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A randomized phase II trial of concurrent temozolomide and radiotherapy followed by dose dense versus metronomic temozolomide and maintenance cis-retinoic acid for patients with newly diagnosed glioblastoma and other malignant gliomas.

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Participating Institutions	**Site PIs**	**Site Role**
Columbia University Medical Center	Andrew B. Lassman, MD	Data Analysis
Dana Farber Cancer Institute	Lakshmi Nayak, MD	Data Analysis

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a randomized phase II study that will test two different adjuvant temozolomide regimens in patients with newly diagnosed glioblastoma multiforme. The goal of this study is to identify a regimen that would be appropriate to bring to a phase III trial and compare to the standard dosing regimen of temozolomide recently reported by Stupp et al. in the New England Journal of Medicine. Secondary goals of this study include: prospective analysis of the prognostic impact of MGMT status and generation of preliminary data regarding this treatment strategy for other types of malignant glioma.

Focal RT 6000 cGy/ Temozolomide 75 mg/m^2

↓

Randomize

↓

Metronomic TMZ 50 mg/ m^2/ d -or- dose dense TMZ 150 mg/m^2 days 1-7, 15-21

↓

Maintenance CIS Retinoic Acid

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective: To determine the overall survival of patients with newly diagnosed glioblastoma multiforme treated with concurrent temozolomide and radiotherapy followed by dose dense or metronomic dosing of temozolomide and maintenance cis-retinoic acid.

Secondary objectives:
1. Progression free survival
2. To evaluate the prognostic impact of methylated MGMT status.
3. To collect preliminary data on the efficacy of this regimen and impact of MGMT status in other malignant glioma subtypes.

3.0 BACKGROUND AND RATIONALE

3.1 Background

The treatment of recurrent malignant gliomas represents a therapeutic challenge. Even with maximum treatment at initial diagnosis, malignant gliomas have a dismal prognosis. Standard management is optimal surgical resection followed by involved field radiotherapy. Historically, the role of chemotherapy has been controversial since median survival is not improved although a minority of patients may have prolonged survival. A randomized clinical trial failed to show any benefit (Medical research council brain tumor working party, 2001), but a prior meta-analysis of published randomized trials demonstrated a modest survival benefit for patients receiving adjuvant chemotherapy following radiotherapy (Fine et al., 1993).

Temozolomide is a relatively new oral alkylating agent that was developed for the treatment of malignant glioma. Initially approved in the United States for the treatment of recurrent anaplastic astrocytoma, temozolomide has been observed to have activity in the adjuvant treatment of glioblastoma multiforme.[1,2] Furthermore, preclinical studies demonstrated evidence of synergistic activity of temozolomide when given in conjunction with radiotherapy. The promising results of a phase II study of concomitant and adjuvant temozolomide and radiotherapy in newly diagnosed patients led to a large international phase III study to confirm these results.[3] The primary endpoint of this phase III study was to compare overall survival in newly diagnosed glioblastoma multiforme patients treated with radiotherapy alone versus concomitant temozolomide and radiotherapy followed by adjuvant temozolomide. 573 patients with newly diagnosed GBM at 85 institutions were randomized to receive either radiotherapy alone (n= 286) or concomitant and adjuvant temozolomide (n=287). Patients were stratified on the basis of age, performance status, treating institution, and extent of resection. Patients treated with radiotherapy alone received 30 fractions of 200 cGy using standard conformal treatment planning. The schedule of temozolomide used during radiotherapy (concomitant dosing) was 75mg/m^2 daily including weekends (days when radiotherapy was not administered) for six weeks. Adjuvant therapy began four weeks after completion of radiotherapy with the standard recommended dose of temozolomide: 150-200mg/m^2/day, days 1-5; a maximum of six cycles were administered.

