Pilot Study of ^{18}F-FLT-PET Imaging of the Brain in Patients with Metastatic Breast Cancer to the Brain Treated with Whole Brain Radiation Therapy: Comparison with MR Imaging of the Brain

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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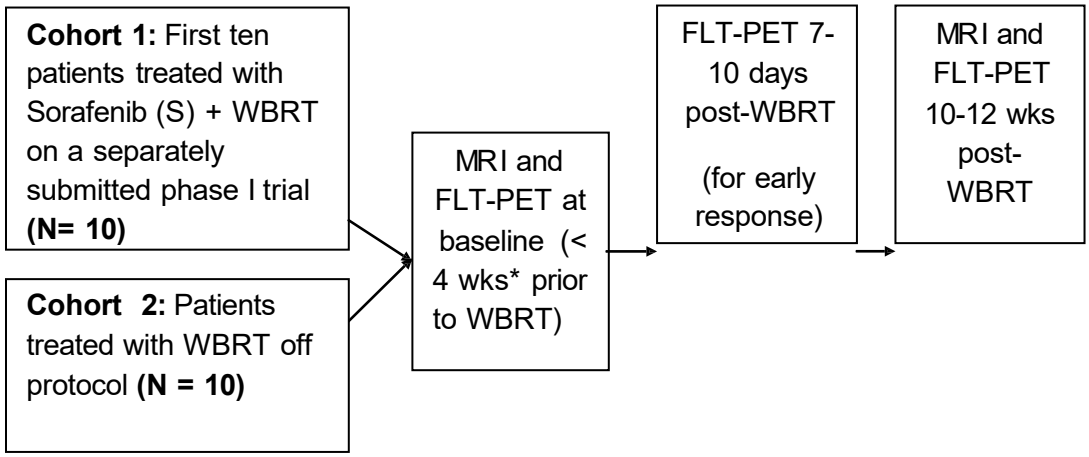
Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

We will perform a pilot study of serial [^{18}F] 3'-deoxy-3'-fluorothymidine (FLT) PET imaging of the brain at baseline (less than 4 weeks of initiation of WBRT), up to 7-10 days post-treatment and 10-12 weeks after treatment in patients with metastatic breast cancer to the brain (N=20) treated with standard whole brain radiotherapy (WBRT) with or without sorafenib to evaluate the radiographic response to WBRT and sorafenib. We will examine if FLT- PET imaging can be used to determine early treatment response to sorafenib. Lastly, we will also assess whether FLT can distinguish residual viable tumor from inflammation or radionecrosis. This exploratory study will include two cohorts with 10 patients each. Cohort 1 will include the first ten patients treated with WBRT concomitantly with sorafenib (The first 10 patients on Dr. Seidman"s Phase I "Whole Brain Radiotherapy (WBRT) with Sorafenib for Breast Cancer Brain Metastases (BCBM): A Phase I Study" will also be enrolled concurrently on this trial). Cohort 2 will include patients treated with standard WBRT alone. Patients in both cohorts will also be assessed with standard non-invasive MRI imaging of the brain in addition to [^{18}F] FLT PET at baseline and then 10-12 weeks after completion of WBRT. MR imaging will include T1 perfusion sequence (DCE- Dynamic Contrast enhanced Perfusion MR) images. Patients will later be followed with MR imaging of the brain every 3 months (+/- 7 days) during the first year, every 6 months (+/- 7 days) thereafter until CNS progression or death. FLT PET is considered investigational, and thus these scans will be performed under an FDA-approved Investigational New Drug (IND) application. The results of the FLT scans will have no impact on patient management. On 3/26/2009 an IND (#104742) was approved for the fluorothymidine (FLT). We will cross file this IND for the use of FLT in this protocol.

Schema:



* MRI will be done within one week before FLT PET scan

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective: The primary objectives of this study are as follows:

1) To examine the radiographic response to WBRT by FLT-PET and MRI for each cohort of 10 patients separately.
2) To examine and quantify changes in response as assessed by serial FLT PET images taken over the course of treatment for each cohort of 10 patients separately.

Secondary Objectives: The secondary objectives of this study are as follows:

1) To correlate treatment response as measured by FLT-PET with response assessment based on MRI of the brain in all patients and assess duration of response (i.e., CNS progression-free survival) during follow-up with MR imaging.

Exploratory Objective: The exploratory objectives of this study are as follows:

1) To correlate the ability of FLT-PET and MRI of the brain imaging to differentiate viable tumor, inflammation and necrosis with surgical resection specimens (if available) obtained in patients with a medical indication for craniotomy.

3.0 BACKGROUND AND RATIONALE

3.1 Brain metastasis from breast cancer

Brain metastasis affects 10-30% of women with metastatic breast cancer depending on subtype of breast cancer. The incidence of brain metastases appears to be rising as a result of superior imaging modalities, earlier detection, and more effective treatment of systemic disease. Survival remains poor despite treatment modalities like surgical resection and whole brain radiotherapy (WBRT). Prognosis depends largely on brain metastases recursive partitioning analysis (RPA) of Radiation Therapy Oncology Group prognostic class I to III (Table 1) [1,2] and biologic subtypes (Table 2) [3-5]. Effective treatment of brain metastases in these patients remains an unmet medical need.

