology report(s), operative and radiology reports</td>
</tr>
<tr>
<td>(Form 3) Systemic Therapy Report ARM 2 ONLY</td>
<td>At 4 weeks after the end of radiotherapy and at the end of each cycle of adjuvant temozolomide</td>
<td>Within 2 weeks of the end of the cycle</td>
<td>Relevant radiology reports</td>
</tr>
<tr>
<td>(Form 4) Radiotherapy Report</td>
<td>1 week after the end of radiotherapy</td>
<td>Within 6 weeks of the completion of radiation therapy</td>
<td>For RTQA purposes only (see section 8.1.11): Daily treatment records, isodose distributions, simulation or DRR images, portal images of the fields and radiotherapy summaries.</td>
</tr>
<tr>
<td>(Form 5) Follow-up Report PRIOR to Progression, Arm 1: At 4 weeks after the end of radiotherapy and then every 3 months until disease progression PRIOR to Progression, Arm 2: Every 3 months, from when treatment stops until disease progression</td>
<td>Within 8 weeks of follow up visit</td>
<td>Relevant radiology reports</td>
<td></td>
</tr>
<tr>
<td>(Form 5S) Short Follow-up Report AFTER Progression: Every 3 months</td>
<td>Within 8 weeks of follow up visit.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Form 6) Death Report</td>
<td>When patient dies</td>
<td>Within 8 weeks of patient’s death</td>
<td>Autopsy report, if done.</td>
</tr>
<tr>
<td>(Form 9) Relapse/Progressive Disease Report</td>
<td>Upon disease progression</td>
<td>Within 8 weeks of progression</td>
<td>Relevant radiology and pathology reports.</td>
</tr>
</tbody>
</table>

* Supporting documents should be mailed immediately after the form they refer to has been submitted electronically.
The PAPER CRFs to be used in this trial are as follows:

<table>
<thead>
<tr>
<th>Paper Form</th>
<th>Timing</th>
<th>Due in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology Information Form (PIF)</td>
<td>Within 6 weeks of randomization</td>
<td>NCIC CTG Central Office/EORTC Data Centre/TROG Trial Centre</td>
</tr>
<tr>
<td>Serious Adverse Event Report Form</td>
<td>At the time of event</td>
<td>To be FAXED within 24 hours of knowledge of event. Paper copy to be mailed within 10 working days</td>
</tr>
<tr>
<td>Quality of Life (EORTC QLQ-C30 and QLQ-BN20)</td>
<td>See sections 6.0 and 9.0</td>
<td>Mail as soon as the corresponding form (Form 1, Form 3, Form 4, Form 5 or From 9) has been submitted electronically</td>
</tr>
</tbody>
</table>
APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS VERSION 3.0 (CTCAE)

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) for adverse events and serious adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page: http://ctep.cancer.gov/reporting/ctc.html. All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.
APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

Quality of life data are collected for research purposes, and will usually not be used for the patient’s individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization or pre-registration (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.
2. **Pretreatment Assessment**

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

   The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. **Assessments During Treatment**

   The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. **Assessments During Follow-up**

   The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

   A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

   *It defeats the whole purpose of the assessment if it is delayed until the patient feels better!*  

5. **What If . . .**

   The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

   There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

   A.  The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

       Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

       If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.
If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if s/he is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.
Quality of Life Questionnaire – ENGLISH

NCIC CTG Trial: CE.6

This page to be completed by the Clinical Research Associate

<table>
<thead>
<tr>
<th>Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC CTG Patient Serial No: __________</td>
</tr>
<tr>
<td>Institution: ____________________________________________</td>
</tr>
</tbody>
</table>

Scheduled time to obtain quality of life assessment: please check (✓)

**BOTH ARMS:**
- Prior to randomization
- At time of Disease Progression

**ARM 1 (RT only):**
- **During Treatment:**
  - Day of 5th RT fraction
  - Day of 10th RT fraction
  - Day of 15th RT fraction
  - 1 wk after last fraction of RT
  - 4 wks after last fraction of RT
- **Off Treatment:**
  - 3 months
  - 6 months
  - 9 months
  - 12 months
  - ____ months

**ARM 2 (RT plus TMZ):**
- **During Treatment:**
  - Day of 5th RT fraction
  - Day of 10th RT fraction
  - Day of 15th RT fraction
  - 1 wk after last fraction of RT
  - 4 wks after last fraction of RT
  - Day 1 cycle 4
  - Day 1 cycle 7
  - Day 1 cycle 10
  - Day 28 cycle 12
- **Off Treatment:**
  - 3 months
  - 6 months
  - 9 months
  - 12 months
  - ____ months

