A PHASE I/II TRIAL OF TEMOZOLOMIDE AND HYPOFRACTIONATED RADIOTHERAPY IN THE TREATMENT OF SUPRATENTORIAL GLIOBLASTOMA MULTIFORME

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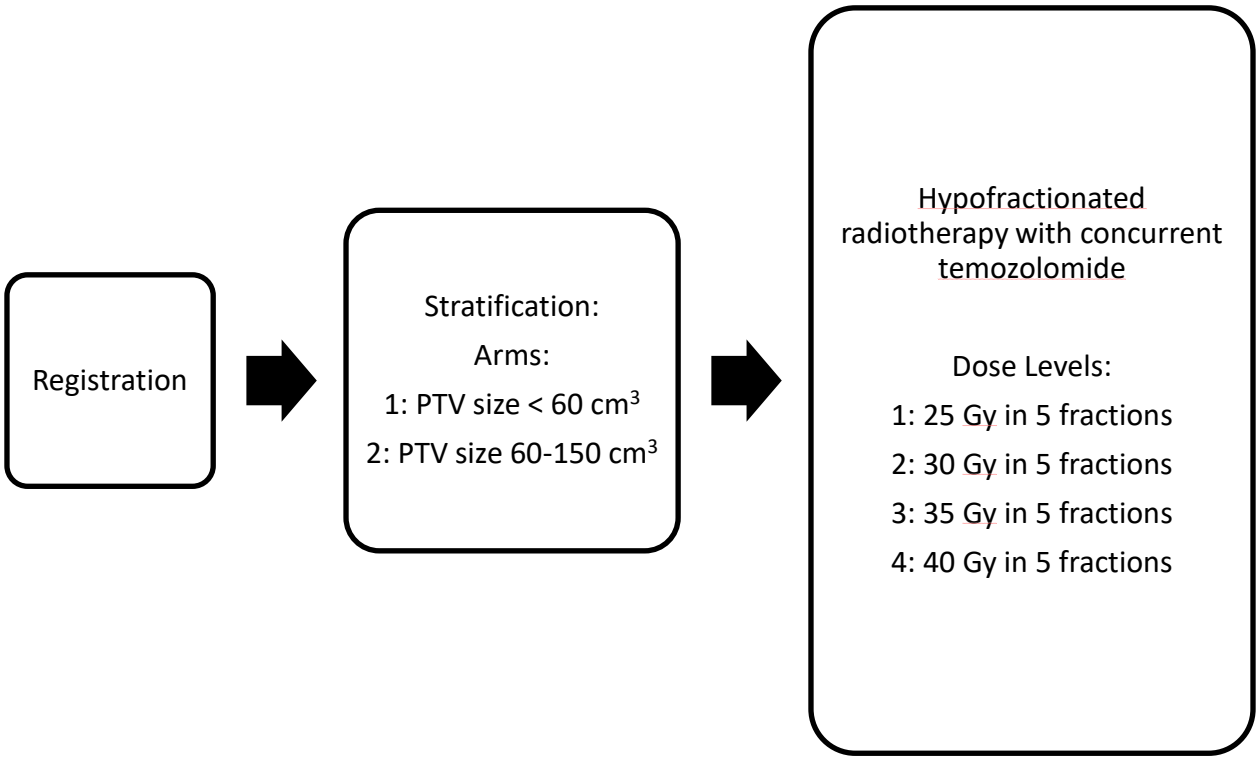
PROTOCOL SYNOPSIS

TITLE	A Phase I/II Trial Of Temozolomide And Hypofractionated Radiotherapy In The Treatment Of Supratentorial Glioblastoma Multiforme
STUDY PHASE	I/II
INDICATION	Newly diagnosed, histologically confirmed supratentorial GBM.
PRIMARY OBJECTVES	**Phase I - Primary Objective** Determine the maximum tolerated dose (MTD) of hypofractionated radiotherapy given in 5 fractions with temozolomide for the treatment of glioblastoma multiforme.
SECONDARY OBJECTIVES	Determine the short- and long-term adverse effects. Determine the radiographic response rate. Determine the overall survival rate. Perform patterns of failure analysis. Assess quality of life during treatment.
HYPOTHESES	Five fraction stereotactic radiosurgery (SRS) with concurrent temozolomide will be well-tolerated; the duration of radiotherapy can safely be shortened to 5 treatments without compromising the local control or overall survival rates.
STUDY DESIGN	Phase I: The MTD for five-fraction SRS concurrent with temozolomide will be determined using a 3+3 study design.
PRIMARY ENDPOINTS AND SECONDARY ENDPOINTS	**Phase I Primary endpoint** The MTD and DLT of hypofractionated radiotherapy with temozolomide will be determined. **Secondary endpoints** The short- and long-term adverse effects will be determined. The overall survival rate will be calculated. Patterns of failure analysis will be performed. Health related quality of life will be measured.
SAMPLE SIZE BY TREATMENT GROUP	Three patients will be enrolled per dose level per arm. The maximum number of patients

	needed for the phase I study will depend on the number of dose levels reached. If all 4 dose levels are reached, the maximum number of patients will be 15 per arm.
SUMMARY OF SUBJECT ELIGIBILITY CRITERIA	**Inclusion Criteria** • Histopathologically confirmed newly diagnosed glioblastoma multiforme. Diagnosis must be made by surgical biopsy or excision. • The tumor must be supratentorial in location. • The planning target volume (tumor plus margin) must measure ≤ 150 cm^3 in volume. • Age ≥18 years. • Life expectancy of at least 12 weeks. • Patient must have adequate organ function to tolerate temozolomide (details in the protocol). **Exclusion Criteria** • Patients who have previously been treated with brain irradiation to the region that would result in overlap of the radiation fields. • Tumor foci detected below the tentorium. • Multifocal disease or leptomeningeal spread. • Prior allergic reaction to the study drugs involved in this protocol. • Inability to have neither an MRI nor a CT scan. Patients with pacemaker will be allowed to undergo CT instead of MRI. • Pediatric patients (age <18), pregnant women, and nursing patients will be excluded.
INVESTIGATIONAL PRODUCTS DOSAGE AND ADMINISTRATION	N/A
CONTROL GROUP	N/A
PROCEDURES	N/A
STATISTICAL CONSIDERATIONS	N/A

SCHEMA

Phase I:



PTV (Planning Target Volume) is defined as the residual T1 post-contrast enhancing tumor and/or resection cavity + 0.5 cm margin (see Section 4.3.4).

Patient Population: (See Section 3.0 for Eligibility)

Histopathologically confirmed supratentorial glioblastoma multiforme without previous radiation to the same region.

LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute neutrophil count
CBC	Complete blood count
CNS	Central nervous system
CR	Complete response
CRF	Case report/Record form
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Tumor Volume
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
EORTC	European Organisation for Research and Treatment of Cancer
GBM	Glioblastoma multiforme
GI	Gastrointestinal
GTV	Gross Tumor Volume
Hgb	Hemoglobin
HRQOL	Health Related Quality of Life
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
MR	Minor response
MTD	Maximum tolerated dose
OS	Overall survival
P	Progressive diseased
PFS	Progression free survival
PLT	Platelet
PR	Partial response
PTV	Planning Target Volume
QD	Once daily
RT	Radiotherapy
SAE	Serious adverse event
SD	Stable disease
SRS	Stereotactic Radiosurgery
STEAE	Serious treatment emergency adverse event
TMZ	Temozolomide

1. OBJECTIVES

1.1. Phase I - Primary Objective

1.1.1 Determine the maximum tolerated dose (MTD), based on acute CNS toxicity at 30 days, of hypofractionated radiotherapy given in 5 fractions with temozolomide for the treatment of glioblastoma multiforme.

1.2. Secondary Objectives

1.2.1. Assess the short- and long-term adverse effects.
1.2.2. Determine the radiographic response rate.
1.2.3. Determine the overall survival rate.
1.2.4. Determine the patterns of tumor failure.
1.2.5. Assess quality of life during treatment.

2. BACKGROUND

1.1. Glioblastoma Multiforme

High grade gliomas are the most common primary brain tumor. Glioblastoma multiforme (GBM) is characterized by its highly aggressive nature and poor prognosis. The annual incidence of GBM in the U.S. is 12,000 and rising. Multi-modality therapy with surgery, radiation (RT), and chemotherapy is the standard treatment for all patients whose performance status allows aggressive treatment. Even after a gross total resection, the local recurrence rate is high. Post-operative radiotherapy has been shown to increase local control and overall survival rates(1, 2). For elderly patients and patients with poor performance status, radiation therapy without chemotherapy provides palliation and prolongs survival(3).

1.2. Hypofractionated Radiotherapy

Standard therapy for GBM includes 6 weeks of daily radiation treatments. This treatment course can pose a substantial hardship for patients and their families, particularly for those living distant from a radiation facility. Despite aggressive multimodality treatment, the median survival is only 14 months(4).

Compared to standard fractionation, hypofractionated radiotherapy or stereotactic radiosurgery (SRS) delivers higher doses of radiation in fewer treatment sessions (5 treatments versus 30 for conventionally fractionated RT). SRS for GBM has several potential advantages: First, SRS drastically reduces the total treatment time thereby potentially maximizing the patients' quality of life. A five week decrease in treatment time represents approximately 10% of the median lifespan of these patients. Similarly, this goal on the use of SRS to shorten the treatment time for an otherwise incurable tumor

has been studied and achieved for pancreas cancer(5-7). A similar shortening of treatment time has been investigated in breast cancer, where the standard 33 days of therapy have been replaced with a single day(8). Second, by shortening the treatment duration, hypofractionation may lead to suppression of tumor cell repopulation and improve tumor control. An *in vitro* study of glioblastoma cell lines have demonstrated repopulation of glioblastoma cells during fractionated radiotherapy, thereby requiring higher radiation dose to achieve cell kill(9). Likewise, longer treatment duration has been shown to decrease local control in multiple other tumor types(10). Third, GBM may show improved response to higher radiation doses per fraction. Hypofractionated radiotherapy has been shown to cause improved tumor regression in mouse xenografts compared to conventional or hyperfractionated radiotherapy(11). Moreover, GBM tumors carrying a p53 mutation are more resistant to conventionally fractionated radiotherapy, and improved cell kill has been demonstrated with hypofractionation(12).

Several groups have employed hypofractionated radiotherapy alone, without chemotherapy, for treatment of high grade glioma and have shown hypofractionated RT to be well tolerated. Thomas has shown the regimen of 30 Gy in 5 Gy fractions was without acute toxicity(13). Floyd *et al.* delivered 50 Gy in 5 Gy fractions over a 2-week course. While 3 of 20 patients in this study underwent surgical re-excision due to radiation necrosis, these three patients also enjoyed longer survival (range, 9-23 months)(14). Hulshof compared conventional fractionation with hypofractionation using 66 Gy in 2 Gy (conventional fractionation), 40 Gy in 5 Gy, and 28 Gy in 7 Gy fractions. Patients treated with the conventional radiation schedule had similar median survival as the 28 Gy in 7 Gy fraction group despite having patients with significantly worse prognostic factors in the hypofractionation group(15). In a prospective trial of patients older than 60 years, a shorter course of radiotherapy, using 40 Gy in 15 fractions (2.67 Gy fractions) over 3 weeks, decreased treatment time and corticosteroid requirement without negatively affecting survival when compared to conventional radiotherapy (60 Gy in 2 Gy fractions over 6 weeks)(16).

A major concern of using high doses per fraction is the potential for neurotoxicity. Multiple studies have demonstrated doses ranging from 2.5 to 7 Gy per fraction to be well tolerated in patients without prior radiation(13, 17-19). Hypofractionated radiotherapy has also been shown to be safe in patients with prior radiation: In a study by Hudes and colleagues, patients with recurrent or persistent malignant glioma who had previously received a median dose of 60 Gy (range, 44 – 72 Gy) of external beam radiation were treated with stereotactic radiotherapy to target recurrent or persistent tumors in a phase I dose escalation study. Although there was no tumor response to 24 Gy in 3 Gy fractions, 79% responded to 30 Gy in 3 Gy or 35 Gy in 3.5 Gy fractions. There was no grade ≥3 toxicity, and no patient required a re-resection due to toxicity(20). Shepherd *et al.* reported hypofractionated stereotactic radiotherapy in treatment of recurrent glioma using 5 Gy fractions to total doses ranging from 20 to 50 Gy to be well tolerated, with 36% having reversible steroid-dependent toxicity and only 6% requiring reoperation(21).

1.3. Temozolomide

Temozolomide is an oral alkylating agent. The benefit of temozolomide was demonstrated in a phase III trial of GBM patients randomized to post-operative involved field radiation (60 Gy in 2 Gy fractions) with or without concurrent and adjuvant temozolomide. The addition of temozolomide led to a significant improvement in overall survival (14.6 vs. 12.1 months)(4). The safety of radiation dose escalation up to 60 Gy in 3 Gy per fraction with concurrent temozolomide has been reported, with clinical outcomes similar to that of a conventional fractionation regimen. Only one patient in this study suffered a grade 3-4 nausea and vomiting during the adjuvant temozolomide administration(22). Chen and colleagues recently reported their phase I trial of hypofractionated intensity modulated radiotherapy (IMRT) with concurrent TMZ for primary treatment of GBM(23). Patients with a tumor up to 6 cm in size were treated with a 5 mm margin with escalating doses of IMRT, safely reaching 60 Gy in 10 fractions. Even with this extreme hypofractionation with concurrent chemotherapy, with potential tumor volumes up to 180 cm^3 (6 cm tumor + 5 mm margin), no maximum tolerated dose was reached.

A 4-week course of hypofractionated intensity-modulated RT with concurrent and adjuvant temozolomide has been shown to be well tolerated, with eighty-three percent of the patients completing the combined modality treatment. Compared to conventionally fractionated RT, the hypofractionated course decreased the duration of RT treatment down to 4 weeks with comparable median overall survival rates(24).

Hypofractionated RT has been used with concurrent temozolomide in treatment of brain metastases and appears to be well tolerated, even when the entire brain is irradiated: Kouvaris *et al.* treated patients with brain metastases from solid tumors with whole brain radiation to a dose of 36 Gy in 3 Gy fractions with concurrent and adjuvant temozolomide and reported minimal side effects(25). Similarly, Hofman and colleagues showed that whole brain RT (20 Gy in 4 Gy fractions or 30 Gy in 3 Gy fractions) and stereotactic radiosurgery (20 Gy in a single fraction) with concurrent temozolomide were well tolerated(26).

Given the preclinical glioblastoma data demonstrating improved tumor control and decreased tumor cell repopulation with hypofractionated RT, a study of SRS in conjunction with temozolomide for treatment of GBM is warranted. The goal of this phase I study is to determine the maximum tolerated dose (MTD) of five fraction stereotactic radiosurgery with concurrent and adjuvant temozolomide for treatment of GBM.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Inclusion Criteria

3.1.1 Histopathologically confirmed newly diagnosed glioblastoma multiforme. Diagnosis must be made by surgical biopsy or excision.

3.1.2 The tumor must be supratentorial in location.

3.1.3 The planning target volume (PTV), defined as residual T1 post-contrast enhancing tumor and/or resection cavity plus 0.5 cm margin, must measure ≤ 150 cm^3 in volume. This volume will not be known at the initial consultation; it will be determined once the final radiation plan is completed.

3.1.4 Age ≥18 years.

3.1.5 Life expectancy of at least 12 weeks.

3.1.6 Patient must have adequate organ function as indicated by the following laboratory values:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,800 cells /mm^3
Platelets	≥100,000 cells /mm^3
Hemoglobin	≥8 g/dL. If anemia is present to the extent that the hemoglobin is <8 g/dL, then correction by transfusion is indicated before entry into the study.
Renal	
BUN	≤ 30 mg/dL
Creatinine	≤ 1.7
Hepatic	
Serum total bilirubin	≤ 2.0
AST (SGOT) and ALT (SGPT)	≤ 3 X ULN

3.1.8 Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

3.2.1 Patients who have previously been treated with brain irradiation to the region that would result in overlap of the radiation fields.

3.2.2 Tumor foci detected below the tentorium.

3.2.3 Multifocal disease or leptomeningeal spread.

3.2.4 Prior allergic reaction to the study drugs involved in this protocol.

3.2.5 Inability to have neither an MRI nor a CT scan. Patients with a pacemaker must undergo CT instead of MRI to be eligible.

3.2.6 Pediatric patients (age <18), pregnant women, and nursing patients will be excluded.

3.3 Informed Consent Process

Patients who meet the inclusion and exclusion criteria who are seen in the neuro-oncology, neurosurgery, or radiation oncology clinic will be identified for recruitment. Patients will be evaluated by a multi-disciplinary team composed of radiation oncologists, neurosurgeons, and neuro-oncologists. During their visit, either a physician or a research coordinator will explain the study to the patient. They will be given the informed consent form to read. If they agree to participate, they will be asked to sign the consent form prior to participating.

4. TREATMENT PLAN

4.1 Pretreatment evaluation

Patients will be evaluated by a multi-disciplinary team composed of radiation oncologists, neurosurgeons, and neuro-oncologists to assess for their eligibility. Patient's oncologic history, presenting symptoms, physical examination, pathology, and imaging studies will be reviewed. Patients will be evaluated for surgical candidacy and respectability.

4.2 Surgical treatment

Patients who are surgical candidates will undergo a surgical resection prior to radiotherapy. Patients whose tumors are unresectable or are not good surgical candidates will undergo a biopsy for tissue diagnosis.

4.3 Radiation Therapy

1.1.1. Dose specifications/escalation

Radiation will be delivered in five fractions. Provided that the MTD has not been reached, the total dose will be increased as follows:

Dose Level	Dose Per Fraction (Gy)	Total Dose (Gy)
1	5	25
2	6	30
3	7	35
4	8	40

There will be 2 arms to this study:

Arm	PTV volume (cm^3)
1	< 60
2	60-150

A minimum observation period of 30 days following radiotherapy is required prior to proceeding with the next higher dose level.

Common Terminology Criteria for Adverse Events (CTCAE) v4.0 will be used to grade adverse events:

(http://evs.nci.nih.gov/ftp1/CTCAE/About.html)

A dose limiting toxicity (DLT) is defined as a treatment related grade 3 - 5 CNS toxicity. Acute toxicity is defined as occurring within <30 days of the end of

radiotherapy. Late toxicity is defined as occurring ≥30 days of the end of radiotherapy. The highest dose achieved with an acceptable level of toxicity will be considered the MTD. The highest dose level allowed in this study is 40 Gy. The occurrence of late toxicities will be continuously monitored. If a late DLT occurs in 2 patients at a certain dose level after the radiation dose had already been escalated to the next level, the MTD will be backtracked to the level below the one at which the DLTs occurred.

Dose escalation will follow a traditional 3 + 3 design:

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
1 out of 3	Enter at least 3 more patients at the current dose level. • If 0 of these 3 experiences a DLT (i.e., 1 out of 6), then proceed to next dose level. • If 1 or more of these 6 experiences a DLT (2 or more out of 6), then dose escalation will be stopped. Three additional patients will be entered at the next lower dose level if only 3 patients were previously entered.
>1 out of 3	Dose escalation will be stopped. Three additional patients will be entered at the next lower dose level if only 3 patients were previously entered.

Should a patient not be evaluable at 30 days (due to death unrelated to protocol treatment or loss to follow-up or discontinuation of the protocol follow-up per patient preference), then additional patients may be enrolled on each arm such that at least 3 are evaluable for DLT.

1.1.2. **Technical factors**

Treatment shall be delivered using the Trilogy™ or TrueBeam Linear Accelerator (Varian Medical Systems, Palo Alto, CA) or the CyberKnife™ Robotic Radiosurgery System (Accuray, Sunnyvale, CA).

1.1.3. **Localization, simulation, and immobilization**

The patient shall be treated in the supine position. An aquaplast head mask will be used to ensure adequate immobilization during therapy.

1.1.4. Target Definition

1.1.4.1. Gross Tumor Volume (GTV)

The gross tumor volume (GTV) will be contoured using the post-operative contrast-enhanced MRI and is defined depending on the type of resection as follows:

- Gross total resection: GTV = tumor resection cavity;
- Partial resection: GTV = residual enhancing tumor plus resection cavity;
- Biopsy only: GTV = enhancing tumor only.

1.1.4.2. Clinical Tumor Volume (CTV)

The clinical tumor volume (CTV) is defined as GTV plus a 0.5 cm margin. This margin may be as small a 0 mm near structures which represent an anatomic border for tumor spread (e.g., falx, calvarium, tentorium). No attempt will be made to include a T2 or FLAIR signal.

1.1.4.3. Planning Target Volume (PTV)

The planning target volume (PTV) is the same as the CTV, without additional margin.

1.1.5. Radiation Dosimetry

1.1.5.1. The prescription isodose line shall cover at least 90%, with a goal of at least 95% of the PTV, typically with 10-30% heterogeneity (i.e., the prescription isodose line shall be at 70-90%). The PTV coverage may be lower than 95% in order to meet the dose constraints of critical structures. The conformity indices should be between 1.0 and 1.75.

1.1.6. Critical Structures

Critical normal structures (e.g., optic apparatus, brain stem) will be contoured and their doses minimized. Maximum doses to critical structures are as follows:

1.1.6.1. Optic nerves and optic chiasm: 98% of volume to receive <27.5 Gy in 5 fractions. This value is radiobiologically equivalent to 47 Gy in 2 Gy fractions.

1.1.6.2. Brain Stem: 98% of volume to receive <30 Gy in 5 fractions. This value is radiobiologically equivalent to 54 Gy in 2 Gy fractions.

1.1.6.3. The radiation isodose line coverage of the PTV shall be decreased in order to meet these dose limits.

4.4 Drug therapy

1.2.6. Temozolomide

Temozolomide (3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-*as*-tetrazine-8-carboxamide). At physiologic pH, temozolomide undergoes spontaneous hydrolysis to the active compound MTIC (3-methyl-(triazen-1-yl)imidazole-4-carboxamide). MTIC is thought to kill cells by alkylation of DNA.

1.2.7. Dose definition and administration

Oral temozolomide (75 mg/m^2/day) will be administered daily during radiotherapy. The first dose of temozolomide will begin the day before the first fraction of radiation. The last dose will be taken the day of the last fraction of radiation. Following radiotherapy, maintenance temozolomide will be prescribed at the discretion of the treating neuro-oncologist.

1.2.8. How Supplied

Temozolomide capsules are made in 5 mg, 20 mg, 100 mg, and 250 mg doses.