Table 1: Recursive Partitioning Analysis (RPA) for patients with breast cancer brain metastases

RPA Class	Description	Median survival
I	Age <65 KPS ≥70 Controlled primary site, AND … Absence of extracranial metastases.	7.1 months
II	KPS ≥70, and one of the following … Age ≥65 Uncontrolled or synchronous primary, OR … Presence of non-CNS metastases	4.2 months
III	KPS <70	2.3 months

Table 2. Prognosis by histologic subtypes

Subtype	PFS	OS
ER + [3,4]	4-6	6-7
HER-2 + [3,4]	12	10-22
Triple Negative (ER, PR and HER-2 negative) [3-5]	3.7	5

3.2 Treatment of brain metastases

Therapeutic approaches to brain metastases include surgery, WBRT, stereotactic radiosurgery, chemotherapy and more recently novel molecularly targeted therapy. Sorafenib is an oral anti vascular endothelial growth factor (VEGF) and multi- tyrosine kinase inhibitor with demonstrated safety and activity in various tumor types including breast cancer [6]. VEGF TKI have the potential for increased CNS penetration compared to VEGF monoclonal antibodies and recently, long lasting successful cerebral response of sorafenib has been reported in brain metastases [7].

3.3 Sorafenib and cranial radiation in the treatment of brain metastases

In preclinical models, radiation treatment followed sequentially by sorafenib was found to be associated with delay in tumor growth [8]. Sorafenib has been given safely with concurrent cranial radiation for brain metastases [9]. Ongoing studies are further evaluating the feasibility and activity of tyrosine kinase inhibitors in combination with cranial radiotherapy. We are currently conducting an open label phase I, standard 3+3 design, trial of sorafenib given concurrently with WBRT for patients with metastatic breast cancer to the brain. The first ten patients from this trial will have to agree and be enrolled on this study in addition to patients who receive standard WBRT for treatment of brain metastases from breast cancer.

3.4 [^{18}F] FLT PET imaging

3'-deoxy-3'-[^{18}F] fluorothymidine ([^{18}F] FLT) is a new PET radiotracer that can be used to assess tumor cell proliferation [10]. FLT is a thymidine analog that tracks the salvage pathway of DNA synthesis, becoming phosphorylated by thymidine kinase 1 (TK1). FLT differs from thymidine in that it does not become incorporated into DNA; however phosphorylation by TK1 traps in the cell. TK-1 activity is up-regulated in cells entering the S-phase, whereas the protein is nearly undetectable in growth arrested cells. Thus, the uptake of FLT correlates with thymidine uptake, thymidine kinase activity, and the percentage of cells in S-phase. It can therefore be used to image and measure tumor proliferation in cells that predominantly use the salvage pathway.

Shields et al [11] published the first human studies using FLT-PET in a patient with non–small cell lung cancer, demonstrating the high image quality and low background afforded by FLT. Good images were obtained from injection of 5 mCi or less of FLT, and imaging stable

uptake was noted at around 45 to 60 minutes after injection. Recently, dosimetry date for FLT have been published [12], showing that patient imaging is feasible with clinically acceptable radiation exposure for the subject. This is a critical issue for FLT because it is likely to be used in clinical applications that require repeated studies to measure response to therapy. These studies paved the way for a series of pilot studies examining FLT-PET imaging for a variety of tumors. We elected to use an activity of up to 10 mCi per injection for the proposed dynamic imaging studies, based on dosimetry estimates (see section 11.2)

3.4.1 [^{18}F] FLT PET imaging to image cellular proliferation and treatment response

Preclinical studies have identified the potential of FLT as a PET imaging agent for cellular proliferation. Cellular proliferation has a number of potential advantages over imaging with FDG-PET, particularly the low background activity of normal brain tissue in contrast to the high FDG uptake (glucose utilization) by normal brain tissue. In addition, FLT is expected to be more specific to malignant processes since high glucose metabolism, measured by FDG PET, is also seen in a variety of benign conditions, including inflammation and tissue healing. Changes in cellular proliferation occur early in response to treatment and proliferation imaging likely provides an earlier and more definitive assessment of response than imaging with FDG, which can be compounded by a variety of issues, including cellular repair. In the case of cytostatic agents, which stop cell division but not necessarily lead to cell death, tumor proliferation declines, but tumor energy metabolism may not change. All these considerations provide an impetus for PET cellular proliferation imaging, especially as a tool for measuring early response [13].

Although preclinical models demonstrate the potential utility of FLT-PET for measuring therapeutic response, limited data are available for this use in humans. Preliminary studies used FLT to monitor neoadjuvant breast cancer treatment and showed that FLT could measure changes early in the course of treatment [14]. Our own ongoing studies in large cell lymphoma confirm this. The appropriate clinical application of FLT is for characterizing known tumors and assessing their response to treatment through serial imaging studies.