Were ALL questions answered? __Yes__ __No__ If no, reason: ________________________________

Was assistance required? __Yes__ __No__ If yes, reason: ________________________________

Where was questionnaire completed: □ home □ clinic □ another centre

Comments: ________________________________________________________________________________

__________________________________________________________________________________________

Date Completed: __________ - __________ - __________

yyyy   mmm   dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

NCIC CTG use only

<table>
<thead>
<tr>
<th>Logged: __________</th>
<th>Study Coord: __________</th>
<th>Res Assoc: __________</th>
<th>Data Ent’d: __________</th>
<th>Verif: __________</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**European Organization for Research and Treatment of Cancer (EORTC)**

**Quality of Life Questionnaire CE.6**

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you need to stay in a bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**During the past week:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
### During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your <em>family</em> life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your <em>social</em> activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall *health* during the past week?

<table>
<thead>
<tr>
<th>Rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Excellent</td>
</tr>
</tbody>
</table>

30. How would you rate your overall *quality of life* during the past week?

<table>
<thead>
<tr>
<th>Rating</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Excellent</td>
</tr>
</tbody>
</table>
Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Did you feel uncertain about the future?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Did you feel you had setbacks in your condition?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Were you concerned about disruption of family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Did you have headaches?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Did your outlook on the future worsen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Did you have double vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Was your vision blurred?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Did you have difficulty reading because of your vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Did you have seizures?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Did you have weakness on one side of your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Did you have trouble finding the right words to express yourself?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you have difficulty speaking?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you have trouble communicating your thoughts?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you feel drowsy during the daytime?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you have trouble with your coordination?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did hair loss bother you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did itching of your skin bother you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you have weakness of both legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you feel unsteady on your feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Did you have trouble controlling your bladder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: ______________

Today's date (Year, Month, Day): ________________________________

Thank you.
APPENDIX VII - THE MINI-MENTAL STATUS EXAMINATION

The Mini-Mental Status Examination (MMSE) was developed in 1975 [Folstein 1975] and takes about 5-10 minutes to administer. It includes 11 questions which test cognitive aspects of mental function and can be categorized in two sections: the first requires the patient to provide vocal responses only and tests orientation, memory and attention; the second part tests the patient’s ability to name, follow verbal and written commands, write a sentence spontaneously and copy a complex polygon. Each question receives a pre-defined score. The highest score that can be obtained is 30.

The tester (investigator or CRA) should first make the patient comfortable and establish rapport. During the test he/she should praise success and avoid pressing on items which the patient finds difficult. The following table provides a general overview of the MMSE [Folstein 1975]:

<table>
<thead>
<tr>
<th>Question/Task</th>
<th>Instructions for the tester</th>
<th>Scoring</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Orientation</td>
<td>First ask for the date. Then ask specifically for items the patient omitted (for example “Can you also tell me the year?” or “Can you also tell me the season?”)</td>
<td>One point each for year, season, date, day of the week and month.</td>
<td>5</td>
</tr>
<tr>
<td>Place Orientation</td>
<td>First ask “Where are you?”. Then ask specifically for items the patient omitted (for example “Can you also tell me the province?” or “Can you also tell me the floor or room?”)</td>
<td>One point each for province, county, town, building and floor or room.</td>
<td>5</td>
</tr>
<tr>
<td>Registration</td>
<td>Ask the patient if you may test his/her memory. Then say the names of 3 unrelated objects clearly and slowly. Then ask the patient to repeat them. This first repetition determines the score for this task. However, because it is important to the question testing “recall” (see below) that the patient learns these three objects, if not learnt after the first repetition, keep repeating them for up to 6 trials.</td>
<td>One point for each item correctly repeated.</td>
<td>3</td>
</tr>
<tr>
<td>Attention and Calculation</td>
<td>Ask the patient to begin with 100 and count backwards by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). If the patient cannot or will not do this task ask him/her to spell the word “world” backwards.</td>
<td>Subtraction by 7: one point for each correct answer Backwards spelling: one point for each letter in the correct order (e.g. “dlorw”=3)</td>
<td>5</td>
</tr>
<tr>
<td>Recall</td>
<td>Ask the patient to recall the three objects you previously asked him to remember.</td>
<td>One point for each object correctly remembered.</td>
<td>3</td>
</tr>
<tr>
<td>Language</td>
<td>Show a patient a wrist watch and ask him/her what it is. Repeat for pencil.</td>
<td>One point for each object correctly named.</td>
<td>2</td>
</tr>
<tr>
<td>Repetition</td>
<td>Ask the patient to say “no ifs, ands or buts”</td>
<td>One point if successful on the first try.</td>
<td>1</td>
</tr>
<tr>
<td>3-Stage Verbal Command</td>
<td>Give the patient a blank piece of paper and say “Take this paper in your right hand, fold it in half and put it on the floor”.</td>
<td>One point for each correct action.</td>
<td>3</td>
</tr>
<tr>
<td>Written Command</td>
<td>Show the patient a piece of paper with “CLOSE YOUR EYES” printed on it.</td>
<td>One point if the patient closes eyes.</td>
<td>1</td>
</tr>
<tr>
<td>Writing</td>
<td>Ask the patient to write a sentence.</td>
<td>One point if the sentence has a subject, a verb and makes sense. Correct grammar and spelling are not important.</td>
<td>1</td>
</tr>
<tr>
<td>Drawing/Copying</td>
<td>On a clean piece of paper draw intersecting pentagons, each side about 2.5 cm (1 inch). Ask the patient to copy this exactly as it is.</td>
<td>One point if the figure has ten corners and two intersecting lines. Tremor and rotation should be ignored.</td>
<td>1</td>
</tr>
</tbody>
</table>

Total 30
Previous studies have shown that age and education influence the MMSE scores that are obtained from normal (i.e. brain-cancer- and mental-disease-free) individuals [Crum 1993].

Due to copyright considerations, the Folstein’s Mini Mental State Examination [Folstein 1975] cannot be included in this protocol or distributed electronically via the CE.6 web page. It is available in paper copies upon request from the NCIC CTG CE.6 central office, EORTC Data Centre and TROG Trial Centre. When your supply is low, please contact the appropriate Trial/Data Centre.

In this study, the paper copies of the Mini Mental State Examination are intended for use as WORKSHEETS only. The person administering the MMSE to the patient should use a paper copy of the test to facilitate easy scoring and record keeping. Please file all completed MMSE worksheets with the rest of the patient trial records retained at your centre. DO NOT submit these sheets to the NCIC CTG, EORTC or TROG. The score from each MMSE test will be recorded on the corresponding electronic Case Report Form (see Appendix IV).
APPENDIX VIII - 6TH EDITION OF THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 6th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org/initiatives.html). These staging criteria should be used for new trials.
APPENDIX IX - CALCULATION OF THE BIOLOGICAL EFFECTIVE DOSE

1. Prescribed dose in protocol:
   40.05 Gy/15 fractions/3 weeks
   \[ \text{BED}^* = 40.05 \left(1 + \frac{2.67}{2.00}\right) \]
   \[ = 93.52 \]

2. TD** 5/5 for optic chiasm:
   50.00 Gy/25 fractions/5 weeks
   \[ \text{BED}^* = 50.00 \left(1 + \frac{2.00}{2.00}\right) \]
   \[ = 100.00 \]

3. Maximum dose allowed for organs at risk:
   40.05 Gy/15 fractions/3 weeks
   \[ \text{BED}^* = 40.05 \left(1 + \frac{2.67}{2.00}\right) \]
   \[ = 93.52 \]

* Biologically effective dose (BED) = Total dose (1 + fraction size/$\alpha$/β)
Utilizing linear quadratic equation $\alpha$/β = 2 (late CNS effects with necrosis) [Van der Kogel 1993]

** The radiation dose that gives 5% incidence of complications in 5 years
(in each case with a dose per fraction of 2 Gy) [Emami 1991]
APPENDIX X - PSEUDOPROGRESSION OF MALIGNANT GLIOMA

Implications for Management on the CE.6 Trial:

In the landmark randomized study of temozolomide in glioblastoma, 22% of patients on the temozolomide arm did not proceed to the adjuvant phase of their management, presumably on the basis of these changes noted at the time of their one month assessment and MRI changes were suggestive of progression. During the study, most clinicians assumed that this represented tumour progression, and decided not to proceed to the adjuvant phase of their management with temozolomide. In the last few years, it has become apparent that a proportion of these cases are in fact not tumour progression, but are examples of pseudoprogression, where it is felt that these MRI changes are likely related to treatment effect rather than tumour progression.