1.2.9. Known Adverse Events

	Concomitant Phase Radiotherapy + TEMODAR® (n=228)		Maintenance Phase TEMODAR® (n=224)	
Adverse event	Number (%) of patients			
	All	Grade ≥ 3	All	Grade ≥ 3
Alopecia	199 (69)	0	124 (55)	0
Fatigue	156 (54)	19 (7)	137 (61)	20 (9)
Nausea	105 (36)	2 (1)	110 (49)	3 (1)
Vomiting	57 (20)	1 (<1)	66 (29)	4 (2)
Anorexia	56 (19)	2 (1)	61 (27)	3 (1)

Headache	56 (19)	5 (2)	51 (23)	9 (4)
Constipation	53 (18)	3 (1)	49 (22)	0
Convulsions	17 (6)	10 (3)	25 (11)	7 (3)
Thrombocytopenia	11 (4)	8 (3)	19 (8)	8 (4)

1.2.10. Contraindications

Temozolomide is contraindicated in patients with hypersensitivity to temozolomide, any of the capsule components, or DTIC.

4.5 General Concomitant Medication and Supportive Care Guidelines

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol.

4.5.1. Steroids may be given as clinically indicated. The total dose must be recorded pretreatment and at the time of each treatment evaluation. Steroids will be used in the smallest dose that will afford the patient satisfactory neurologic function and the best possible quality of life.

4.5.2. Antiemetics: Patients may be given antiemetics prior to each daily dose of temozolomide. The antiemetic and dosing will be left to the treating physician's discretion. Other antiemetics such as 5HT3 antagonists or lorazepam (Ativan®) may be used at the discretion of the investigator for late nausea and vomiting.

4.5.3. Anticoagulants: Patients who are taking warfarin (Coumadin®) may participate in this study; however, it is recommended that international normalization ration (INR) or prothrombin time be monitored carefully. The frequency of INR determinations is left to the clinical judgment of the investigator. Subcutaneous heparin or fractionated heparin products are also permitted.

4.5.4. Pneumocystis prophylaxis: Prophylaxis against Pneumocystis carinii pneumonia is typically recommended for all patients receiving concomitant temozolomide and radiotherapy for the 42-day regimen. Since the duration of radiotherapy/temozolomide regimen is shorter on this protocol, the use of pneumocystis prophylaxis is left to the clinical judgment of the investigator. All patients receiving temozolomide, particularly patients receiving steroids, should be observed closed for the development of Pneumocystis pneumonia. Acceptable regimens are:

4.5.4.1. *Trimethoprim-sulfamethoxazole*: Trimethoprim will be given at 160 mg/sulfamethoxazole 800 mg daily for 3 days each week, beginning on day 1 of radiation therapy and continuing for 14 days after completion or radiation therapy.

4.5.4.2. For subjects allergic to sulfa compounds, pentamidine (or dapsone or atovaquone) may be the drug used. The choice is left to the discretion of the investigator.

4.5.5. Infections are to be treated with the appropriate antibiotics and recorded.

4.5.6. Analgesics and any other medications are to be specified and their doses recorded.

4.5.7. Recall blisters post-sun exposure can be treated with Domeboro soaks. If neuropathy occurs, patients may be placed on gabapentin.

4.5.8. No other chemotherapy treatment is permitted during protocol treatment.

4.6 Duration of Therapy

The first dose of temozolomide will begin the day before the first fraction of radiation. It will be taken through the day of the last fraction of radiation. Following radiotherapy, maintenance temozolomide will be prescribed at the discretion of the treating neuro-oncologist.

4.7 Duration of Follow Up

Patient follow-up schedule is summarized under section 8. Study Calendar.

The following will be obtained at pre-treatment evaluation and at each follow-up time points: Neurologic history and physical examination, KPS, steroid use assessment, and toxicity evaluation (see Follow-up assessment form). MRI with gadolinium will be obtained pre-treatment and at 1, 6, and 12 months following treatment until progression is documented.

In addition to the follow-up schedule outlined in section 8, additional clinical follow-up and MRI scans will be obtained based on clinical progress during the first 12 months following radiation.

After the first 12 months or after the documentation of disease progression, patients will be followed every 3-6 months at the discretion of the treating physician.

For those subjects who are unable to come for clinic visits, clinical follow-up information will be obtained via 1) a phone call to the patient and/or 2) clinic source document from his/her local physician. For patients unable to return to for imaging studies, source documents from outside institutions will be used to document imaging follow-up.

4.8 Criteria for Removal from Study

- Disease progression or death
- Intercurrent illness that prevents further administration of treatment: a condition, injury, or disease unrelated to cancer, that renders continuing temozolomide or radiation treatment unsafe or regular study visits impossible, including, but not limited to, active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, pregnancy, or psychiatric illness that would limit compliance with study requirements.
- Unacceptable adverse event(s) (see adverse events)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition that render the patient ineligible for the study
- Non-compliance with study medication or protocol-required evaluations and study visits
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- Patients who inadvertently become pregnant
- At the discretion of the treating investigators

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator if he/she violates the study plan or for administrative and/or other safety reasons. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed until resolution or stabilization.

Subjects who are discontinued from the study will still be followed for disease progression and survival.

If the reason for withdrawal from the trial is the death of the subject, the two options for categorizing withdrawal are either progressive disease or an adverse event (AE; more than one AE may be documented as a reason for withdrawal). Only one event will be captured as the cause of death. Note that death is an outcome and not an AE.

All trial treatment-related toxicities and SAEs must be followed up until resolution.

Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g., personal reasons, or adverse events after registration but prior to receiving study therapy) may be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will be made by the treating investigator. The replacement will generally receive the same treatment or

treatment sequence (as appropriate) as the allocation number replaced.

4.9 Alternatives

Alternative treatments include conventionally fractionated external beam radiotherapy with or without temozolomide or no therapy.

4.10 Compensation

Subjects will not be paid for their participation in the study.

5. DOSING DELAYS/DOSE MODIFICATIONS

Not applicable due to the short treatment duration of this study.

6. ADVERSE EVENTS AND REPORTING PROCEDURES

6.1 Potential Adverse Events

6.1.1. Radiation

6.1.1.1. Early, < 30 days from treatment: Expected adverse events include fatigue, alopecia, skin erythema, serous otitis, radiation pharyngitis, headache, neck pain, nausea and vomiting, and lethargy.

6.1.1.2. Late, > 30 days from treatment: Possible adverse events include focal neurologic deficits, memory difficulties, dementia, radiation necrosis, and radiation induced neoplasms.

6.1.2. Temozolomide

During the concomitant phase (temozolomide (TMZ) + radiotherapy) of the Stupp's trial(4), adverse reactions including thrombocytopenia, nausea, vomiting, anorexia, and constipation were more frequent in the TMZ + RT arm. The incidence of other adverse reactions was comparable between the arms with and without temozolomide. The most common adverse reactions across the cumulative TMZ experience were alopecia, nausea, vomiting, anorexia, headache, and constipation. Forty-nine percent (49%) of patients treated with TMZ reported one or more severe or life-threatening reactions, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%).

Number (%) of patients with adverse reactions:

	RT Alone	TMZ + conventional	Maintenance phase

	n=285		RT; n=288		TMZ; n=224	
	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
General						
Anorexia	25 (9)	1 (<1)	56 (19)	2 (1)	61 (27)	3 (1)
Dizziness	10 (4)	0	12 (4)	2 (1)	12 (5)	0
Fatigue	139 (49)	15 (5)	156 (54)	19 (7)	137 (61)	20 (9)
Headache	49 (17)	11 (4)	56 (19)	5 (2)	51 (23)	9 (4)
Weakness	9 (3)	3 (1)	10 (3)	5 (2)	16 (7)	4 (2)
Central Nervous System						
Confusion	12 (4)	6 (2)	11 (4)	4 (1)	12 (5)	4 (2)
Convulsions	20 (7)	9 (3)	17 (6)	10 (3)	25 (11)	7(3)
Memory Impairment	12 (4)	1 (<1)	8 (3)	1 (<1)	16 (7)	2 (1)
Eye						
Vision Blurred	25 (9)	4 (1)	26 (9)	2 (1)	17 (8)	0
Immune						
Allergic Reaction	7 (2)	1 (<1)	13 (5)	0	6 (3)	0
Gastrointestinal						
Abdominal pain	2 (1)	0	7 (2)	1 (<1)	11 (5)	1 (<1)
Constipation	18 (6)	0	53 (18)	3 (1)	49 (22)	0
Diarrhea	9 (3)	0	18 (6)	0	23 (10)	2 (1)
Nausea	45 (16)	1 (<1)	105 (36)	2 (1)	110 (49)	3 (1)
Stomatitis	14 (5)	1 (<1)	19 (7)	0	20 (9)	3 (1)
Vomiting	16 (6)	1 (<1)	57 (20)	1 (<1)	66 (29)	4 (2)
Injury						
Radiation injury NOS	11 (4)	1 (<1)	20 (7)	0	5 (2)	0
Musculoskeletal						
Arthralgia	2 (1)	0	7 (2)	1 (<1)	14 (6)	0
Platelet						
Thrombocytopenia	3 (1)	0	11 (4)	8 (3)	19 (8)	8 (4)
Psychiatric						
Insomnia	9 (3)	1 (<1)	14 (5)	0	9 (4)	0
Respiratory						
Coughing	3 (1)	0	15 (5)	2 (1)	19 (8)	1 (<1)
Dyspnea	9 (3)	4 (1)	11 (4)	5 (2)	12 (5)	1 (<1)
Skin						
Alopecia	179 (63)	0	199 (69)	0	124 (55)	0
Dry skin	6 (2)	0	7 (2)	0	11 (5)	1 (<1)
Erythema	15 (5)	0	14 (5)	0	2 (1)	0
Pruritus	4 (1)	0	11 (4)	0	11 (5)	0
Rash	42 (15)	0	56 (19)	3 (1)	29 (13)	3 (1)

Other						
Taste perversion	6 (2)	0	18 (6)	0	11 (5)	0

6.1. Adverse Event Reporting

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for grading of all adverse events.

(http://evs.nci.nih.gov/ftp1/CTCAE/About.html)

An adverse event is defined as any unfavorable and unintended change in the structure or function of the body temporally associated with the treatment. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with treatment, is also an adverse experience.

In the event of an adverse event the first concern will be for the safety of the subject. All subjects/patients with serious adverse experiences must be followed up for outcome.

Serious Adverse Experiences are:

Any untoward medical occurrences that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate 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 other outcomes listed in the definition above. These should also usually be considered serious.

If disease progression is noted during a protocol-specified reevaluation of the status of a patient's cancer, and the progression is manifested solely by result of radiologic imaging, that occurrence of progressive disease will NOT be recorded as an adverse experience.

Each occurrence of a given adverse event will be recorded. Only the most severe grade over the course of a given episode will be recorded.

Serious adverse events occurring after a patient is discontinued from the study will NOT be reported unless the investigator feels that the event may have been caused by a protocol procedure. Study-specific clinical outcomes of death because of disease progression are exempt from serious adverse event reporting, unless the investigator deems them related to a protocol procedure.

In general, serious adverse events assessed as clearly being due to disease progression and not due to a protocol procedure should be excluded from adverse event reporting.

However, in cases where the specificity or severity of an event is not consistent with the risk information, the event should be reported.

All STEAEs will be recorded on Adverse Events Communication Form and reported to:

1) Study Coordination Center/Principal Investigator
   Stanford University/ Dr. Scott Soltys

2) Stanford University Cancer Clinical Trials Office (Study Coordination Center)
   Stanford University Cancer Center
   Administrative Panels Office
   Stanford University, Stanford, CA 94305-5548

RETENTION OF RECORDS

All documentation of adverse events and all IRB correspondence will be retained for at least 2 years after the investigation is completed.

7. CORRELATIVE/SPECIAL STUDIES

N/A

8. STUDY CALENDAR

Parameters	Pre-Entry	1 month[a]	6 month[e]	12 month[e]
History/ Physical Exam	X	X	X	X
KPS	X	X	X	X
HRQOL[b]	X	X	X	X
Labs[c]	X			
Brain MRI or CT[d]	X	X	X	X
Steroid use Assessment	X	X	X	X
Toxicity Evaluation		X	X	X
	[a] ± 7 days			

	[b] EORTC-QLQ C30 and BN-20, MDASI-BT [c] Laboratory tests: complete blood count, general chemistry panel, and comprehensive metabolic panel [d]MRI schedule may change as indicated should patient have clinical deterioration; CT instead of MRI is acceptable if patient has pacemaker. [e] ± 1 month

9. MEASUREMENT OF EFFECT

9.1 Anti-tumor Effect

Brain MRI will be obtained at 1st, 6th, and 12th months following radiotherapy until disease progression. Patients may require imaging prior to the study defined assessment points should clinical deterioration warrant; should this occur, effort will be made to return to the protocol defined imaging schedule. However, clinical evaluation by the treating physicians may warrant an altered schedule. After the first year or after the documentation of disease progression, brain MRI will be obtained every 3-6 months at the discretion of the treating physician.

For patients unable to return to for imaging studies, source documents from outside institutions will be used to document imaging follow-up.

9.1.2 Disease Parameters

Local tumor progression is defined as the radiographic appearance of a new or increasing enhancing lesion within the radiosurgical target volume. Patients with increased tumor size on MRI may continue on the protocol until true tumor progression (i.e., not pseudo-progression) is determined by the treating physicians.

9.1.3 Methods for Evaluation of Measurable Disease

9.1.4 Response Criteria

The primary measure of response will be by serial measures of the product of the two largest cross-sectional diameters. Response will also be evaluated in this study using the following criteria:

9.1.4.1 Complete response (CR): Circumstance when the enhancing tumor is no longer seen by neuroimaging.

9.1.4.2 Partial response (PR): Decrease of >50% in the product of the two greatest diameters on the follow-up MRI scan. No new lesions may appear. The dose of dexamethasone must be the same or lower than at baseline.

9.1.4.3 Minor response (MR): Decrease of <50% in the product of the two greatest diameters on the follow-up MRI scan. Neither partial response or progressive disease.

9.1.4.4 Progression (P): A >25% increase in tumor area (product of the two greatest diameters) provided that the patient has not has a decrease in steroid dose since the last evaluation period. A concomitant decrease in steroid dose will rule out a progression designation during the first 2 months after the completion of XRT.

9.2 Other Response Parameters

9.2.1 Acute and late side effects will be assessed.

Common Terminology Criteria for Adverse Events (CTCAE) v4.0 will be used to grade adverse events. Acute toxicity is defined as occurring within 30 days of radiotherapy. Late toxicity is defined as occurring more than 30 days following the radiotherapy treatment.

9.2.2 The progression-free survival rate will be determined.

9.2.3 The overall survival rate will be determined.

9.2.4 The patterns of tumor recurrence will be determined.

9.2.5 The Health Related Quality of Life (HRQOL) will be measured used the validated EORTC QLQ-C30 general and BN-20 brain tumor specific scales as well as the M.D. Anderson Symptom Inventory –Brain Tumor (MDASI-BT)

For those subjects unable to appear in person for clinic visits, HRQOL questionnaires will be completed via a telephone interview or mail.

10. DATA REPORTING / REGULATORY CONSIDERATIONS

10.1 Monitoring plan

Stanford Cancer Center (SCC) Data and Safety Monitoring Committee (DSMC) will be responsible for monitoring the research yearly and will operate independently from the clinical investigators. The primary responsibility of the DSMC is to review the reported study data to confirm it is accurate, complete, and verifiable from source documents. The DSMC will also confirm that the conduct of the trial maintains the safety and well being of human subjects, and is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirements. Study

safety data will be reviewed by the DSMC in the form of summary reports or data listings on a regular basis.

10.2 Stopping rules (for the individual patient and for the study as a whole)

Dose escalation will follow a traditional 3 + 3 design.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
1 out of 3	Enter at least 3 more patients at the current dose level. • If 0 of these 3 experiences a DLT (i.e., 1 out of 6), then proceed to next dose level. • If 1 or more of these 6 experiences a DLT (2 or more out of 6), then dose escalation will be stopped. Three additional patients will be entered at the next lower dose level if only 3 patients were previously entered.
>1 out of 3	Dose escalation will be stopped. Three additional patients will be entered at the next lower dose level if only 3 patients were previously entered.

Should a patient not be evaluable at 30 days (due to death unrelated to protocol treatment or loss to follow-up or discontinuation of the protocol follow-up per patient preference), then additional patients may be enrolled on each arm such that at least 3 are evaluable for DLT.

The occurrence of late toxicities will be continuously monitored. If a late DLT occurs in 2 patients at a certain dose level after the radiation dose had already been escalated to the next level, the MTD will be backtracked to the level below the one at which the DLTs occurred.

10.3 Confidentiality

All signed informed consents and data files (contains patients' names, medical record numbers, treatment, and follow-up information) for this study will be kept in a secure office in the department of Neurosurgery and Radiation Oncology. The electronic data file for this study, which contains patients' names, medical record numbers, treatment, and follow-up information, is kept under password protection.

11. STATISTICAL CONSIDERATIONS

11.1Endpoints

11.1.1 Phase I Primary endpoint

The MTD and DLT of hypofractionated radiotherapy with temozolomide will be determined.

11.1.2 Secondary endpoints

The short- and long-term adverse effects will be determined. The overall survival rate will be calculated. Radiographic response rates and patterns of local tumor recurrence will be determined. Health related quality of life will be assessed.