Most early series focused on testing the feasibility of FLT-PET imaging and comparing FLT uptake with in vitro measures of tumor proliferation, typically the Ki-67 (MIB-1) index. Some studies also compared FLT-PET with FDG-PET, given the established clinical role of FDG for staging in the tumor types studied. Studies have shown good correlation between FLT uptake and the Ki-67 index for a variety of tumors [15, 16]. In cases where FDG-PET was also performed, the correlation for FLT uptake versus Ki-67 index was much better than the correlation for FDG uptake versus Ki-67. In one study, when FLT-PET was compared side to side with FDG-PET in 25 patients with newly diagnosed or previously treated gliomas, it was found that FLT- PET was more sensitive to FDG-PET to image recurrent high-grade gliomas, correlated better with Ki-67 values and was a more powerful predictor of tumor progression and survival [17].

[^{18}F] FLT PET imaging of the brain has been used by the University of Washington, Wayne State University, UCLA, MSKCC, and others to image proliferation.

3.4.2 [^{18}F] FLT PET imaging and MR imaging of the brain

It is difficult to distinguish between genuine tumor progression and radionecrosis using conventional gadolinium MRI imaging or FDG-PET imaging of the brain [18 - 20]. To enable improved discrimination of radionecrosis versus progression of disease, fluoro-L-thymidine (FLT)-PET imaging may be useful as it allows for a noninvasive assessment of cell proliferation in vivo, a key feature of malignancy.

3.5 Rationale for this study

Despite the treatment advances in the treatment of brain metastases, prognosis remains poor and there are no specific biomarkers available to predict response of brain metastases to available therapies. FLT-PET has been used as an imaging biomarker in patients with brain tumors to predict response to anti-angiogenic therapy. This was achieved by performing serial FLT PET imaging [21].

Following WBRT, patients often progress clinically or on MR imaging. Furthermore, radiation necrosis, a well-known phenomenon can complicate cranial radiotherapy and patients could decline quickly, often not because of disease progression in the brain, but as a result of mass effect and edema caused by necrosis [22]. Also, there is a suggestion that targeting VEGF can reduce radionecrosis by decreasing capillary leakage and the associated brain edema [23, 24] as well as potentiate the antitumor effects of external beam radiotherapy [17]. A small randomized controlled trial has shown benefit of antiangiogenic therapy for established radionecrosis [Grommes *et al. Proceedings of AAN;* 2010]. This however has not been confirmed in a well-powered randomized trial. As an antiangiogenic agent, sorafenib could potentially reduce complications of cranial radiation such as increased edema and radionecrosis. We therefore aim to explore the effect of sorafenib on the development of suspected or proven radionecrosis.

Our hypothesis is that FLT-PET will be a more accurate non-invasive biomarker than MRI in patients with metastatic breast cancer with metastases to the brain treated with WBRT with or without sorafenib. This is expected based on the higher specificity of FLT for viable residual disease. The hypothesis will be tested by having patients undergo

FLT PET and MR at baseline, FLT PET within 7-10 days after radiotherapy (for early response assessment) and again dual imaging at 10-12 weeks post WBRT.

3.6 Analysis of surgical specimen

Comparing FLT PET findings with tissue analysis will enable us to determine if imaging results are concordant with histological findings and thus allow for confirmation of this hypothesis. In this manner, we propose to generate a bridge between tissue analysis and FLT-PET brain imaging studies. For patients needing to undergo craniotomy for resection of a brain metastasis after WBRT, tissue findings (radionecrosis versus viable tumor) will be correlated with radiologic assessment in an exploratory manner.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

We will perform a pilot study of serial FLT-PET imaging of the brain at baseline (< 4 weeks prior to initiation of WBRT), up to 7-10 days post-WBRT and 10-12 weeks after WBRT in patients with metastatic breast cancer to the brain (N=20) treated with WBRT with or without sorafenib. We will assess and quantify the radiographic response of WBRT, measure the impact of sorafenib on radiographic response, determine early treatment response and distinguish tumor progression from radionecrosis.

This exploratory study will include two cohorts with 10 patients each. Cohort 1 will include the first ten patients treated with WBRT concomitantly with sorafenib (on a separate phase I trial). Cohort 2 will include patients treated with standard WBRT alone. Patients in both these cohorts will also be assessed with standard non-invasive MRI in addition to [^{18}F] FLT PET at baseline (< 4 weeks of WBRT) and 10-12 weeks after completion of WBRT. Patients will later be followed with MR imaging of the brain every 3 months (+/- 7 days) during the first year, every 6 months (+/- 7 days) thereafter until CNS progression or death. These follow-up scan time-points are considered standard of care. Of note, patients with a negative FLT-PET at baseline will be taken off study.

Tissue from patients who have medical indication for craniotomy and have a signed consent will be assessed for radiation necrosis and these findings will be correlated with the imaging studies and treatment (Section 9.3).

4.3 Intervention

All patients will be imaged using FLT-PET scans at baseline (within 4 weeks of initiation of WBRT), 7-10 days after completion of WBRT and then 10-12 weeks after WBRT.

Patients will also be evaluated with MRI imaging at baseline and then 10-12 weeks after WBRT.

Patients will be followed with MRI every 3 months (+/- 7 days) for the first year and then every 6 months (+/- 7 days) thereafter which is the standard of care.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

[^{18}F] FLT

The radiotracer, ^{18}F-FLT, has been synthesized by the MSKCC cyclotron facility for approximately two years, and has been used in humans in this and other institutions in this country and Europe. The primary source of the FLT will be the MSKCC cyclotron facility; however, alternative commercial sources are available to ensure consistent supply of FLT. If a commercial supplier of FLT is used for a particular study (such as Cardinal Health), the supplier will be required to meet all of the acceptance criteria outlined in the FDA-approved MSKCC FLT IND (#104742) prior to administration. The FLT will be tested to ensure radiochemical purity is > 95% and for pyrogenicity.