With a median follow up for surviving patients of more than two years, there was a statistically and clinically significant improvement in median (14.6 v. 12.1 months) and two year overall survival (26 v. 10%) for patients treated with concomitant and adjuvant temozolomide as compared with radiotherapy alone. Median progression free survival was also significantly improved in the concomitant treatment group ($p<0.0001$). Of importance, the two treatment groups were well balanced for known prognostic variables and the treatment was well tolerated in both groups with no unexpected toxicity observed. No cases of Pneumocystis carinii pneumonia were reported. Ten percent or less of those patients receiving temozolomide developed grade 3 or higher myelosuppression or fatigue. This was the first prospective phase III study to definitively show that chemotherapy has a clear role in the treatment of glioblastoma multiforme.[7] Previously, there was significant evidence that chemotherapy played an important role in the treatment of glioblastoma multiforme[4]; however, the lack of level I evidence may have dissuaded conservative practitioners from pursuing aggressive therapy. While the overall prognosis remains poor even with the addition of concomitant and adjuvant temozolomide, a significant proportion of patients remain alive at two years.

A subset analysis of patients enrolled on the phase III trial found that benefit of concomitant and adjuvant temozolomide was maintained across most known prognostic variables. Those patients with a poor performance status, or whose tumors were only biopsied, derived less benefit. Subset analysis was also performed using the RTOG RPA classification[5]. Improvement in progression free survival was maintained in all relevant classes (classes III, IV, V). Class III and IV patients treated with concomitant and adjuvant therapy maintained the survival benefit. Correlative tissue analysis of patients enrolled suggests that patients whose tumors have a methylated form of an excision repair enzyme, O-6-methylguanine-DNA methyltransferase (MGMT), are particularly likely to benefit from concomitant and adjuvant temozolomide.[6,8] Patients with methylated *MGMT* had approximately a 50% chance of surviving for two years. Methylation functionally inactivates the MGMT which in the active form is known to result in resistance to alkylating agents. This observation may be critical to the development of other successful therapeutic strategies to enhance chemosensitivity. MGMT analysis should be incorporated into prospective clinical trials of alkylating agents.

Experimentally and in vivo, temozolomide is schedule dependent.[9] Recent studies in recurrent malignant gliomas used 150-200 mg/m^2/daily for 5-days in a 28-day cycle.[1,2] However, a phase-I study of low dose continuous temozolomide defined a maximum tolerated dose (MTD) at 75 mg/m^2/day for 42-days in a 70-day cycle (Brock et al., 1998). This regimen provides 2.1 fold greater drug exposure over 4-weeks compared to the standard 200 mg/m^2 dose with comparable toxicity. There was no evidence of drug accumulation and furthermore, this extended schedule may deplete O(6)-alkyl guanine-DNA alkyl transferase (AGT) levels, a potential mechanism of drug resistance. This treatment schedule may have improved efficacy as a result of increased drug exposure and decreased drug resistance without having an increase in treatment related toxicity.

Other temozolomide schedules can also be used to increase the dose density or to deliver continuous drug without interruption, thereby exploiting successful chemotherapy dosing strategies used in other solid tumors.

3.2 Rationale for the proposed study

This study is an effort to build on the results of the recently presented EORTC/NCIC study demonstrating that concurrent temozolomide and radiotherapy followed by 6 months of adjuvant temozolomide can significantly extend the life and disease free survival of patients with glioblastoma multiforme. The proposed study will provide preliminary data regarding several important questions:

Is it feasible and effective to increase the delivered dose of adjuvant temozolomide (dose dense chemotherapy)?

The concept of dose dense chemotherapy was pioneered by Larry Norton, MD and others at MSKCC in an effort to improve outcomes of patients with metastatic and high risk breast cancer. In this model dose density (body size adjusted dose divided by unit time) seeks to improve the overall impact of therapy by decreasing the time between dosing intervals and thereby decreasing the regrowth of resistant tumor cells between cycles of chemotherapy. This model can be easily applied to glioma by utilizing one of the alternate dosing regimens for temozolomide that delivers 150mg/m^2 daily for 7 days on 7 days off. This schedule is well tolerated and effectively delivers more than twice the standard dosing regimen and decreases the interval between cycles from 23 days to 7 days.[11]

Is it feasible and effective to deliver continuous low dose temozolomide without interruption (metronomic chemotherapy)?

