Mathematical Model-Adapted Radiation Fractionation Schedule for Patients with Recurrent Glioblastoma (MARS-Glio)

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TITLE: Mathematical Model-Adapted Radiation fractionation Schedule for patients with recurrent Glioblastoma (MARS-Glio)

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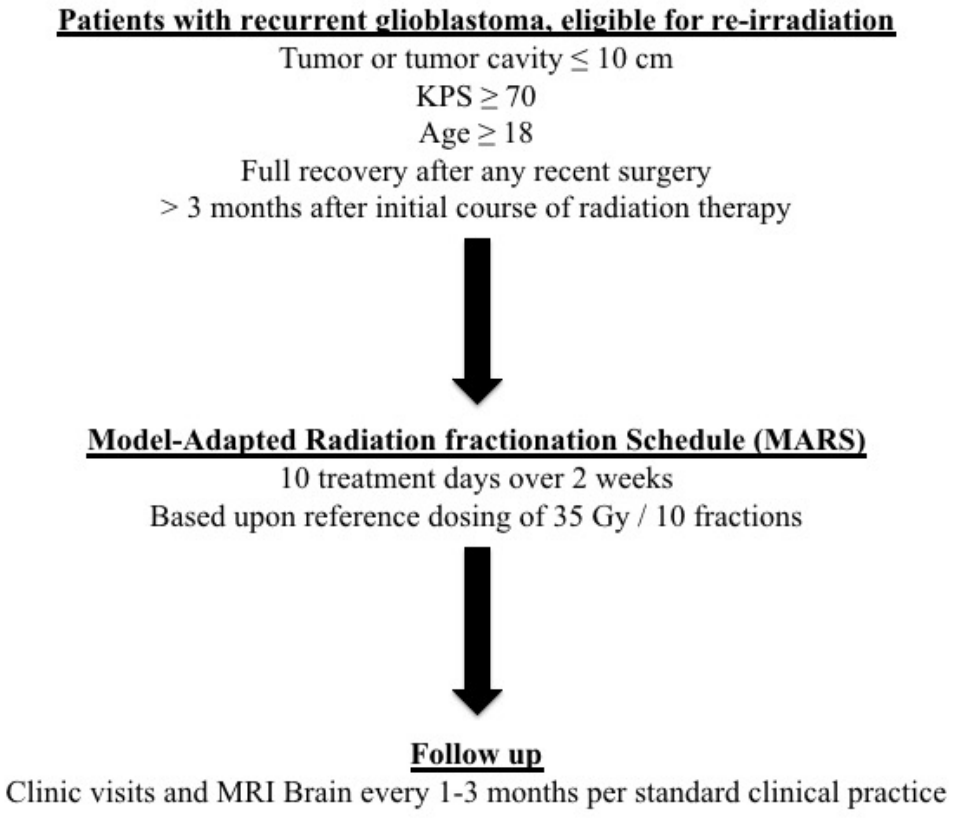
SCHEMA


Patients with recurrent glioblastoma, eligible for re-irradiation
Tumor or tumor cavity ≤ 10 cm
KPS ≥ 70
Age ≥ 18
Full recovery after any recent surgery
> 3 months after initial course of radiation therapy
Model-Adapted Radiation fractionation Schedule (MARS)
10 treatment days over 2 weeks
Based upon reference dosing of 35 Gy / 10 fractions
Follow up
Clinic visits and MRI Brain every 1-3 months per standard clinical practice

1. INTRODUCTION

1.1 Study Disease

Glioblastoma is the most common primary malignant brain tumor in adults, occurring at a rate of 3.66 new cases per 100,000 people per year in the United States (1). The role of adjuvant radiation therapy after surgical resection for glioblastoma was established in the 1970s and 1980s through several historic randomized trials comparing radiotherapy to observation (2–4), chemotherapy (3–5), or combination therapy (3–5). These studies largely showed that post-operative radiotherapy increased the median survival from 3.2-6.0 months to 8.0-12.8 months, establishing radiation therapy as a standard component to treatment for glioblastoma.

Modern treatment for glioblastoma has built upon this backbone of post-operative radiotherapy to include concurrent and adjuvant temozolomide chemotherapy, following a landmark study in 2005 showing the addition of chemotherapy to raise median survival from 12.1 months to 14.6 months (6). Despite optimal combined modality therapy with surgery, radiation, and chemotherapy, survival outcomes remain poor with most patients progressing within 10-15 months and surviving only 14.6-16.2 months from their initial diagnosis (7). The prognosis for patients upon first progression is similarly poor, with most patients only surviving approximately 4 months from progression (8,9).

Re-irradiation is a common treatment component for locally recurrent glioblastoma, often in combination with surgery and/or chemotherapy. Based on a large institutional series of 147 patients with recurrent high grade glioma treated with fractionated stereotactic re-irradiation resulting in a median survival of 11 months with excellent treatment tolerance, a standard regimen for re-irradiation is 35 Gy delivered in 10 fractions over two weeks (10). Based on these data the RTOG is actively testing this regimen in a prospective randomized study with and without concurrent bevacizumab therapy for recurrent glioblastoma (11).

The predominant pattern of initial and subsequent failure in glioblastoma is local, with 75-93% of first recurrences occurring within the high-dose volume of radiotherapy (12–18). Accordingly, several prior studies have investigated intensification of local therapy. In the era before modern chemotherapy, such studies showed improved overall survival with conventionally fractionated radiation doses to 60 Gy over 45 Gy (19). However, efforts to dose-escalate further to 70 Gy (20) and 80 Gy (21) did not significantly improve survival or patterns of failure. Similarly, randomized studies investigating intensification of local therapy with stereotactic boosting (22) and brachytherapy (23) showed no improvement in outcomes.

Explanations for this paradoxical risk of local recurrence that is refractory to intensive local therapy have included intratumoral hypoxia, genomic and phenotypic heterogeneity, and limitations of current models of radioresistance. Conventionally “fractionated” radiation schedules are based largely on the linear-quadratic model which is commonly used to estimate the probability of tumor control and normal tissue complications (24). Despite good concordance with experimental results in other cancers (25,26), efforts to optimize radiation schedules based on the linear-quadratic model have not proven effective in the clinical setting for aggressive gliomas (27).

1.2 Rationale

These limitations have drawn interest in re-designing radiation schedules, accounting for mechanisms of treatment resistance. Recent work by Leder, Michor and colleagues has created a novel mathematical model of a major mechanism of treatment resistance by accounting for intratumor heterogeneity. Specifically, they modeled the evolutionary dynamics of radioresistant, slowly proliferating stem-like cells and radiosensitive, rapidly proliferating differentiated cells. They used this model to determine an optimized radiation fractionation schedule. They parametrized the mathematical model and validated the predicted optimal schedules using a genetically engineered mouse model of PDGF-driven proneural glioblastoma (28,29). The investigators refined their mathematical model and its underlying biological assumptions through an iterative process of mathematical modeling and experimental validation. The mathematical model suggested that survival could be prolonged by enriching the tumor for slowly proliferating stem-like cells. The model predicted that the stem-like cell fraction could be substantially increased by timing the radiation administrations such that the radiation-induced dedifferentiation from differentiated to stem-like cells was maximized. When the initial predicted optimal schedule was tested in a mouse model of PDGF-driven glioblastoma, this model-adapted radiation schedule did, as predicted, significantly increase the stem-like cell fraction and significantly improved survival relative to conventionally fractionated radiation among treated mice (median survival 50 days vs. 33 days, HR = 0.30, p=0.001) (29). A second optimal schedule, based on updating the model to account for time-dependent dedifferentiation from differentiated to stem-like cells, resulted in a further, non-significant, improvement in survival compared with the original optimal schedule (HR = 0.88, p = 0.18). The updated mathematical model fit the experimental data better than the original model.