FLT will be administered as part of an FDA-approved IND application, based on dosimetry estimates (see section 8.2). Whereas the primary source of the FLT will be the MSKCC cyclotron facility, alternative commercial sources are available and used provided that supplier meet all of the acceptance criteria outlined in the FDA-approved MSKCC FLT IND (#104742) prior to administration.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Histologically-confirmed (confirmation done at MSKCC) metastatic adenocarcinoma of the breast
- Radiologic evidence of new and/or progressive brain metastases (≥10 mm in longest dimension) by MRI imaging of the Brain
- Planned WBRT based on number (≥ 3 lesions) and/or size (≥ 1 cm) of brain metastases.
- Age ≥18 years; males and females
- Patients who require additional clinically indicated stereotactic radiosurgery (SRS) in addition to WBRT will also be eligible.
- Life expectancy of >12 weeks.
- Karnofsky Performance Status (KPS) ≥ 70%.
- Creatinine ≤2.0 times the upper limit of normal.
- Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to enrollment, must be non-lactating and must agree to use adequate contraception prior to enrollment and for the duration of study participation.
- No limit to prior therapies with last anti-cancer treatment ≥2 weeks from initiation of WBRT. Please note: there is no washout period required for trastuzumab, pertuzumab for patients who have developed new parenchymal brain metastases while on these agents.

6.3 Subject Exclusion Criteria

- Leptomeningeal metastases. Please note: leptomeningeal metastases may be allowed if it is limited to cranial metastasis (MRI spine should be completed, within 4 weeks of enrollment, to show that no other leptomeningeal metastases is present) and is not the only metastasis present in the brain.
- Concurrent administration of lapatinib or other tyrosine kinase inhibitors other than sorafenib
- Craniotomy or any other major surgery, open biopsy, or significant traumatic injury within 4 weeks of randomization.
- Concurrent anti-cancer therapy (chemotherapy, hormonal therapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than sorafenib, and protocol-specified whole-brain radiotherapy.
- Use of any investigational drug within 30 days or 5 half-lives, whichever is longer, preceding enrollment.
- Inability to comply with protocol and /or not willing or not available for follow-up assessments.

- Any condition which in the investigator"s opinion makes the patient unsuitable for the study participation.
- Patient is incontinent of urine or stool (which would make them unable to tolerate lying still for 60 minutes).
- Claustrophobia
- Known allergic reaction to Gd-DTPA
- Renal insufficiency with recent (<3 month old) creatinine >2.0
- Any contraindication to MRI (e.g., pacemaker, aneurysm clip, tissue expander)

7.1 RECRUITMENT PLAN

Recruitment of patients will be through the participating investigators from the Breast Service and referrals from staff physicians at Memorial Hospital. Patients could be identified through clinic lists. A detailed description of the study procedures will be provided to each referring physician and a simpler version to each patient by the principal investigator or one of the investigators of this research proposal.

Patients will be required to sign a statement of informed consent that meets the requirements of the code of Federal Regulations (Federal register Vol.46, No. 17, Jan.27, 1981, part 50) and the IRB of this center. The medical record will include a statement that written informed consent was obtained (and document in the record the date written consent was obtained before) and the patient is enrolled in the study.

All patients who meet the above inclusion and exclusion criteria will be invited to participate in the study by their primary oncologist. Study Investigators will invite men and women and all minorities on an equal basis as they present to their oncologist during routine cancer care visits. Consenting professionals will meet the patients and obtain informed consent.

It is important to note that the first ten patients on cohort 1 on this protocol would have agreed to and signed informed consent for a separate but simultaneous phase I trial of sorafenib with WBRT. This protocol is currently undergoing the IRB review process simultaneously.

8.0 PRETREATMENT EVALUATION

- MR Brain will be obtained within 4 weeks prior to initiation of WBRT to ensure evidence of new/progressive brain metastases. MR imaging will include images before and after the administration of gadolinium-diethylenetriamine - pentaacetic acid (Gd-DTPA).
- FLT-PET will be obtained within 4 weeks prior to initiation of WBRT and within 2 weeks of the MR Brain.History and physical Examination within 1 week prior to initiation of WBRT.
- Patients will also undergo CBC, comprehensive metabolic panel within 1 week prior to initiation of WBRT.
- Women with childbearing potential will also undergo a serum pregnancy test. See Appendix A for study calendar.

9.1 TREATMENT/INTERVENTION PLAN

9.2 FLT PET

Twenty patients will receive an injection of up to 10 mCi of FLT, followed by FLT PET scan and a blood draw for pharmacokinetic analysis. These twenty patients will also be imaged using MR before and after the administration of gadolinium- diethylenetriamine-pentaacetic acid (Gd-DTPA).