Metronomic chemotherapy (antiangiogenic scheduling) has been proposed as an alternate dosing schedule for conventional chemotherapy. The theory is that the obligatory rest period in conventional chemotherapy permits the recovery of endothelial cells and that altering the dosing regimen to allow for continuous low dose exposure without myelosuppression and other dose limiting side effects will prevent the repair and recovery of tumor endothelium.[12-15] Therefore we will plan to administer temozolomide at 50mg/m^2 daily without interruption to half of the patients enrolled on this trial and assess feasibility and efficacy. This schedule was chosen because it can be administered in a continuous fashion in patients with recurrent glioma for as long as 2 years (personal communication, J. Perry, Toronto), all other schedules of temozolomide require interruption to recover from treatment related toxicity.

Is it possible to improve the outcome of patients with unmethylated or active MGMT by the use of alternate dosing regimens that effectively deplete* MGMT *levels?

An important mechanism of resistance to alkylating agents is the presence of active repair enzymes such as MGMT. In the study by Stupp et al. patients with methylated or inactive *MGMT* were retrospectively described as having the greatest benefit while patients with unmethylated or active *MGMT* had substantially less benefit from the addition of temozolomide. However, patients with active MGMT still had a statistically significant benefit in terms of progression free survival and 2 year overall survival with the addition of temozolomide. Both of the alternate dosing regimens that we will randomize patients to have been demonstrated to result in significant depletion of MGMT.[16] Therefore, in theory either regimen may result in increased treatment sensitivity.

Does maintenance therapy help to maintain remission?

One of the down sides of administering a 6 month course of adjuvant therapy to patients with glioblastoma is the high risk of tumor recurrence. As a result many patients and clinicians are uncomfortable truncating therapy after 6 months in a patient who is doing well. There is some data to suggest that some sort of maintenance therapy may be effective and substantially less toxic than continuing myelosuppressive chemotherapy indefinitely. One such study found that high grade glioma patients with a complete remission treated with maintenance 13-cis retinoid acid maintained their remission for an average of 74 weeks after starting maintenance therapy.[10] This promising result merits further prospective investigation.

Is the EORTC/NCIC regimen beneficial for patients with other types of high grade gliomas?

The definitive answer to the above question will require a prospective randomized trial. However, given the relative scarcity of these patients and numerous competing trials a prospective randomized trial may not be feasible. We would propose allowing patients with other malignant gliomas to enroll in our trial to obtain preliminary data. The sample size and statistical design/accrual goals will be built around the glioblastoma population, other tumor types would be accrued and reported descriptively as part of the whole and as a subset.

MGMT Correlative study:

We plan to prospectively assay available tissue for *MGMT* methylation status to see if our results correlate with disease control/patient outcome. If so, this would support the retrospective observation of the EORTC/NCIC.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This will be a single institution randomized phase II study that will allow us to concurrently assess the efficacy and toxicity of two different schedules of adjuvant temozolomide. The prospective analysis and stratification based on *MGMT* status will allow us to confirm the observation of the EORTC/NCIC study.

4.2 Intervention

The goal of this study is to look at two alternative ways to enhance chemotherapy delivery for patients with newly diagnosed malignant glioma. All patients will receive concurrent temozolomide and radiotherapy followed by one of 2 different adjuvant temozolomide regimens. They will be randomized to these adjuvant regimens on the basis of tumor histology and KPS. At the completion of 6 cycles all patients will receive maintenance cis-retinoic acid until tumor progression.

4.3 Statistics

A Simon mini-max two stage design will be used for each arm of the protocol. If either regimen shows a one year survival probability of 70% or greater (27 patients surviving at one year) then a phase III trial comparing this regimen to the regimen reported by Stupp et al. will be proposed.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Temozolomide is an oral cytotoxic alkylating agent which undergoes spontaneous conversion to MTIC, the active metabolite of dacarbazine, at physiologic pH. It has demonstrated activity against malignant glioma.

Temozolomide is manufactured by Schering Plough, Inc. It is available as 5, 20, 100 and 250 mg capsules. The 20mg and 100mg capsules are projected to be stable for at least 30 months when stored between 2 and 30C in amber glass bottles. The 5mg and 250mg capsules are projected to be stable for at least 12 months under the same conditions.