11.2Sample Size

11.2.1 Accrual estimates

Three patients minimum enrolled per dose level, plus 3 additional at the dose level of the MTD. The maximum number of patients needed for the phase I study will depend on the number of dose levels reached. If all four dose levels are reached, the maximum number of patients will be 15 per arm.

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APPENDICIES

A. **Participant Eligibility Checklist**

I. Protocol Information:

Protocol Title:	**A Phase I/II Trial of Temozolomide and Hypofractionated Radiotherapy in Treatment of Supratentorial Glioblastoma Multiforme**
Protocol Number:	**17774**
Principal Investigator:	**Scott Soltys, MD**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Article I. Supporting Documentation***
1. Histopathologically confirmed newly diagnosed glioblastoma multiforme. Diagnosis must be made by surgical biopsy or excision.	☐	☐	
2. Is the tumor must be supratentorial in location?	☐	☐	
3. Does the planning target volume (PTV), defined as residual T1 post-contrast enhancing tumor and/or resection cavity plus 0.5 cm margin, measure ≤ 150 cm^3 in volume?	☐	☐	
4. Is the patient age 18 years or greater?	☐	☐	
5. Does the patient have a life expectancy of at least 12 weeks?	☐	☐	
6. Does the patient have adequate organ function? Laboratory values are documented below:	☐	☐	

Laboratory Test **(Date of test: _____)**	**Test is within protocol guideline (Check box if**	**Patient Value:**	**Protocol Guideline:**

– From CBC	YES)		
Absolute neutrophil count (ANC)	☐		**≥1,800 cells /mm^3**
Platelets	☐		**≥100,000 cells /mm^3**
Hemoglobin	☐		**≥8 g/dL**
Renal – From Basic or Comprehensive Metabolic Panel			
BUN	☐		**≤ 30 mg/dL**
Creatinine	☐		**≤ 1.7**
Hepatic – From Comprehensive Metabolic Panel			
Serum total bilirubin	☐		**≤ 2.0**
AST (SGOT) and ALT (SGPT)	☐		**≤ 3 X ULN**

Exclusion Criteria (From IRB approved protocol)			
1. Has the patient been previously treated with brain irradiation to the region that would result in overlap of the radiation fields?	☐	☐	
2. Are tumor foci detected below the tentorium?	☐	☐	
3. Is there multifocal disease or leptomeningeal spread?	☐	☐	
4. Is there any documentation of prior allergic reaction to the study drugs involved in this protocol?	☐	☐	
5. Is the patient unable to undergo an MRI OR CT scan?	☐	☐	
6. Is the patient under age 18, pregnant, or nursing?	☐	☐	

* All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

B. Participant Initial Evaluation and Follow-Up Forms:

Protocol ID: Hypofractionated Radiotherapy for Treatment of GBM
Patient Initial Consult Form

Date of visit: _____
Study Arm: ☐ #1: PTV <60mL ☐ #2: PTV 60-150mL
☐ Pt deemed ineligible based on final PTV volume of: _____mL
Dose Level: ☐ 25Gy ☐30Gy ☐35Gy ☐40Gy
Patient Number at this Dose Level: _____

	Done	**If done:**	**Not Done**
History/Physical Exam	☐	Date of H/P: _____	☐
KPS Assessment	☐	KPS: _____	☐
QOL Forms: **EORTC QLQ-C30 + BN-20** **MDASI-BT**	☐	Date: _____	☐
Decadron	☐	☐ No/☐ Yes; Dose _____	☐
Brain MRI Date: _____	☐	Protocol Lesion Size (from treatment plan): Volume _____mL Measurement (2 greatest cross sectional diameters): _____ mm x _____ mm = _____ Final PTV size: _____mL	☐

Protocol ID: Hypofractionated Radiotherapy for Treatment of GBM
Patient Follow-up Form

Date of follow-up visit: _____ **Treatment Date:** _____

Study Arm: ☐ #1: PTV <60mL ☐ #2: PTV 60-150mL
Dose Level: ☐ 25Gy ☐30Gy ☐35Gy ☐40Gy
Patient Number on this Dose Level: _____
Follow-up time:
☐ 1 month; ☐ 6 months; ☐ 12 months; ☐ Other: _____

	Done	If done:	Not Done
KPS Assessment	☐	KPS: _____	☐
QOL Forms: **EORTC QLQ-C30 + BN-20** **MDASI-BT**	☐	Date: _____	☐
Decadron	☐	☐ No ☐ Yes; Dose _____	☐
Brain MRI Date: _____	☐	Protocol Lesion Size (from current MRI): Measurement (2 greatest cross sectional diameters): _____ mm x _____ mm = _____ Assessment (see below): ☐ Complete Response ☐ Partial Response ☐ Minor Response ☐ Progression	☐
Toxicity Evaluation	☐	☐NONE ☐Toxicity Present (Grade per CTCAE): CNS Toxicity is related to Protocol Treatment: ☐Not applicable ☐Yes ☐No	☐

Comments / Notes:

Date of next follow-up visit: _____

Orders for next follow-up visit:

1 month F/U	6 month F/U	12 month F/U	Other
MRI @ 1 mo	MRI @ 6 mo	MRI @ 12 month	

MRI Assessment:

Complete response (CR): Circumstance when the enhancing tumor is no longer seen by neuroimaging.

Partial response (PR): Decrease of >50% in the product of the two greatest diameters on the follow-up MRI scan. No new lesions may appear. The dose of dexamethasone must be the same or lower than at baseline.

Minor response (MR): Decrease of <50% in the product of the two greatest diameters on the follow-up MRI scan. Neither partial response or progressive disease.

Progression (P): A >25% increase in tumor area (product of the two greatest diameters) provided that the patient has not has a decrease in steroid dose since the last evaluation period. A concomitant decrease in steroid dose will rule out a progression designation during the first 2 months after the completion of XRT.