Investigators in Rotterdam demonstrated in a series of 32 cases of malignant gliomas treated with radiotherapy only, that 9 of these patients had MRIs that were suggestive of progression. Progression was defined as per Macdonald’s criteria. In 3 of these 9 patients, their MRIs either improved (2 cases) or stabilized (1 case) without any further additional therapy, such that in retrospect these cases were regarded as having demonstrated pseudoprogression in retrospect.

In a subsequent report on 65 patients with malignant gliomas who had been managed by concurrent temozolomide and radiotherapy, they have noted that apparent progression occurred in 23 patients at the 1 month MRI assessment, and that in 12 of these 23 cases the MRI changes either stabilized or improved with simply carrying on with the adjuvant phase of their temozolomide (8 patients) or no additional treatment (4 patients), for an apparent pseudoprogression rate of approximately 50% of apparent patients with progression at one month, or approximately 20% of all patients in this series.

Brandes and colleagues noted that in 103 patients managed with concurrent temozolomide and radiation therapy, that apparent progression was evident in 50 patients at one month, and that it was determined to be pseudoprogression in 32 of these 50 patients. Moreover, pseudoprogression was more often associated with a methylated MGMT promoter status.

Gertstner et al demonstrated in a retrospective review that the incidence of apparent worsening of imaging at one month post-radiotherapy was increased from 38% with RT alone to 53% with RT and concurrent temozolomide.

Currently there are no reliable MRI patterns of worsening or adjunctive imaging techniques that are reliably able to differentiate true progression from pseudoprogression at the one month scan either following radiotherapy only or radiotherapy plus concomitant temozolomide.

Generally it appears that the situation between true progression versus pseudoprogression seems to become more evident by the 3 month post-RT assessment, and has usually been the standard by which the above mentioned studies classified their cases in retrospect.

As a result of this challenge of response assessment at one month post-radiotherapy in patients with glioblastoma, Canadian guidelines recommend that patients remain on the adjuvant phase of their temozolomide until at least the 3rd adjuvant monthly cycle prior to a decision to discontinue adjuvant temozolomide in patients with glioblastoma multiforme.
Implications for Management:

In an attempt to standardize management across sites and both arms of this study, it is recommended that patients who were randomized to the concurrent RT/temozolomide and who exhibit clinical and/or imaging changes suggestive of progression, begin the adjuvant phase of their temozolomide as long as they are well enough to continue with any form of active management.

Along the same lines, it is recommended that patients who were randomized to the radiotherapy only arm and who exhibit clinical and or imaging changes suggestive of progression at the one month post-RT assessment, be managed expectantly until subsequent evidence of decline prior to being determined to have progressed.

References for Appendix X:


### LIST OF CONTACTS

<table>
<thead>
<tr>
<th>Contact</th>
<th>Tel. #</th>
<th>Fax #</th>
</tr>
</thead>
</table>
| **STUDY SUPPLIES**
Forms, Protocols | Available on NCIC CTG Website: [http://www.ctg.queensu.ca](http://www.ctg.queensu.ca) under: Clinical Trials | | |
| Sara Rushton
Clinical Trials Assistant
NCIC CTG
Email: srushton@ctg.queensu.ca | 613-533-6430 | 613-533-2941 |
| or:
Chad Winch
Study Coordinator
NCIC CTG
Email: ewinch@ctg.queensu.ca | | |
| or:
Dr. Chris O’Callaghan
Project Coordinator
NCIC CTG
Email: cocallaghan@ctg.queensu.ca | | |
| **PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES**
(including eligibility questions and protocol management) | | |
| Dr. Normand Laperriere
Study Co-Chair
Email: norm.laperriere@rmp.uhn.on.ca | 416-946-2127 | 416-946-6556 |
| Dr. James Perry
Study Co-Chair
Email: james.perry@sunnybrook.ca | 416-480-6124 | 416-480-7802 |
| **STUDY CHAIRS** | | |
| **SERIOUS ADVERSE EVENT REPORTING**
See protocol section 11.0 for details of reportable events. | | |
| Dr. Chris O’Callaghan
Project Coordinator
NCIC CTG
or:
Chad Winch
Study Coordinator
NCIC CTG | 613-533-6430 | 613-533-2941 |
| **DRUG ORDERING**
See Appendix III for full details. | Details will be provided at study initiation
Contact Chad Winch if additional questions | 613-533-6430 | 613-533-2941 |