Commercially available drug supply will be used for this study.

Cis-retinoic acid is an oral retinoid that is manufactured by Roche Pharmaceuticals, Inc. and supplied as 10, 20 and 40mg capsules.

Commercially available drug will be used for this study.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Any adult patient with a newly diagnosed malignant glioma with available tissue would be eligible to participate.

6.1 Subject Inclusion Criteria

- Pathologic evidence of a malignant glioma.
- Tissue block or unstained slides must be available for *MGMT* analysis.
- Age 18-70
- KPS > 50
- Granulocyte count >1.5 X 10^9/L
- Platelet count >99 X 10^9/L
- SGOT < 2.5X upper limit of normal (ULN).
- Serum creatinine < 2X ULN.
- Bilirubin < 2X ULN.
- All patients must sign written informed consent.

6.2 Subject Exclusion Criteria

- Any prior chemotherapy, radiotherapy and biologic therapy for glioma.
- Any prior experimental therapy for glioma.
- Other concurrent active malignancy (with the exception of cervical carcinoma in situ or basal cell ca of the skin).
- Serious medical or psychiatric illness that would in the opinion of the investigator would interfere with the prescribed treatment.
- Pregnant or breast feeding women.
- Refusal to use effective contraception.

7.0 RECRUITMENT PLAN

Recruitment Plan

Patients will be recruited from the Neurology and Neurosurgery clinics at Memorial Sloan Kettering Cancer Center. All patients will be seen by a Neuro-oncology attending. All patients enrolled on the trial must sign written informed consent. There are no gender or racial restrictions.

8.0 PRETREATMENT EVALUATION

The following studies are required within two weeks prior to starting concurrent chemotherapy and radiotherapy:

- Complete history and physical exam including neurologic exam.

- Height and weight.
- CBC including WBC differential and platelet count.
- Comprehensive chemistry panel.
- Contrast enhanced MRI scan of the Brain* (this scan should ideally be performed within 72 hours of surgery and does not need to be repeated within the two weeks prior to treatment onset)

9.0 TREATMENT/INTERVENTION PLAN

9.1 Concurrent temozolomide and radiotherapy

This treatment should start within 6 weeks of surgical resection.

Standard focal external beam radiotherapy will be delivered using conventional radiation planning (3D conformal). The total dose should be approximately 6000 cGy (+/- 5%). Stereotactic boost is not allowed. Patients may receive their radiotherapy at MSKCC or locally provided that treatment planning and summary is available.

Temozolomide will be given at a dose of 75mg/m2 daily for the complete course of radiotherapy. Patients will start temozolomide the night before they receive the first dose of radiotherapy and take the last dose on the final day of radiotherapy. Patients will dose on weekends and holidays when radiotherapy is not scheduled. Supportive anti emetic therapy will be prescribed per institutional guidelines or at the discretion of the treating physician.

9.2 Randomized adjuvant therapy

This therapy will begin 2- 4 weeks after the completion of radiotherapy and will last for a total of 6 cycles (1 cycle = 28 days). Patients will be randomized to receive dose dense or metronomic temozolomide on the basis of histology and KPS.

9.21 Dose dense temozolomide

Temozolomide 150 mg/m^2 will be given to patients on days 1-7 and 15-21 of each 28 day cycle. Supportive anti-emetic therapy will be prescribed per institutional guidelines or at the discretion of the treating physician. Growth factors may be used to treat low blood counts but may not be given prophylactically.

9.22 Metronomic temozolomide

Temozolomide 50mg/m^2 will be given to patients on days 1-28 of each 28 day cycle. Supportive anti-emetic therapy will be prescribed per institutional guidelines or at the discretion of the treating physician. Growth factors may be used to treat low blood counts but may not be given prophylactically.

9.3 Maintenance cis-retinoic acid.

This therapy will start at the completion of 6 cycles of adjuvant temozolomide in all patients who have had no clinical or radiographic evidence of tumor progression. Treatment will continue in 28 day cycles until tumor progression.