Further evidence from human data suggest that enriching the stem-like cell fraction may represent a suitable strategy to prolong survival in patients. In a study by Pallini and colleagues. the stem-like cell fraction was measured at the time of primary surgery and at recurrence, i.e. before and after chemo-radiation therapy, in glioblastoma patients (30). The stem-like cell enrichment was significantly associated with recurrence-free survival, survival following recurrence and overall survival.

We have used the validated mathematical model to translate the optimal schedule used in the mouse experiments (based on delivering 10 Gy in 5 days) to humans, using the same toxicity constraints and overall treatment time as in the RTOG 1205 trial. The mathematical model predicts that tumor growth delay is increased by enriching the slowly proliferating, stem-like cell population. The model predicts that this is achieved in two ways: by increasing the total radiation dose delivered and by increasing the fraction of differentiated cells that dedifferentiate to stem-like cells. Ultrafractionation (three fractions per day) greatly increases the stem-like cell fraction leading to a slower tumor regrowth following the end of treatment. However, by enriching for stem-like cells early during treatment the number of radioresistant cells increases and, hence, the effectiveness of the remaining fractions of radiation decreases. In addition to enriching the stem-like cell population, survival can be prolonged by minimizing the total number of cells. The total cell number is minimized by increasing the total radiation dose. Through using the model to simulate different treatment strategies, it is apparent that it is

desirable to obtain a balance between minimizing the total cell number and maximizing the stem-like cell fraction at the end of treatment. This can be achieved, within toxicity and practicality constraints, using an initial phase of hypofractionation to deliver a relatively high dose in a short period to reduce the total cell number with a small number of fractions. By following this with an ultrafractionation phase the slowly proliferating stem-like cell population is enriched at the end of treatment resulting in slower tumor regrowth and, hence, prolonged survival. The proposed treatment schedule consists of 3.96 Gy delivered once per day for the first seven treatment days followed by 1.0 Gy delivered three times per day with a 3.25-hour interval between fractions for the final three treatment days.

Indeed, ultrafractionation has been investigated in glioblastoma with promising results relative to historical controls and no reported grade 3-4 acute adverse events (31), emphasizing the promise and safety of this approach.

We hypothesize that this novel, model-based radiation fractionation scheme will be safe and deliverable for patients with recurrent glioblastoma. This study will use the previously derived mathematical model to optimize a commonly used 2-week dose-fractionation scheme for re-irradiation in glioblastoma (2), currently the standard re-irradiation regimen of the Radiation Therapy Oncology Group (11).

2. OBJECTIVES

2.1 Study Design

This is a non-randomized feasibility trial of a novel mathematical model-adapted radiation fractionation schedule, adapted from a standard 2-week treatment regimen for re-irradiation in glioblastoma (10).

2.2 Primary Objective

To assess the feasibility of delivering a mathematical model-adapted radiation schedule over 2-weeks for re-irradiation in recurrent glioblastoma.

2.3 Secondary Objectives

To evaluate patient-reported outcomes and patient satisfaction among participants receiving re-optimized radiation schedules.

To prospectively evaluate acute treatment-related toxicity from this re-optimized re-irradiation regimen.

To prospectively evaluate the following other endpoints among patients receiving this re-optimized re-irradiation regimen:

1. All-cause mortality

2. Incidence and time to local recurrence
3. Incidence and time to development of radiation necrosis
4. Incidence and time to salvage craniotomy
5. Incidence and time to systemic treatments after re-irradiation
6. Incidence and time to the development of seizures

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria to be eligible for the study:

3.1.1 Participants must have recurrent glioblastoma (WHO Grade IV), as defined on brain imaging with CT or MRI, after prior receipt of definitive therapy including neurosurgical biopsy or resection and radiation therapy with or without systemic therapy.
3.1.2 Participants must be deemed appropriate candidates for re-irradiation
3.1.3 Histopathologic confirmation of disease as part of routine clinical care is required either at the time of initial diagnosis and/or at the time of recurrent disease. There is no requirement for central pathologic review.
3.1.4 Age $\geq$ 18 years at the time of enrollment
3.1.5 Karnofsky Performance Status (KPS) of at least 70

3.2 Exclusion Criteria

3.2.1 Participants who have received more than one prior course of radiotherapy to the local site of progressive disease
3.2.2 Participants who have received prior radiotherapy to the local site of progressive disease within < 3 months of the anticipated start of re-irradiation
3.2.3 Participants with recurrent tumor extensively abutting or involving the optic structures or brainstem, as assessed by the treating radiation oncologist
3.2.4 Participants without a definable tumor cavity on MRI or CT obtained at study enrollment
3.2.5 Participants receiving concurrent cytotoxic chemotherapy (i.e. temozolomide, CCNU, vincristine, procarbazine) or concurrent immunotherapy (i.e. pembrolizumab, nivolumab); however, participants may receive sequential chemotherapy before or after radiation without limitation. Participants may receive concurrent corticosteroid and/or anti-angiogenic therapy (i.e. bevacizumab) if clinically indicated.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. PRETREATMENT EVALUATIONS/MANAGEMENT

Patients presenting to Brigham and Women's Hospital who meet the eligibility criteria above will be identified by a radiation oncologist, medical oncologist, or neurosurgeon and offered participation in the study. All patients must have undergone an MRI of the brain with T1 post-contrast sequences (standard of care) or a CT scan (if MRI is not available due to non-compatible devices). No other pretreatment evaluations are required.

5. REGISTRATION PROCEDURES

5.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

5.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

6. RADIATION THERAPY

6.1 Dose Specifications:

6.1.1 Treatment Schedule: Treatment shall consist of a regimen that is biologically equivalent (in terms of biologically effective dose with an alpha/beta ratio of 2) to 35 Gy delivered in 10 fractions over two weeks. Using the regimen developed by Fogh et al (10) and used by RTOG 1205 (35 Gy in 10 fractions) as a standard (11), this protocol has re-optimized the radiation schedule. Radiation therapy will be delivered in 2 phases over 2 weeks with fractions delivered on Monday through Friday only (with no treatments on Saturday or Sunday). All patients will aim to have their first fraction on Monday of week 1. In phase 1, participants will receive 7 daily fractions of 3.96 Gy per fraction. In phase 2, participants will receive 9 fractions of 1.00 Gy per fraction, 3 fractions per day with 3.25 hour interfraction intervals, over 3 days. This idealized treatment schedule is shown in Table 1 and in Figure 1a. Target homogeneity limits and deviations are listed in Table 2. Should any part of the treatment schedule have an anticipated conflict for clinical or logistical reasons (i.e. scheduled department closure for holiday) in which case treatment will not be administered on a given day over the 2-week course, an alternative treatment schedule will be generated utilizing the prediction model for the missing fraction(s). A separate sensitivity analysis was conducted and predicted for a similar benefit of the novel schedule over standard re-irradiation schedule, irrespective of which day of the week treatment is started, as shown in Figure 1b.

Table 1. Idealized Model-Adapted Radiation Schedule*

Week 1	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**
Dose	1 x 3.96 Gy	1 x 3.96 Gy	1 x 3.96 Gy	1 x 3.96 Gy	1 x 3.96 Gy
Week 2	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**
Dose	1 x 3.96 Gy	1 x 3.96 Gy	3 x 1.00 Gy (3.25-hour interval)	3 x 1.00 Gy (3.25-hour interval)	3 x 1.00 Gy (3.25-hour interval)

** Schedule subject to predetermined adaptation due to anticipated conflicts (i.e. holidays, department closures, etc.…)*

Figure 1a. Idealized Model-Adapted Radiation Schema

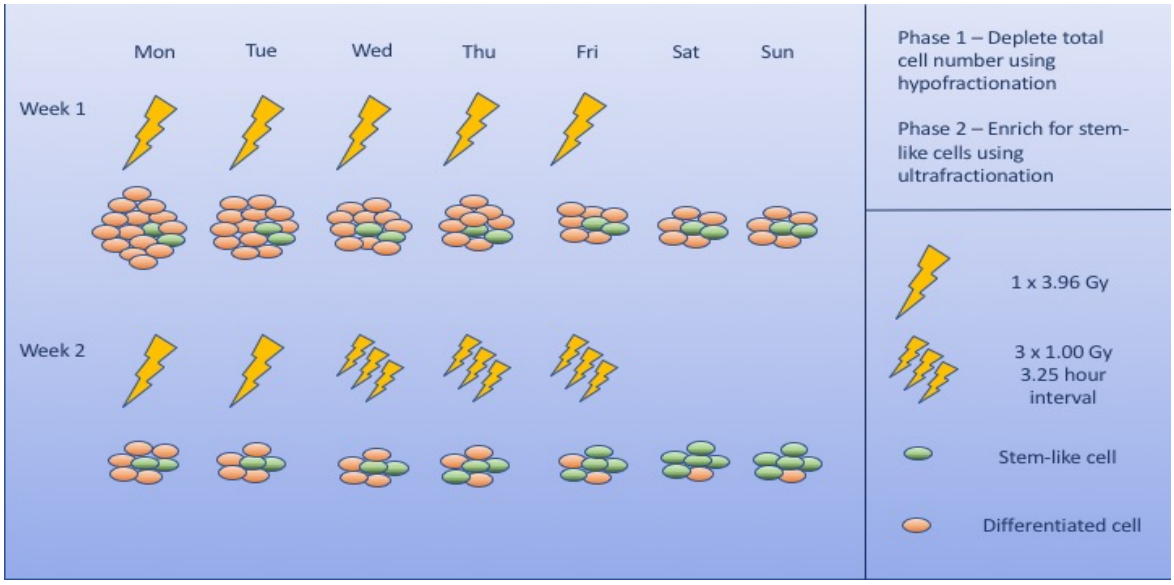
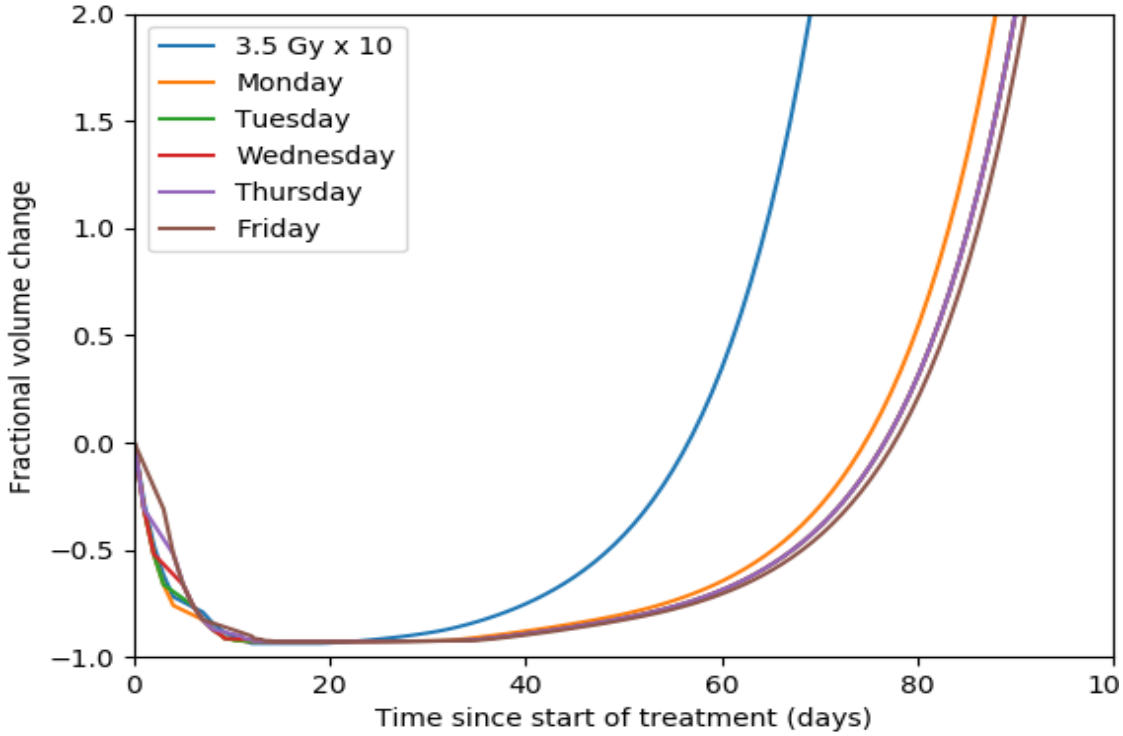


Figure 1b. Sensitivity Analysis for Tumor Response by Day of Treatment Initiation



6.1.2 Tumor Dose Coverage Objectives: The tumor dose coverage objectives are equivalent, in terms of the percentages of the prescription dose, to those used in RTOG 1205 (11). The tumor Planning Target Volume (PTV) dose coverage objectives, for the total absorbed dose delivered in 10 fractions, employed in the RTOG 1205 trial are shown in Table 2.

Table 2. RTOG 1205 Tumor Dose Coverage Objectives (given as absorbed dose)

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Volume of PTV covered by the prescription dose 35 Gy	≥ 95% of the PTV should receive the prescription dose or higher	≥ 90% of the PTV should receive the prescription dose or higher	< 90% of the PTV should receive the prescription dose or higher
Minimum dose to the PTV (0.03 cc)	≥ 85% of the prescription dose (29.75 Gy)	≥ 80% of the prescription dose (28.00 Gy); minimum doses < 80% of the prescription dose are permissible if they occur at an area of overlap with an organ at risk (OAR)	< 80% of the prescription dose (28.00 Gy); minimum doses < 80% of the prescription dose are unacceptable if they do not occur at an area of overlap with an OAR
Maximum dose to the PTV (0.03 cc)	≤ 120% of the prescription dose (42.00 Gy)	≤ 130% of the prescription dose (45.50 Gy)	> 130% of the prescription dose (45.50 Gy)

For MARS-Glio phase 1 the prescription absorbed dose is 3.96 Gy per fraction, giving a cumulative (over 7 fractions) absorbed dose for phase 1 of 3.96 x 7 = 27.72 Gy. The tumor dose coverage objectives for phase 1 are shown in Table 3.

Table 3. MARS-Glio phase 1 tumor dose coverage objectives (given as absorbed dose)

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Volume of PTV covered by the prescription dose 27.72 Gy	≥ 95% of the PTV should receive the prescription dose or higher	≥ 90% of the PTV should receive the prescription dose or higher	< 90% of the PTV should receive the prescription dose or higher
Minimum dose to the PTV (0.03 cc)	≥ 85% of the prescription dose (23.56 Gy)	≥ 80% of the prescription dose (22.18 Gy); minimum doses < 80% of the prescription dose are permissible if they occur at an area of overlap with an organ at risk (OAR)	< 80% of the prescription dose (22.18 Gy); minimum doses < 80% of the prescription dose are unacceptable if they do not occur at an area of overlap with an OAR
Maximum dose to	≤ 120% of the	≤ 130% of the	> 130% of the

the PTV (0.03 cc)	prescription dose (33.26 Gy)	prescription dose (36.04 Gy)	prescription dose (36.04 Gy)

For MARS-Glio phase 2 the prescription absorbed dose is 1.00 Gy per fraction, giving a cumulative (over 9 fractions) absorbed dose for phase 2 of 1.00 x 9 = 9.00 Gy. The tumor dose coverage objectives for phase 2 are shown in Table 4.

Table 4. MARS-Glio phase 2 tumor dose coverage objectives (given as absorbed dose)

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Volume of PTV covered by the prescription dose 9.00 Gy	≥ 95% of the PTV should receive the prescription dose or higher	≥ 90% of the PTV should receive the prescription dose or higher	< 90% of the PTV should receive the prescription dose or higher
Minimum dose to the PTV (0.03 cc)	≥ 85% of the prescription dose (7.65 Gy)	≥ 80% of the prescription dose (7.20 Gy); minimum doses < 80% of the prescription dose are permissible if they occur at an area of overlap with an organ at risk (OAR)	< 80% of the prescription dose (7.20 Gy); minimum doses < 80% of the prescription dose are unacceptable if they do not occur at an area of overlap with an OAR
Maximum dose to the PTV (0.03 cc)	≤ 120% of the prescription dose (10.80 Gy)	≤ 130% of the prescription dose (11.70 Gy)	> 130% of the prescription dose (11.70 Gy)

For MARS-Glio phases 1 and 2 combined the prescription absorbed dose is 3.96 x 7 + 1.00 x 9 = 36.72 Gy. The tumor dose coverage objectives for phases 1 and 2 combined are shown in Table 5.

Table 5. MARS-Glio phases 1 and 2 combined tumor dose coverage objectives (given as absorbed dose)

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Volume of PTV covered by the prescription dose 36.72 Gy	≥ 95% of the PTV should receive the prescription dose or higher	≥ 90% of the PTV should receive the prescription dose or higher	< 90% of the PTV should receive the prescription dose or higher
Minimum dose to the PTV (0.03 cc)	≥ 85% of the prescription dose (31.21 Gy)	≥ 80% of the prescription dose (29.38 Gy);	< 80% of the prescription dose (29.38 Gy);

		minimum doses < 80% of the prescription dose are permissible if they occur at an area of overlap with an organ at risk (OAR)	minimum doses < 80% of the prescription dose are unacceptable if they do not occur at an area of overlap with an OAR
Maximum dose to the PTV (0.03 cc)	≤ 120% of the prescription dose (44.06 Gy)	≤ 130% of the prescription dose (47.74 Gy)	> 130% of the prescription dose (47.74 Gy)

6.1.3 Normal Tissue Constraints: Participants shall receive prescription doses to the PTV (with the above constraints). All attempts should be made to deliver the PTV dose with the above heterogeneity constraints with adherence to critical structure dose constraints. The normal tissue dose constraints are designed to be equivalent in terms of biologically effective dose (BED), to those used in the RTOG 1205 trial. The BED is defined as:

$$BED_{\alpha/\beta} = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

where n is the number of fractions and d is the dose per fraction. For central nervous system toxicity an alpha/beta ration of 2 was used. The MARS-Glio dose constraints for the two phases combined in BED with an alpha/beta ratio of 2 are thus given by

$$c_{MARS\text{-}Glio,total,BED} = c_{RTOG\ 1205,AD}\left(1 + \frac{c_{RTOG\ 1205,AD}/10}{2}\right)$$

where $c_{RTOG\ 1205,AD}$ is the RTOG 1205 absorbed dose. For the individual phases the dose constraints, in absorbed doses, are given by

$$c_{MARS\text{-}Glio,phase\ x,AD} = n_{phase\ x}\left(-1 + \sqrt{1 + \frac{4c_{MARS\text{-}Glio,total,BED}\frac{BED_{\alpha/\beta,phase\ x}}{BED_{\alpha/\beta,total}}}{n_{phase\ x}\alpha/\beta}}\Big/ 2/\alpha/\beta\right)$$

$$BED_{2,phase\ 1} = 7\times 3.96\left(1 + \frac{3.96}{2}\right) = 82.61\ Gy_2$$

$$BED_{2,phase\ 2} = 9\times 1.00\left(1 + \frac{1.00}{2}\right) = 13.50\ Gy_2$$

$$BED_{2,total} = BED_{2,phase\ 1} + BED_{2,phase\ 2} = 96.11\ Gy_2$$

$$\frac{BED_{2,phase\ 1}}{BED_{2,total}} = \frac{82.61}{96.11} = 0.861$$

$$\frac{BED_{2,phase\ 2}}{BED_{2,total}} = \frac{13.50}{96.11} = 0.140$$

$$c_{MARS\text{-}Glio,phase\ 1,AD} = 7\left(-1 + \sqrt{1 + \frac{4c_{MARS\text{-}Glio,total,BED}\times 0.861}{7\times 2}}\right)$$

$$c_{MARS\text{-}Glio,phase\ 2,AD} = 9\left(-1+\sqrt{1+\frac{4c_{MARS\text{-}Glio,total,BED}\times 0.140}{9\times 2}}\right)$$

The dose constraints for the RTOG 1205 trial, in absorbed dose, are displayed in Table 6.

Table 6. RTOG 1205 Normal Tissue Dose Constraints (given as absorbed dose)

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Scenario (1): Previous radiation to the local area including critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm ($D_{0.03\ cc}$)	Less than or equal to 20.00 Gy	Greater than 20.00 Gy but less than or equal to 25.00 Gy	Greater than 25.00 Gy
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 24.00 Gy	Greater than 24.00 Gy but less than or equal to 30.00 Gy	Greater than 30.00 Gy
Scenario (2): No previous radiation to the local area or critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 35.00 Gy (the prescription dose)	Greater than 35.00 Gy but less than or equal to 36.75 Gy (105 % of the prescription dose)	Greater than 36.75 Gy (105% of the prescription dose)
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 35.00 Gy (the prescription dose)	Greater than 35.00 Gy but less than or equal to 36.75 Gy (105 % of the prescription dose)	Greater than 36.75 Gy (105 % of the prescription dose)

Table 7 shows the dose constraints for the combined phases in BED with an alpha/beta ratio of 2 for the optic nerves, optic chiasm and brainstem (BED_2).

Table 7. MARS-Glio phases 1 and 2 combined normal tissue dose constraints (given as BED with an alpha/beta ratio of 2)

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Scenario (1): Previous radiation to the local area including critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm ($D_{0.03\ cc}$)	Less than or equal to 40.00 Gy_2	Greater than 40.00 Gy_2 but less than or equal to 56.25 Gy_2	Greater than 56.25 Gy_2
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 52.80	Greater than 52.80 Gy_2 but less than or equal	Greater than 75.00 Gy_2

	Gy_2	to 75.00 Gy_2	
Scenario (2): No previous radiation to the local area or critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 96.11 Gy_2 (the prescription dose)	Greater than 96.11 Gy_2 but less than or equal to 104.28 Gy_2	Greater than 104.28 Gy_2
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 96.11 Gy_2 (the prescription dose)	Greater than 96.11 Gy_2 but less than or equal to 104.28 Gy_2	Greater than 104.28 Gy_2

Tables 8 and 9 give the phase 1 and phase 2 normal tissue dose constraints in absorbed doses, respectively.

Table 8. MARS-Glio phase 1 normal tissue dose constraints (given as absorbed dose)

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Scenario (1): Previous radiation to the local area including critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm ($D_{0.03\ cc}$)	Less than or equal to 16.05 Gy	Greater than 16.05 Gy but less than or equal to 19.96 Gy	Greater than 19.96 Gy
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 19.18 Gy	Greater than 19.18 Gy but less than or equal to 23.87 Gy	Greater than 23.87 Gy
Scenario (2): No previous radiation to the local area or critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 27.75 Gy	Greater than 27.75 Gy but less than or equal to 29.14 Gy	Greater than 29.14 Gy
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 27.75 Gy	Greater than 27.75 Gy but less than or equal to 29.14 Gy	Greater than 29.14 Gy

Table 9. MARS-Glio phase 2 normal tissue dose constraints (given as absorbed dose)

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Scenario (1): Previous radiation to the local area including critical organs at risk			
Maximum Dose to	Less than or	Greater than 4.48 Gy	Greater than 5.93

PRV for Optic Nerves and Chiasm ($D_{0.03\ cc}$)	equal to 4.48 Gy	but less than or equal to 5.93 Gy	Gy
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 5.63 Gy	Greater than 5.63 Gy but less than or equal to 7.43 Gy	Greater than 7.43 Gy
Scenario (2): No previous radiation to the local area or critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 8.98 Gy	Greater than 8.98 Gy but less than or equal to 9.54 Gy	Greater than 9.54 Gy
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 8.98 Gy	Greater than 8.98 Gy but less than or equal to 9.54 Gy	Greater than 9.54 Gy

See Section 6.5 below for specifics regarding when to implement a dose reduction. The final prescription dose will be reported specifically to the study coordinator and recorded on a patient-by-patient basis.

6.2 Technical Factors

6.2.1 RT will be delivered with megavoltage equipment at energies ≥6 MV. Any FDA cleared external beam radiation delivery system may be used (including conventional linear accelerators). All treatment fractions (as specified above in Table 1) will be delivered on consecutive treatment days. All patients will be positioned via a combination of rigid immobilization and daily image guidance to ensure positioning accuracy of 3 mm or better, and of a magnitude that justifies the PTV margin applied (the treating radiation oncologist must document the immobilization and localization methods applied).

6.3 EBRT Localization, Simulation, and Immobilization

6.3.1 Simulation will be CT- and/or MRI-based (if available) in all cases. The use of contrast at the time of simulation is not required. Participants will be positioned on a flat tabletop with a customized immobilization for stabilization and setup reproducibility, with the patient in the same position and immobilization device as for treatment. CT images should be acquired at a slice thickness of ≤3 mm. Target volumes (Section 6.4.1) and normal critical structures (Section 6.4.1.5) will be defined in the slices in which they are visualized.

6.4 Treatment Planning/Target Volumes

6.4.1 The definition of volumes will be in accordance with the ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.

6.4.1.1 The Gross Tumor Volume (GTV) is defined will be defined using a CT and/or contrast-enhanced MRI (obtained prior to the initiation of re-irradiation). If no residual enhancing tumor is noted, the post-operative resection cavity will be outlined.

6.4.1.2 The Clinical Target Volume (CTV) is the GTV plus areas considered to contain microscopic disease. A CTV expansion of no more than 5 mm is optional for lesions measuring less than 3.5 cm in maximum diameter or if this is a new lesion, but must be reported when used. Otherwise, no CTV expansion is expressly recommended.

6.4.1.3 The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variability of treatment set up and internal organ motion. A range of 1-5 mm around the CTV is required to define each respective PTV. As noted above in Section 6.3.1, daily image guidance to ensure positioning accuracy of 3 mm or better.

6.4.1.4 The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

6.4.1.5 The PTV forms the entire target as described. 3D-conformal, intensity modulated radiation therapy (IMRT), Volumetric Arc Therapy (VMAT), and/or fractionated stereotactic radiotherapy (SRT) are all acceptable modalities of radiation treatment delivery. If IMRT or SRT are intended, to avoid delays resulting from unplanned equipment availability, photon therapy may be administered using 3D-conformal radiotherapy at the discretion of the treating radiation oncologist.

6.5 Critical Structures

Critical structure dose constraints shall remain consistent with Tables 7-9 above. While every effort should be made to deliver prescription doses to the PTV as specified while adhering to these constraints, it is recognized that certain anatomical factors may prevent this.

For purposes of compliance, up to a 5% absolute increase in the volume of critical structure receiving greater than the specified dose will be considered “variation acceptable,” without a protocol deviation. Any increase in critical structure volume greater than 5% receiving more than the specified dose will be considered a “deviation unacceptable.” It is at this point that a dose reduction should be considered.

6.6 Quality Assurance

6.6.1 Documentation Requirements

The institution will archive treatment prescription and verification images for later review by the study chair if requested. At least one port film or pretreatment alignment film per

field along with the digital reconstructed radiographs (DRRs) from the treatment planning program or, alternatively, a simulation verification radiograph shall be acquired and kept for evaluation if requested except where geometrically impractical.

6.6.2 Radiation Quality Assurance Reviews

The study chair will oversee quality assurance reviews for patients treated on this study. RT quality assurance reviews will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by study chair.

6.6.3 Compliance Criteria

Cases that meet criteria as stated in Section 6.1.1 will be scored as per protocol. See Table 2 and Table 3 for target and normal tissue compliance criteria respectively.

6.7 Radiation Adverse Events

All participants will be seen weekly by their treating radiation oncologist while undergoing therapy. Any observations with respect to symptoms/side effects that are possibly, probably, or definitely related to recurrent glioblastoma or irradiation to the brain will be followed for adverse event (AE) reporting.

Clinical discretion may be used in managing radiotherapy-related side effects.

6.8 Radiation Adverse Event Reporting

Any observations with respect to symptoms/side effects that are possibly, probably, or definitely related to recurrent glioblastoma or irradiation to the brain will be followed for AE reporting. See Section 9 for listing of particular AEs that will be monitored. This is not an all-inclusive list, and any AE that is considered by the treating physician to be related to recurrent glioblastoma and/or irradiation to the brain will be followed with attributions and grading according to CTCV 4.0. Routine solicited AEs not considered by treating physicians to be related to recurrent glioblastoma or irradiation to the brain will be treated according to institutional guidelines and managed by the patient's oncology team in the best clinical judgment of the responsible physician.

6.9 Criteria for Discontinuation of Protocol

Disease progression

Unacceptable toxicity to the participant (at the discretion of the treating physician). Reasons for removal must be clearly documented on the appropriate case report form/flowsheet.

The participant may withdraw from the study at any time for any reason.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol

7. DRUG THERAPY

This protocol does not specify any investigational drug therapy. Participants receiving re-irradiation may not receive concurrent cytotoxic chemotherapy (i.e. temozolomide, CCNU, vincristine, procarbazine) or concurrent immunotherapy (i.e. pembrolizumab, nivolumab). Participants may receive sequential systemic therapy before or after radiation without limitation. Participants may receive concurrent corticosteroid and/or anti-angiogenic therapy (i.e. bevacizumab) if clinically indicated.

8. SURGERY

This protocol does not mandate neurosurgical resection prior to receipt of re-irradiation. Participants may undergo a planned neurosurgical resection prior to registration and receipt of re-irradiation at the discretion of the treatment multidisciplinary team. Such participants will be required to have recovered from the acute effects of neurosurgery prior to initiating re-irradiation at the judgment of the treating radiation oncologist. There is no maximum or minimum interval from the time of prior surgery to initiation of re-irradiation. If participants underwent a preceding neurosurgical resection, the target volume for re-irradiation will include the surgical cavity plus any residual enhancing disease.

9. ADVERSE EVENTS

Toxicity assessments will be performed using the active version of the NCI CTCAE which is available at: http://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Grade 1-2 fatigue will be managed supportively. Activity will be encouraged.
Grade 3 fatigue can be managed per above, with the additional of low-dose dexamethasone and/or methylphenidate 2.5-5.0 mg daily, as needed.

Grade 1-2 nausea can be managed with as-needed antiemetics such as Zofran 8 mg prn, steroids (dexamethasone preferred, e.g. 2 mg PO BID), and hydration.
Grade 3 nausea can be managed per above with the addition of intravenous fluids and electrolyte repletion. Hospitalization and a treatment break can be considered.

Grade 1 headache can be managed with Tylenol 650 mg BID and consideration of low-dose dexamethasone (2 mg PO BID)
Grade 2 headache can be managed per above, with narcotics as needed.
Grade 3 headache can be managed per above, with consideration of high-dose dexamethasone (4 mg PO TID) and a treatment break.

Symptomatic edema can be managed with dexamethasone (2 mg PO BID) at discretion of treating physician.

Seizures will be managed with antiepileptic drugs, consideration of a treatment break, and referral to Neuro-oncology or admission, depending on the nature and severity of the episode.

Any observations with respect to symptoms or side effects that are possibly, probably, or definitely related to brain metastases or radiation to the brain will be followed for AE reporting.

10. PARTICIPANT ASSESSMENTS

Table 10 presents the schedule of treatment and follow up visits. Visits should occur within 2 weeks of the scheduled day. If a participant fails to appear for a visit, the investigator will make every attempt to contact them and determine the reason for the missed visit. A participant will be deemed lost to follow-up only after at least 3 attempts to contact him/her have been made over a 4-week period. For participants who present with significant transportation or other barriers that would prevent them from being followed at the Dana-Farber/Brigham and Women's Cancer Center clinics, they may be followed closer to home at outside institutions by local oncologists, and clinical notes will be requested by the study team.

The primary endpoint (feasibility of receipt of fractions) will be assessed at the completion of all treatment fractions.

Medical history and physical exam, which includes general questions about health, medications being taken, current allergies, and assessment of the development of seizures will be taken at

screening, at each weekly visit during radiation therapy, at 4 ± 2 weeks after completion of radiation, and at subsequent follow-up visits every 1-3 months thereafter per usual clinical practice.

Karnofsky Performance Status (KPS) will be assessed at screening, at each weekly visit during radiation, at 4 ± 2 weeks after completion of radiation, and at subsequent follow-up visits every 2-4 months thereafter per usual clinical practice.

Toxicity review will consist of a history at each visit to monitor for relevant toxicity as described in section 9.Toxicity will be assessed at each weekly visit during radiation therapy, at 4 ± 2 weeks after completion of radiation, and at subsequent follow-up visits every 2-4 months thereafter per usual clinical practice.

Quality of life, as per the MDASI-BT: M. D. Anderson Symptom Inventory – Brain Tumor survey) will be assessed at baseline, at 4 ± 2 weeks after completion of radiation, and at subsequent follow-up visits every 2-4 months thereafter per usual clinical practice. The MDASI-BT is performed as part of an institution-wide effort to collect patient-reported outcomes. This is the usual care pattern for such patients. Patients who have significant transportation limitations may follow-up with their local oncologist and forgo the questionnaire.

Head imaging will be obtained at baseline, at 4 ± 2 weeks after completion of radiation, and at subsequent follow-up visits every 2-4 months thereafter per usual clinical practice. Typically, this will consist with an MRI of the brain with contrast (although CT Head and non-contrast scans will be permitted if participants cannot receive standard MRIs). Head imaging will be used to define response as outline in section 12.7.

Follow-up data from these visits will continue to be collected after active participation in the study concludes. Therefore, participants will be followed per protocol for 6 months after completion of radiation treatment. Additional clinical follow up per standard of care will continue until death or loss to follow up, and relevant outcome data will be collected retrospectively during that time.

The length of follow up for the primary outcome measure (feasibility of receipt of fractions) will be 1 month after treatment completion. The length of follow up for all other endpoints will be until death or loss to follow up. This is because the usual clinical care for patients with brain metastases involves a radiation or neuro-oncology visit, history, and an MRI brain every 2-6 months until death or other loss to follow up.

Table 10. Study Calendar

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Every 2-4 months*
	Screening	Radiation Planning	Radiation Start	Week 1 Visit	Week 2 Visit	4-week follow up*	
Informed Consent	X						
Medical History (including assessment of development of seizures) & Physical Exam	X			X	X	X	X
Neurologic Exam	X			X	X	X	X
Karnofsky Performance Status (KPS)	X			X	X	X	X
CT or MRI	X	X				X	X
MDASI-BT	X					X	X
Toxicity Assessment	X			X	X	X	X
Radiation Planning		X					
Radiation Treatment			X	X	X		

*Patients who have significant transportation limitations may follow-up with their local oncologist and also forgo the MDASI-BT

Abbreviations: MDASI-BT: M. D. Anderson Symptom Inventory – Brain Tumor survey

11. DATA COLLECTION

11.1 Summary of Data Submission

Item	Due
Demographic Form Initial Evaluation Form Pathology Report Head Imaging Report	Within 2 weeks after registration
Treatment Form	Within 2 weeks of the end of radiotherapy
MDASI-BT	Within 2 weeks of each follow up as above
Follow-Up Form	Within 2 weeks of each follow up as above Within 2 weeks of progression/relapse and death

11.2 Summary of Dosimetry Data Submission for Protocol Treatment

Item	Due
Final Dosimetry Information Radiotherapy Form Daily Treatment Record	Within 1 week of RT end

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

Primary Endpoint

The primary outcome measure is the feasibility of delivering a model-adapted radiation fractionation schedule. Feasibility is defined as successful completion of radiation therapy for at least 13 of 14 patients. Successful completion of radiotherapy is defined as receipt of all scheduled fractions of daily radiotherapy within 24 hours of once daily fractions and within 1 hour of three-times daily fractions.

A sensitivity analysis has been performed on the mathematical model, which revealed no significant effect on tumor kill from the timing of once daily radiotherapy. This analysis did reveal the importance of the timing of three-times daily radiation therapy, for which feasibility was defined as treatment within 1 hour of the scheduled time.

Secondary Endpoints

Secondary outcomes and analytic techniques to assess these outcomes will include:

1. Quality of life, as determined by the MDASI-BT index (Appendix B), ascertained at the time of study enrollment, 4 weeks after completion of reirradiation, and every 2-4 months thereafter. We will conduct a longitudinal / repeated measures analysis to assess quality of life (mean MDASI-BT score for items 1-22 in APPENDIX B between 0-24 weeks)
2. Incidence (exact binomial distribution with 95% confidence intervals)

and time to the development of Grade 3+ acute or delayed CNS toxicity
3. Incidence and time to development of radiation necrosis (Kaplan-Meier plot, Cox regression)
4. Incidence and time to the development of seizures (Kaplan-Meier plot, Cox regression)
5. Performance status (longitudinal regression)
6. Overall survival, defined as the interval from registration to death from any cause (Kaplan-Meier plot, Cox regression)
7. Progression-free survival, defined as the interval from registration to progression or death, whichever occurs first (Kaplan-Meier plot, Cox regression)
8. Local recurrence, defined as the interval from registration to local recurrence (Kaplan-Meier plot)
9. Incidence and time to salvage craniotomy (Kaplan-Meier plot, Cox regression)
10. Incidence and time to additional systemic treatments after reirradiation (Kaplan-Meier plot)

12.2 Sample Size and Power Justification

The final target accrual for this study will be 14 cases.

A recent trial attempted to deliver 90 fractions of radiation therapy to glioblastoma patients in 6 to 7 weeks, 5 days per week, 3 fractions per day (32). The schedule was successfully administered in 22/27 (81%) patients who started radiation therapy. The one-sided 95% upper limit (exact binomial distribution) for the population non-adherence was, therefore, 35%. Based on this adherence rate delivery of the schedule was deemed feasible.

The schedule proposed in this protocol is substantially simpler to deliver. If 13 out of 14 patients are able to complete the proposed schedule (86%), this study would demonstrate that the one-sided 95% upper limit (exact binomial distribution) for the population non-adherence is 30%. This non-adherence rate, or lower, would be deemed acceptable to progress to a subsequent efficacy trial. If all patients are able to complete the proposed schedule, this study would demonstrate that the one-sided 95% upper limit for the population non-adherence is no higher than 20%.

12.3 Sample Size, Accrual Rate and Study Duration

This study is expected to accrue 8-10 cases per year. Therefore, the target accrual should be completed within 22 months of study activation, allowing slow accrual in the first 6 months. If the average accrual over two months (6 months after trial activation) is less than 1 case, the study will be re-evaluated with respect to feasibility.

The study duration will be approximately 28 months; 22 months of accrual and 6 months of follow-up on the last participant enrolled.
Accrual should be well-balanced for males, females, and minorities.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	1	+	1	=	2

Not Hispanic or Latino	6		+	6		=	12	
Ethnic Category: Total of all subjects	7	(A1)	+	7	(B1)	=	14	(C1)
Racial Category								
American Indian or Alaskan Native	0		+	0		=	0	
Asian	1		+	1		=	2	
Black or African American	1		+	1		=	2	
Native Hawaiian or other Pacific Islander	0		+	0		=	0	
White	5		+	5		=	10	
Racial Category: Total of all subjects	7	(A2)	+	7	(B2)	=	14	(C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)	

12.4 Stratification Factors

No stratification factors will be used in this non-randomized study. There will be no dose escalation in this cohort.

12.5 Interim Monitoring Plan

Futility: If two or more patients experience non-adherence events no further patients will be recruited.

12.6 Analysis of Primary Endpoints

Specified above

12.7 Analysis of Secondary Endpoints

Specified above

Local control will be defined as the interval from registration to local recurrence as determined by the Response Assessment in Neuro-Oncology (RANO) working group (33).

Response/Progression Categories

Complete response (CR). *All of the following criteria must be met*:

- Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
- No new lesions.
- All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
- Participants must be on no steroids or on physiologic replacement doses only.
- Stable or improved non-enhancing (T2/FLAIR) lesions.
- Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related.

Participants with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial response (PR). *All of the following criteria must be met*:

- ≥50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
- No progression of non-measurable disease.
- No new lesions.
- All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
- The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
- Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
- Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

Participants with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Progressive disease (PD). *The following criterion must be met*:

> 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of corticosteroids and/or one or more of the of the following:

- Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids steroids compared to baseline scan or best response following initiation of therapy not due to co-morbid events (radiation therapy, demyelination, ischemic injury,infection, seizures, post-operative changes, or other treatment effects).
- Any new lesion

- Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration, unless attributable to comorbid events or changes in corticosteroid dose.
- Failure to return for evaluation due to death or deteriorating condition
- *NOTE: If there is uncertainty whether the patient has progressed it is permissible to repeat the scan in 1 month. If that scan confirms progression, the date of progression will be the original date when progression was suspected to deal with ambiguities related to pseudoprogression.*

Stable disease (SD). *All of the following criteria must be met*:

- Does not qualify for CR, PR, or progression.
- All measurable and non-measurable sites must be assessed using the same techniques as baseline.
- Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
- Stable clinically.

Unknown response status.

- Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

These RANO Response Criteria are also summarized in the following table:

Table 11. Summary of RANO Response Criteria

	CR	**PR**	**SD**	**PD**
T1-Gad+	None	≥50% decrease	< 50% decrease – <25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for Response	All	All	All	Any

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

#: Progression occurs when any of the criteria with * is present

NA: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

12.8 Reporting and Exclusions

Participants who never start protocol therapy will be considered "inevaluable" and will be excluded from analysis of all endpoints. In terms of grade 3+ toxicity and acute/delayed toxicity, all patients receiving any or partial protocol treatment should be included.

12.8.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment. Toxicity endpoints will be reported separately for participants who complete all prescribed radiotherapy per protocol and for those who do not.

We will monitor for the following:

Fatigue

Fatigue is common after brain radiation; it is less common and typically short-lived after shorter courses of radiation but can still occur.

Nausea
Nausea may occur with re-irradiation although typically not commonly.

Headache
Headache that occurs with re-irradiation is typically mild in severity.

Symptomatic edema
Symptomatic edema occurs when radiation interacts with the tumor, leading to death of tumor cells and resulting inflammation. It may be more common with re-radiation.

Seizure
Seizures are uncommon in patients receiving fractioned radiation but may be more common among patients receiving re-irradiation. Seizures generally do not stem from infratentorial lesions, however.

Intracranial hemorrhage
Intracranial hemorrhage has never been definitively associated with radiation, although patients with glioblastoma may have a propensity to bleed and may display hemorrhage post radiation, especially if patients are on anticoagulation for other reasons. Intratumoral hemorrhage will

require only close monitoring with MRI. Extratumoral hemorrhage may require referral to Neuro-oncology, admission, a treatment break, and possible discontinuation of agents that predispose to bleeding, depending on the nature and severity of the bleed.

Radiation necrosis
Radiation necrosis can occur after re-irradiation. Enhancing lesions that increase in size after radiation will be evaluated for the possibility of radiation necrosis using a dual-phase PET scan, at the discretion of the primary investigator and the treating neuro-oncologists. Asymptomatic radiation necrosis will be monitored on brain MRI. Symptomatic necrosis will initially be managed with a brief (e.g. three week) course of dexamethasone. If refractory, referral to Neuro-oncology for consideration of bevacizumab and neurosurgery for consideration of resection will be arranged.