9.2.1 Patient Preparation for FLT PET

No specific dietary restrictions or hydration are required for FLT PET scans, however, patients will be urged to drink plenty of water before and after the PET studies. [^{18}F]FLT will be prepared under RDRC guidelines by the MSK Radiochemistry Core and assessed for quality control following "good manufacturing practice" criteria. The radiopharmaceutical will immediately be brought to the Nuclear Medicine Radiopharmacy for dispensation in the PET suite. Patients will receive up to 370 MBq (10 mCi) [^{18}F]-FLT by intravenous infusion.

9.2.2 FLT PET scanning

Following scout view, a low dose CT (80mA) of the brain will be obtained for an anatomic localization and attenuation correction. Following intravenous injection of [^{18}F] FLT, dynamic PET emission data of the brain will be obtained for up to 60 min to obtain kinetic information on tumor uptake for modeling. Image acquisition shall start immediately after injection using the following sequence: 4 frames of 15 seconds, 4 frames of 30sec, 7 frames of 1-minute, then 10 frames of 5-minutes, i.e. for a full scan duration of 60-minutes. After the 60 minutes dynamic scan, if the patient is capable and willing, an additional 10 minute static acquisition will be acquired at 90 minutes. Dynamic FLT scans will be using standard clinical protocol. Patients may take a break and get off the table, for instance for bathroom break before the additional 10 minute static acquisition.

FLT PET scans will be obtained at baseline (within 4 weeks of WBRT and within 2 week after MR imaging), 7-10 days after WBRT and 10-12 weeks after WBRT.

9.3 MR imaging of the brain

MR imaging before and after the administration of gadolinium-diethylenetriamine-pentaacetic acid (Gd-DTPA) will be obtained within 2 weeks of the PET scan. All baseline imaging scans (FLT-PET and MR Brain) will be obtained within 4 weeks prior to initiation of WBRT. MR imaging will be repeated 10-12 weeks after WBRT. MR imaging during the follow-up scan only will include the T1-Perfusion sequence (DCE) images.

FLT-PET scans are the research scans and MR imaging is considered standard of care.

9.4 Tissue Analysis

For patients who need to undergo a craniotomy for resection of a brain metastases after WBRT, tissue findings (radionecrosis versus viable tumor) will be correlated with radiologic assessment in an exploratory manner.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 FLT PET

Schema illustrating the duration of FLT scans and the time-point for the blood draw

Intervention	Low dose CT	FLT PET Dynamic Scan for 60 min	FLT PET 10 min Static scan (optional) at 90 min
Low Dose CT	X		
[^{18}F] FLT injection[1]		X	X
Blood Draw[2]		X	

[1] A low-dose CT will be obtained following scout view. After 10 mCi of [^{18}F] FLT infusion, dynamic FLT scans will be obtained for 60 min. If the patient agrees then static scans will be obtained at 90 min and will last for 10 min.

[2] One blood draw will be done 60 min (+ 10 min window) after the FLT injection.

10.1.1 Blood Samples during FLT PET

A venous catheter will be placed in a superficial hand or arm vein for administration of the radiopharmaceuticals. A second venous catheter will be placed in the opposite hand or arm for venous blood sampling. If a central venous catheter is present, it will be used for blood sampling or radiopharmaceutical administration, and only a single venous catheter will be placed. All catheters will be removed at the end of the day. One 3 ml venous blood samples will be drawn in a green top tube 60 minutes (+ 10 min window) post-radiopharmaceutical injection from a vein in the arm opposite that used to inject the radiopharmaceutical by research staff. [^{18}F] radioactivity in the [^{18}F] FLT blood/plasma sample will be measured by research staff.

10.1.2 FLT PHARMACOKINETIC ANALYSIS

Pharmacokinetic modeling will be done on a voxel-wise basis across the entire segmented tumor. This kinetic modeling algorithm will compute voxel-wise parameter estimates of the compartmental model parameters (K1, k2, k3, and k4) defining tracer exchange between the blood and tumor tissue compartments, as well as Vb, the intravascular blood volume fraction, which will be estimated as a fifth parameter. Parametric maps will then be determined using the estimated proliferation rate constant

(k3) values that, for kinetic FLT PET data, are expected to reflect the spatial distribution of rates of cellular proliferation. A composite parameter, Ki (K1k3/(k2+k3) estimating the irreversible uptake of FLT at equilibrium, will also be evaluated due to its decreased sensitivity to noise and robustness as a measure of irreversible uptake. The information derived from these analyses will not be used for treatment planning, but shall retrospectively be used in the assessment of treatment response. Non-invasive input functions will be obtained from the image data using regions of interest of the superior sagittal sinus. These measurements will be compared with arterial blood activity-concentrations from an image containing the internal carotid artery and will be calibrated using the measurement of a single intravenous blood sample acquired at one post-injection time point.

The utility of static (SUV) versus parametric measures derived from compartmental analysis (i.e., k3 and Ki) of ^{18}F-FLT PET represent different approaches. The SUV metric provides a simple measure of the amount of FLT within the defined region of interest at a specific time e.g. 60-minues post injection. This metric is rapidly obtained and has become the main reporting metric used in FDG PET studies assessing treatment response.

However, when response metrics are sought following aggressive therapies that may significantly impact upon radiotracer delivery to the tumor, such as following high dose radiotherapy or the use of anti-angiogenic agents, compartmental analysis may offer the advantage in that such approaches estimate the rate of tracer entrapment accounting for the radiotracer input function.

To summarize, patient assessment and evaluation will be based on voxel-wise and region of interest (ROI) measurements of the tumor. The tumor will be identified on the CT image of the PET/CT. Standardized uptake values (SUVs) will be estimated from the late time frames of the study. Kinetic rate constants (K1 - k4) and the composite parameter Ki will be estimated from the dynamic data. These measurements will be made on both an ROI and voxel-wise basis. Input functions necessary for the kinetic modeling will be made from the either the sagittal sinus or the carotid artery. Measures from both imaging methods (static SUV and parametric measures) will be used in analyses.

10.2 MR Imaging

MR imaging will be done as routine before and after Gd-DTPA.

The time-points of FLTPET and MR Imaging for this study are shown in the study calendar below:

Study Calendar

Tests	Screening (within 4 weeks of WBRT)	7-10 days after WBRT	10-12 weeks after WBRT
MRI Brain*	X		X
FLT-PET*	X	X	X

*MRI and FLT-PET will all be done within 4 weeks prior to initiation of WBRT. MRI will be done within 2 weeks of the FLT-PET scan. MR imaging during the follow-up scan only will also include T1-perfusion images (DCE).

11.0 TOXICITIES/SIDE EFFECTS

The PET scan has no known or expected side-effects. The radiotracer drug, FLT, has been given to patients in other studies and no side effects have been reported. However, in the unlikely event that an adverse reaction (such as an allergic reaction) to the radiopharmaceutical occurs, the results will be documented and reported by the Principal Investigator to the Institutional Review Board Chairman and IND Committee. Patients could experience claustrophobia due to the MRI scanner. If they have difficulty tolerationg the study, it will be stopped. THE PET/CT scanner is not confining like the MRI scanner. Additionally, patients are advised not to become preganant or father a baby while on this study. Women should also not breastfeed the baby. Patients will be required to use birth control while on study. Very rarely, patients can develop nephrogenic systemic fibrosis which has been correlated with the use of gadolinium based contrast material used during the MRI scans.

Placement of a catheter for infusion of ^{18}F-FLT and blood samples may cause pain, bruising, itching, infections and venous scarring. Standard medical care will be used to minimize these risks.

11.1 PET SCANNING

Potential risks to the patient are small and present more of an inconvenience (multiple scans on consecutive days). The PET has a large bore to accommodate the whole body and the environment is much less confining than the head cage of a MR tomograph.

11.2 DOSIMETRY

Table 1. F18-Fluorothymidine (FLT) Patient Dosimetry

					Absorbed Dose			
					1 FLT *PET-CT* scans			TOTAL for
					0.9	CT rads		3*0.9
		F18-FLT[2]			10 mCi F18-FLT			3 FLT *PET-CT* scans
Target Organ		rad/mCi	rad/10 mCi		rad	-	-	rad
Adrenals		0.0766	0.77		1.67			5.00

Bone Surfaces		0.0585	0.58		1.48			4.45
Brain		0.0125	0.13		1.03			3.08
Breasts		0.0310	0.31		1.21			3.63
Gall Bladder Wall		0.0625	0.63		1.53			4.58
Heart Wall		0.0618	0.62		1.52			4.55
Kidneys		0.132	1.32		2.22			6.65
Large Intestine - Lower Wall		0.0168	0.17		1.07			3.21
Large Intestine - Upper Wall		0.0459	0.46		1.36			4.08
Lens of Eye		0.0389	0.39		1.29			3.87
Liver		0.1680	1.68		2.58			7.74
Lungs		0.0374	0.37		1.27			3.82
Muscle / Other tissue		0.0622	0.62		1.52			4.56
Pancreas		0.0851	0.85		1.75			5.25
Red Marrow		0.0888	0.89		1.79			5.36
Skin		0.0164	0.16		1.06			3.19
Small Intestine		0.0525	0.53		1.43			4.28
Stomach Wall		0.0522	0.52		1.42			4.27
Testes		0.0488	0.49		1.39			4.17
Thyroid		0.0385	0.38		1.28			3.85
Total Body		0.0466	0.47		1.37			4.10
Urinary Bladder Wall								
45-min Voiding Interval		0.0297	0.30		1.20			3.59
1-hr Voiding Interval		0.0396	0.40		1.30			3.89
1.5-hr Voiding Interval		0.0593	0.59		1.49			4.48
2-hr Voiding Interval		0.0791	0.79		1.69			5.07

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

MR Imaging

Response assessment for MR Imaging of the brain during the follow-up period will be done by using Macdonald Criteria [25] as follows:

12.1 Measurable lesion

In the presence of multifocal disease, up to five bi-dimensionally measurable enhancing mass lesions will be followed for objective response. The bidimensional perpendicular measurements for each lesion should always be assessed in the same plane of axis (axial, coronal, sagittal or other). The largest perpendicular diameters of enhancement for each mass lesion will be recorded. Any and all remaining enhancing lesions will be followed as a single site and classified as an evaluable lesion. Objective response of the measurable lesion will be assessed by comparison of the changes in the product of the largest perpendicular measurements of the lesion at each visit. Comparisons of objective assessments for a measurable lesions(s) excluding progressive disease, are based upon major changes in tumor size on the Gd-MRI scan compared to the baseline scan. Determination of progressive disease is based upon comparison to the previous scan with the smallest measurements. Comparisons should always be made with measurements assessed in the same plane of axis (axial, coronal, sagittal or other).

12.2 Evaluable lesion(s)

For multifocal disease, all remaining enhancing tumor lesions, beyond the 5 measurable or any lesions that cannot be measured, will be followed as a single site and classified as an evaluable lesion. For an evaluable lesion(s), comparison of assessments for response designation will be assessed based upon major changes in tumor size on Gd-MRI scan. Comparisons of assessments for evaluable lesions(s) excluding progressive disease, are based upon major changes in tumor size on Gd-MRI scan compared to the baseline scan. Determination of progressive disease is based upon comparison to the previous scan with the smallest amount of evaluable tumor. Tumors may be classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

A complete response will always be disappearance of all enhancing tumor. Progressive disease will always include any new enhancing tumor.

12.3 Criteria for current objective status

At each tumor assessment visit the current objective status is determined. This takes into account measurable and evaluable lesion(s). Comparisons of assessments for measurable and evaluable lesions, excluding progressive disease, are based upon major changes in tumor size on Gd-MRI scan compared to the baseline scan. The assessment is adapted from Macdonald et al. Determination of progressive disease is based upon comparison to the previous scan with the smallest measurements. Scan changes are emphasized, but are interpreted in light of steroid use and to a lesser extent, neurological findings. Categories of overall response include:

Complete response (CR): Disappearance of all enhancing tumor on consecutive MRI scans at least one month apart, off steroids and neurologically stable or improved. No new lesions may arise.

Partial response (PR): Greater than or equal to a 50% reduction (< 100%) in the sum of the products of the largest perpendicular diameters of contrast enhancement for measurable lesions and if an evaluable lesion(s) is present at baseline, no worsening for an evaluable lesion(s) on consecutive Gd-MRI scans at least one month apart, steroids stable for 72 hours prior to each scan at the same dose administered at the time of the previous scan or at a reduced dose, and neurologically stable or improved. No new lesions may arise.

Progressive disease (PD): Greater than or equal to a 25% increase in size of the product of the largest perpendicular diameters of contrast enhancement for any measurable lesions or if an evaluable(s) lesion is present at baseline, worsening for an evaluable lesion(s) or any new tumor on Gd-MRI scans or greater than or equal to 25% increase in the unidimensional measurement of the any lesion in an additional plane of axis, steroids are stable for 72 hours prior to each scan at the same dose administered at the time of the previous scan or at an increased dose, with or without neurological progression. The following will also apply:

Unknown (UNK): If any measurable or evaluable lesions have not been assessed or the assessment was made using a technically inferior method compared to baseline, the current objective status is “unknown”, even if the bulk of disease was evaluated. An exception would be if the objective status is PD because either a new lesion was detected, evaluable disease clearly worsened or the remaining lesions classify for a PD even without the lesions which were not assessed, i.e. the sum of all lesions which can still be measured show an increase of more than 25% over the smallest sum of all measurable lesions which were present at baseline.

Stable disease (SD): All other situations.

12.4 Best response

The best response for each patient is determined from the sequence of objective statuses. The terminology for the five categories of objective status is identical to those that describe best response.

12.4.1 Determination of best response

The best response for each patient is determined from the sequence of objective statuses according to the following rules:

CR = at least two determinations of CR a minimum of 4 weeks apart before progression, preceded by lower statuses, or preceded, separated or followed by unknown statuses.

PR = at least two determinations of PR or better a minimum of 4 weeks apart before progression (but not qualifying for CR), preceded by lower statuses, or preceded, separated or followed by UNK statuses.

SD = at least one determination of stable disease or better

PD = a determination of progression in one of the first two assessments

UNK = the status is UNK only if all assessments before progression are UNK.

If there is a defined objective that includes the assessment/measurement of therapeutic response to the defined treatment intervention, then detailed description of the measure, methods to be used (e.g., scales and/or definitions to assess response) and the criteria to determine each level of therapeutic response should be included.

FLT-PET

Response assessment for FLT-PET will be as follows:

SUV max and average (42% threshold) for brain lesions will be measured (for FLT using summed images 45-60min). In addition, we will explore other measures such as metabolic tumor volume. For comparison, activity will also be measured in remote normal cortex and white matter. Tumor - to-normal ratios will be computed. Treatment induced changes in these parameters will be expressed as % decrease in radiotracer uptake. Tentatively, a decline by 25% [26] will be considered significant.

13.0 CRITERIA FOR REMOVAL FROM STUDY

- If the patient has a negative FLT-PET at baseline
- If the patient is no longer able to participate in the protocol and imaging schedule.
- If the patient"s primary physician and the PI consider that further participation in the protocol would not be in the best interest of the patient.
- If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (e.g., a change in diagnosis), the patient will be removed from the study.

14.0 BIOSTATISTICS

This is a small pilot study involving 20 patients with brain metastases from breast cancer. The first cohort will include the first ten patients that are enrolled to a separate but simultaneous phase I study evaluating patients receiving concurrent sorafenib + whole brain radiotherapy (WBXRT). *The goal of the phase I study is to determine the MTD of sorafenib in breast cancer patients with brain metastases receiving WBRT.* Ten additional patients who do not enter the parallel phase I trial and receive WBXRT without sorafenib, will be consented to this imaging study. Both cohorts have the same eligibility criteria.

The first ten patients recruited into the Phase I trial of sorafenib + whole brain radiotherapy will have to agree to consent to the FLT-PET imaging study. The cohort receiving WBRT alone will be recruited independently.

The primary objective of this study is to examine radiographic response to WBRT by two modalities: FLT-PET and MRI. MRI is considered standard of care and response assessments are recorded as

CR, PR, PD, SD, and unknown (see section 12.0). FLT–PET response assessments will be recorded as SUV-MAX and a decline by 25% is considered as significant (see Section 12.0). MRI measurements will be recorded at baseline and 10 to 12 weeks post WBRT. FLT-PET measurements will be recorded at baseline, 10 days post WBXRT, and 10-12 weeks post WBXRT.

This is a small pilot study and as such, we are limited in the scope of our analyses by sample size. Data from each modality will be examined descriptively and graphically at baseline and over the course of treatment. Specifically, the distribution of response at baseline and the 10-12 week post WBXRT timepoint as assessed by MRI and FLT-PET will be examined. The median, mean, min and max of SUV max for FLT-PET will be summarized at each timepoint. Significant or nonsignificant change in SUV from baseline to the 10-12 weeks post WBRT timepoint (decline by 25%) will also be calculated and the frequency of patients with significant change will be calculated. These descriptive analyses will be done for each cohort separately. Because FLT-PET can be used to assess early treatment response, SUV values and significant SUV change from baseline to 10 days post WBRT will be examined descriptively.

As written in Section 10.1, FLT-PET imaging provides assessments in addition to SUV. These additional assessments are kinetic rate constants based on a compartmental model. These parameters will also be analyzed using the approach described above (median, mean, min and max summarize at each timepoint for each cohort). .

Based on these analyses, we will explore whether treatment response for the two modalities correlate To compare the two modalities, the proportion of patients with significant change in SUV (FLT-PET) as a dichotomous variable, will be calculated in the following two MRI response groups: CR+PR vs. PD+SD. The McNemar"s test for paired samples will be done to test the agreement of the two modalities. In addition, boxplots of SUV will be graphed for each MRI response category for each cohort. Based on the literature in this patient population, there is a 65-70 percent response rate as per MRI. Median duration of response will be calculated and summarized overall and for each cohort separately.

Any clinical, tissue, or other correlations are entirely exploratory in nature. It is expected that 2 patients will be accrued per month, with accrual for all 20 patients taking approximately 1 year.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria.

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

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

The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

There will be no randomization in this study.

16.1 DATA MANAGEMENT ISSUES

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

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

16.2 Quality Assurance

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

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

16.3 Data and Safety Monitoring

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

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

Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center"s Research Council and Institutional Review Board.

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

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects.

Risks: Potential risks to the patient include pain and discomfort related to phlebotomy and related to time spent undergoing [^{18}F] FLT PET and MR scanning. Specific toxicities and side effects related to [^{18}F] FLT PET imaging and MR imaging including radiation exposure are described in section 11.

Benefits: We do not expect patients to derive any clinical benefit from this clinical trial. We hope in the future that knowledge from this trial will help evaluating treatment response in future patients with metastatic breast cancer to the brain treated with WBRT or WBRT in combination with sorafenib, in better distinguishing tumor progression from radionecrosis.

Alternative, non-protocol options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The financial costs of the study will be discussed; FLT PET scans and blood draw for PK analysis will be done free of charge.

17.2 Privacy

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

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant"s last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject"s initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
  - A explanation of how the AE was handled
  - A description of the subject"s condition
  - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

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

The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

18.1 INFORMED CONSENT PROCEDURES

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

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

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

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

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20.0 APPENDICES

APPENDIX A: Study calendar

APPENDIX B: Performance codes status

APPENDIX A

Study Calendar

Tests	Screening	7-10 days after WBRT	10-12 weeks after WBRT
MRI Brain[1]	X		X
FLT-PET[1]	X	X	X
FLT PK Blood draw[2]	X	X	X
History and Physical examination[3]	X		
CBC, CMP[3]	X		
Pregnancy test[3]	X		

[1]MRI and FLT-PET will all be done within 4 weeks prior to initiation of WBRT. MRI will be done within one week before the FLT-PET scan.

[2] PK Blood draw will be done 60 min (+ 10 min window) after FLT injection

[3] Blood tests will be done within 1 week of initiation of WBRT

APPENDIX B

Description: Karnofsky Scale	**Karnofsky Scale (%)**
No complaints; no evidence of disease. Able to carry on normal activity.	100
Minor signs or symptoms of disease.	90
Some signs or symptoms of disease with effort; cares for self.	80
Unable to carry on normal activity or to do active work.	70
Requires occasional assistance but is able to care for most personal needs.	60
Requires considerable assistance and frequent medical care.	50
Disabled; requires special care and assistance.	40
Severely disabled; hospitalization indicated, although death not imminent.	30
Very sick; hospitalization necessary; requires active support.	20
Moribund; fatal processes progressing rapidly.	10
Dead	0