13-cis retinoic acid 100mg/m^2 will be given on days 1-21 of each 28 day cycle. (Minor variations in dose are allowed given limited pill strength options). On the first cycle patients may be given a titrated dose to evaluate tolerability.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

During concurrent temozolomide and radiotherapy:

- CBC every week.
- Brief physical exam weekly by radiation oncology.
- Contrast enhanced MRI (including perfusion) at the completion of radiotherapy and prior to initiation of adjuvant therapy – this will be considered a new baseline MRI and all patients may continue to adjuvant temozolomide.

During adjuvant temozolomide:

- CBC every week
- Monthly exam
- Contrast enhanced MRI (including perfusion) after every 2 cycles of therapy – patients with evidence of tumor progression as compared to the post radiotherapy MRI will be removed from the study.
- Monthly comprehensive chemistry panel.

During maintenance cis-retinoic acid:

- Approximately monthly exam for 6 months then approximately every 2-3 months thereafter.
- Monthly CBC, comprehensive chemistry panel and lipid panel.
- Contrast enhanced MRI (including perfusion) after every 2-3 cycles of therapy - patients with evidence of tumor progression as compared to the post radiotherapy MRI will be removed from the study.

MGMT analysis:

Unless MGMT analysis was already performed as part of routine care at MSKCC or an MSKCC designated laboratory, *MGMT* methylation analysis will be performed by real-time PCR using TaqMan machine via OncoMethylome Sciences SA. Ten paraffin slides (around 10 micron), heated or baked (maybe less than 65C) per patient will be required. DNA will then be isolated and modified for real-time PCR on modified DNA. The final result will be the relative ratio of *MGMT* methylation / beta-actin as compared with positive control coming with the DNA modification kit.

Greg Jones, (Project Coordinator NA) should be contacted before any shipment. Samples must arrive during business hours from Monday through Friday and shipped overnight to:

OncoMethylome Sciences SA

Attn: Cecilia Svensson

Tour 5 GIGA nivau +3

Avenue the l'Hôpital 11,

4000 Liège Belgium

Phone #: +32 4 364 20 70

Contact information for Greg Jones:

Phone: +1 919 281 09 80

Fax: +1 919 281 09 81

Email: greg.jones@oncomethylome.com

11.0 TOXICITIES/SIDE EFFECTS

Temozolomide: the most common grade 3 or 4 toxicities reported include:

- <10%: nausea/vomiting, elevated liver enzymes, elevated BUN/Cr, constipation.
- <5%: lymphopenia, thrombocytopenia, rash, headache, alopecia, fatigue.
- <1%: lethargy.

NCI CTC version 3.0 will be used to grade all toxicity.

If hematologic toxicity grade 3 or higher occurs patients may be treated with appropriate growth factors. If clinically indicated the dose of temozolomide may be reduced by 25%.

If grade 3 or 4 treatment related non-hematologic toxicity occurs the dose of temozolomide may be reduced by 25%. Temozolomide should be held until all related non hematologic toxicity has resolved to a grade 2 or lower.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

All patients will have their tumor measurements recorded at baseline and at the time of each MRI scan. Lesions must be measured in two dimensions. The dose of gadolinium must be held constant from scan to scan.

Because the first MRI obtained after radiotherapy often shows an increased pattern/area of enhancement of indeterminant significance this scan will not be used to assess response to therapy or to make a decision as to whether or not a patient remains on study. The first MRI after radiotherapy will be used as a new baseline scan for subsequent MRI assessments.

Complete response (CR) is the total disappearance of all measurable contrast enhancing tumor on two MRIs separated by at least 4 weeks. The patient must have no clinical neurologic deterioration or decrease in performance status. The patient must be off dexamethasone.

Partial response (PR) is at least a 50% reduction in the size of measurable contrast enhancement (the sum of the products of the greatest length and maximum width of all measurable lesions). No lesion may progress and no new lesions may appear. All PR should be confirmed by repeat MRI separated by at least 4 weeks. The dose of dexamethasone must be the same or lower than at baseline.

Stable disease (SD) exists when a patient fails to qualify for partial response or progressive disease.