12.8.2 Evaluation of the Primary and Secondary Endpoints

All participants who initiate radiotherapy on protocol will be considered "evaluable" and will be included in analyses for feasibility.

Survival, progression-free survival, and quality of life endpoints will be reported separately for participants who complete all prescribed radiotherapy per protocol and for those who do not.

13. REGULATORY CONSIDERATIONS

13.1 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of

the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

1. Dolecek T a, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol. 2012 Nov;14 Suppl 5:v1-49.
2. Andersen AP. Postoperative irradiation of glioblastomas. Results in a randomized series. Acta Radiol Oncol Radiat Phys Biol. 1978;17(6):475–84.
3. Kristiansen K, Hagen S, Kollevold T, Torvik A, Holme I, Nesbakken R, et al. Combined modality therapy of operated astrocytomas grade III and IV. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian Glioblastoma Study Grou. Cancer. 1981 Feb 15;47(4):649–52.
4. Walker MD, Alexander E, Hunt WE, MacCarty CS, Mahaley MS, Mealey J, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. J Neurosurg. 2010 Sep;49(3):333–43.
5. Walker MD, Green SB, Byar DP, Alexander E, Batzdorf U, Brooks WH, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med. 1980 Dec 4;303(23):1323–9.
6. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005 Mar 10;352(10):987–96.
7. Grossman SA, Ye X, Piantadosi S, Desideri S, Nabors LB, Rosenfeld M, et al. Survival of patients with newly diagnosed glioblastoma treated with radiation and temozolomide in research studies in the United States. Clin Cancer Res. 2010 Apr 15;16(8):2443–9.
8. Wong ET, Hess KR, Gleason MJ, Jaeckle KA, Kyritsis AP, Prados MD, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol. 1999 Aug;17(8):2572–8.
9. Carson KA, Grossman SA, Fisher JD, Shaw EG. Prognostic Factors for Survival in Adult Patients With Recurrent Glioma Enrolled Onto the New Approaches to Brain Tumor Therapy CNS Consortium Phase I and II Clinical Trials. J Clin Oncol. 2007 Jun 20;25(18):2601–6.
10. Fogh SE, Andrews DW, Glass J, Curran W, Glass C, Champ C, et al. Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. J Clin Oncol. 2010 Jun 20;28(18):3048–53.
11. Tsien C, Razier J, Zhang P, Dicker AP, Matuszak M. Randomized Phase II Trial of Concurrent Bevacizumab and Re-Irradiation Versus Bevacizumab Alone As Treatment for Recurrent Glioblastoma. 2015.
12. Minniti G, Amelio D, Amichetti M, Salvati M, Muni R, Bozzao A, et al. Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide. Radiother Oncol. 2010 Dec;97(3):377–81.
13. McDonald MW, Shu H-KG, Curran WJ, Crocker IR. Pattern of failure after limited margin radiotherapy and temozolomide for glioblastoma. Int J Radiat Oncol Biol Phys. 2011 Jan 1;79(1):130–6.
14. Milano MT, Okunieff P, Donatello RS, Mohile NA, Sul J, Walter KA, et al. Patterns and

timing of recurrence after temozolomide-based chemoradiation for glioblastoma. Int J Radiat Oncol Biol Phys. 2010 Nov 15;78(4):1147–55.
15. Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol. 2013 Nov 10;31(32):4085–91.
16. Ogura K, Mizowaki T, Arakawa Y, Ogura M, Sakanaka K, Miyamoto S, et al. Initial and cumulative recurrence patterns of glioblastoma after temozolomide-based chemoradiotherapy and salvage treatment: a retrospective cohort study in a single institution. Radiat Oncol. 2013 Apr 23;8(1):97.
17. Chan JL, Lee SW, Fraass BA, Normolle DP, Greenberg HS, Junck LR, et al. Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. J Clin Oncol. 2002;20(6):1635–42.
18. Gebhardt BJ, Dobelbower MC, Ennis WH, Bag AK, Markert JM, Fiveash JB. Patterns of failure for glioblastoma multiforme following limited-margin radiation and concurrent temozolomide. Radiat Oncol. BioMed Central; 2014 Jun 6;9:130.
19. Bleehen NM, Stenning SP. A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. The Medical Research Council Brain Tumour Working Party. Br J Cancer. 1991 Oct;64(4):769–74.
20. Nelson DF, Diener-West M, Horton J, Chang CH, Schoenfeld D, Nelson JS. Combined modality approach to treatment of malignant gliomas--re-evaluation of RTOG 7401/ECOG 1374 with long-term follow-up: a joint study of the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group. NCI Monogr. 1988;(6):279–84.
21. Lee SW, Fraass BA, Marsh LH, Herbort K, Gebarski SS, Martel MK, et al. Patterns of failure following high-dose 3-D conformal radiotherapy for high-grade astrocytomas: a quantitative dosimetric study. Int J Radiat Oncol Biol Phys. 1999 Jan 1;43(1):79–88.
22. Souhami L, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. Int J Radiat Oncol Biol Phys. 2004 Nov 1;60(3):853–60.
23. Selker RG, Shapiro WR, Burger P, Blackwood MS, Arena VC, Gilder JC, et al. The Brain Tumor Cooperative Group NIH Trial 87-01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. Neurosurgery. 2002 Aug;51(2):343-55-7.
24. Hall E, Giaccia A. Radiobiology for the Radiologist. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.
25. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. Br J Radiol. 1985 Jun;58(690):515–28.
26. Fowler JF. 21 years of biologically effective dose. Br J Radiol. 2010 Jul;83(991):554–68.
27. Gupta T, Dinshaw K. Modified optimal fractionation for poor prognosis malignant gliomas: An elusive search. Acta Oncol (Madr). 2005 Mar 8;44(2):105–13.
28. Badri H, Pitter K, Holland EC, Michor F, Leder K. Optimization of radiation dosing schedules for proneural glioblastoma. J Math Biol. Springer Berlin Heidelberg; 2016;72(5):1301–36.
29. Leder K, Pitter K, Laplant Q, Hambardzumyan D, Ross BD, Chan TA, et al. Mathematical

modeling of PDGF-driven glioblastoma reveals optimized radiation dosing schedules. Cell. 2014 Jan 30;156(3):603–16.

30. Pallini R, Ricci-Vitiani L, Montano N, Mollinari C, Biffoni M, Cenci T, et al. Expression of the stem cell marker CD133 in recurrent glioblastoma and its value for prognosis. Cancer. 2011 Jan 1;117(1):162–74.
31. Beauchesne P, Bernier V, Carnin C, Taillandier L, Djabri M, Martin L, et al. Prolonged survival for patients with newly diagnosed, inoperable glioblastoma with 3-times daily ultrafractionated radiation therapy. Neuro Oncol. Oxford University Press; 2010 Jun 1;12(6):595–602.
32. Beauchesne P, Bernier V, Carnin C, Taillandier L, Djabri M, Martin L, et al. Prolonged survival for patients with newly diagnosed, inoperable glioblastoma with 3-times daily ultrafractionated radiation therapy. Neuro Oncol. 2010 Jun 1;12(6):595–602.
33. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010 Apr 10;28(11):1963–72.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B M. D. ANDERSON SYMPTOM INVENTORY – BRAIN TUMOR SURVEY

M. D. Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern** (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your daily life

Symptoms frequently interfere with how well we can function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○