Progressive disease (PD) is an increase of 25% or more in the size of any lesion or the appearance of a new site of tumor.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at anytime the patient develops progressive disease he/she will be taken off study and referred for alternative therapy.

If at anytime the patient develops unacceptable toxicity he/she will be removed from study.

If at anytime the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

14.0 BIOSTATISTICS

14.1 The primary goal of this study is to determine if either of the two regimens is appropriate to bring to a phase III study as the experimental arm in comparison to the regimen reported by Stupp et al. To do this we will use overall survival as the primary endpoint for consistency.

The primary objective of this study is to determine the overall survival of the two cohorts of patients randomized to either dose dense or metronomic dosing of temozolomide. Overall survival will be calculated from the date of study entry until death or date of last follow up using the Kaplan Meier product limit method. Patients will be censored on the date of last follow up. The primary endpoint is survival probability at 1 year.

In this trial, we will utilize a Simon mini-max two-stage design *for each cohort* of glioblastoma patients, in which a 50% survival probability at one year is considered not promising, a 70% survival probability at one year is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set at 0.10 and 0.10, respectively. In the first stage of this design, 23 patients will be accrued to each cohort. If at least 12 patients are alive at one year among these 23 patients, then an additional 16 patients will be accrued to the second stage. If 11 or less are alive of the 23 patients with one year follow-up then that cohort will be terminated and declared negative. At the end of the trial if 24 or more patients are alive at one year then the regimen would be considered worthy of further study. This design yields at least a 0.90 probability of a negative result if the true survival probability is at least 50% and yields a 0.90 probability of a positive result if the true survival probability is 70%. If both cohorts are considered promising with regard to the primary endpoint then the one with the higher one year survival probability will be considered for further evaluation in the phase III setting.

14.2 Secondary endpoints include progression-free survival defined as the date of study entry to the first scan that demonstrates tumor progression (please note that the MRI after completion of radiotherapy will be used as the baseline scan for response assessment). Frequency of toxicity will be tabulated according to the NCI Common Toxicity Criteria (version 3.0). Methylation *MGMT* status will be assessed using real-time PCR. A Fishers exact test will be used to compare one year survival by MGMT status (methylated/unmethylated) in order to observe any trends similar to that from the retrospective EORTC/NCIC.

In addition, these regimens will be administered to forty patients with all other malignant glioma subtypes. Up to twenty patients in each arm will be accrued. Endpoints such as one-year survival probability, overall survival and progression-free survival will be computed in order to gain preliminary data for these other subtypes.

The minimum anticipated sample size would be 66 patients (23 in each cohort plus 20 patients with other malignant glioma subtypes.) If both cohorts accrue patients to the second stage then a total of 118 evaluable patients will be accrued (39 in each cohort + 40 patients with other malignant glioma subtypes). To ensure 118 evaluable patients, we will accrue 140 patients to guard against a 20% rate of ineligibility and patient drop out observed during an interim analysis. Patients who withdraw consent or are found to be ineligible can be replaced. The anticipated rate of accrual is 6 patients/month requiring 12-18 months to complete the accrual to the trial.

14.3 RANDOMIZATION:

Patients will be randomized to dose dense temozolomide or metronomic temozolomide. After eligibility is established and immediately after consent is obtained, patients will be registered in the Protocol Participant Registration (PPR) system and randomized using the Clinical Research Database (CRDB), by calling the MSKCC PPR registry at 646-735-8000 between the hours of 8:30 am and 5:30 pm, Monday - Friday. Randomization will be accomplished by the method of random permuted block, and patients will be stratified by KPS (<80 vs ≥ 80).

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

Research Participant Registration

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

15.2 Randomization

At registration, patients will be randomized to receive either Dose Dense Temozolomide or Metronomic Temozolomide. Each group will receive 6 months of post radiation chemotherapy. Randomization Codes will be generated by the Clinical Research Database (CRDB) in conjunction with the Department of Epidemiology and Biostatistics.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extext and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event

•Relationship of the adverse event to the treatment (drug, device, or intervention)

- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES