NCT #: NCT02431572

Protocol #: 14-421

TITLE: A pilot study to evaluate PBR PET as an indicator of inflammation in brain tumor patients treated with chemoradiation or immunotherapy.

Coordinating Center: DF/HCC

***Principal Investigator (PI):** *Elizabeth Gerstner, MD*

Version Date: June 20, 2018

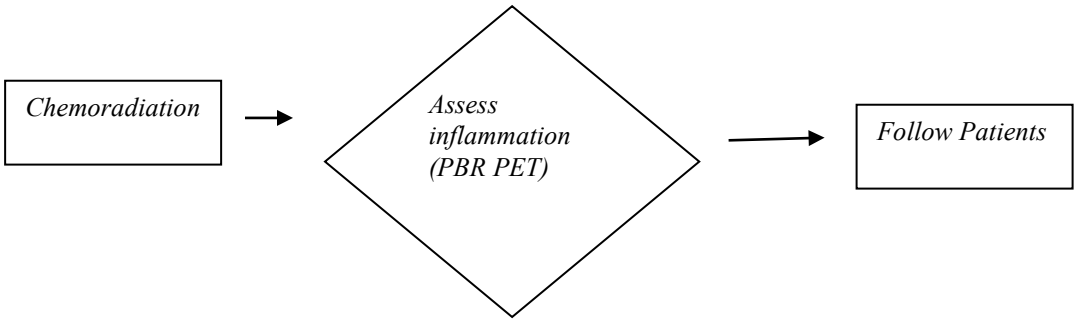
Protocol *A pilot study to evaluate PBR PET as an indicator of inflammation in brain tumor patients treated with chemoradiation or immunotherapy.*

Version Date: June 20, 2018

SCHEMA

Diseases:
Metastatic cancer to the brain (Cohort A)
Primary brain tumors (Cohorts B)

Diseases:
Primary brain tumors (Cohorts C)



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OBJECTIVES

1.1 **Study Design**

This is an imaging pilot study to look at changes in primary and metastatic brain tumor inflammation using PBR PET- a tracer that highlights inflammation. Our goal is to determine if this tracer can be used to detect changes in inflammation during tumor treatment. We will study 3 populations of patients with intracranial tumors: metastatic brain tumor patients treated with immunotherapy, GBM patients undergoing chemoradiation, and GBM patients treated with immunotherapy. PBR PETs will be performed at baseline prior to therapy and then several weeks-months after start of therapy depending on therapy used.

The PET studies will be performed using a simultaneous MR-PET imaging scanner. No diagnostic decisions or therapy decisions will be based on any results obtained from these PET scans, and we expect no change in the care of these patients. The success of these studies should enable methods that could be used in larger studies to more completely understand the role of inflammation in the treatment of cancer.

1.2 **Primary Objectives**

1. To determine whether PET imaging with [11C] PBR28 can measure inflammation related to immunotherapy in patients with brain tumors- specifically metastatic brain tumors and glioblastoma. .

2. To determine whether PET imaging with [11C] PBR28 can measure inflammation related to chemoradiation in patients with glioblastoma.

1.3 **Secondary Objectives**

1. NA

BACKGROUND

2.1 **Study Disease(s)**

An estimated 51,410 primary brain tumors were diagnosed in 2007, and 19% of these tumors were glioblastomas (CBTRUS- Central Brain Tumor Registry of the United States). GBM is the most common malignant primary brain tumor and is a uniformly fatal disease with 5-year survival rates less than 4% despite aggressive treatment with surgery, radiation and chemotherapy. There is no curative therapy for patients with GBM. Current standard of care for patients with newly diagnosed GBM is concomitant involved field radiation and oral temozolomide chemotherapy followed by monthly temozolomide for 6-12 months.[1] If patients

relapse, there is no standard of care treatment. Immunotherapy is increasingly being explored as a tool to improve outcome for these patients.

Metastatic tumors which have spread to the brain are incurable diseases that recently have had modest success with immunotherapy. However, duration of response in the brain is limited for unclear reasons.

2.2 **IND Agent(s)**

2.2.1 *IND Agent #1*

NA

2.2.2 *IND Agent #2*

NA

2.3 ***Other Agent(s)***

NA

2.4 **Rationale**

Cancer immunotherapy is rapidly gaining traction as an effective treatment in some forms of cancer. The last several years have seen FDA approval of active cellular immunotherapy for advanced prostate cancer and immune checkpoint blockade via CTLA-4 inhibition for patients with advanced melanoma. Currently, there is great enthusiasm for PD-1 inhibition (checkpoint blockade) via monoclonal antibodies in patients with solid tumors; phase 2 results have yielded high response rates across a spectrum of cancers with relatively little toxicity. In addition, adoptive T-lymphocyte transfer using ex vivo expanded tumor-infiltrating lymphocytes or chimeric antigen receptors (CAR's) is showing great promise in patients with melanoma and CD19+ leukemia respectively. Also, phase 2 studies have demonstrated convincing activity of immune-based approaches for both metastatic and primary tumors in the central nervous system. For instance, the response rate for intracranial melanoma metastases is roughly equivalent to that of peripheral lesions treated with CTLA-4 blockade, and glioblastoma peptide vaccination and dendritic cell vaccination approaches are currently in randomized phase 3 and phase 2b clinical trials.

Evaluating the impact of immune-based therapies in the short term has been challenging in patients with solid malignancies, including those with brain tumors. Standard imaging evaluation of tumor response, such as the RECIST or RANO criteria, may not accurately reflect what is occurring in the tumor microenvironment during immunotherapy. In essence, contrast-enhancement may reflect therapy-induced inflammation rather than tumor progression. The immunotherapy community has proposed a set of "immune-related response criteria" that may be

more applicable to these patients. However, as these measures require the simultaneous assessment of multiple lesions, they are poorly suited for understanding response in glioblastoma. There is an expanding number of cases of immunotherapy-associated pseudoprogression in which intensely enhancing and space-occupying lesions resolve without other intervention after a few weeks. The ability to distinguish between and inflammatory response and tumor progression (which is characterized by an immunosuppressive environment) is critical for providers. There is, therefore, a need for more specific imaging of immunotherapy-associated inflammation in patients with intracranial tumors.

The 18-kDa translocator protein (TSPO) is a protein that is expressed in mitochondria and is particularly prominently expressed by activated microglia, infiltrating macrophages, and reactive astrocytes. Thus, it is a marker of neuro-inflammation. PET tracers are being developed that bind to this receptor as a means to measure inflammation.[2] One of these tracers, [11C]PBR28, is a second generation PET tracer that binds to TSPO. This tracer has been used in many studies of CNS disease such as cocaine abuse[3], neurocysticercosis[4] depression[5] Alzheimer's disease[6,7] multiple sclerosis[8,9], and seizures[10]. The tracer has also been used in animal models to look at ischemia related inflammation.[11] These studies have shown that this tracer is increased in areas of inflammation in the brain and is safe to use in humans. There are no reported adverse events related to the PBR28 tracer and, in 2014, the Martinos Center manufactured 83 human doses of PBR28 and there were no reports of adverse events related to the doses.

Unfortunately there is little data in human brain tumors so it is unclear if this tracer will be equally useful in this patient population. Conflicting data exists regarding TSPO expression in gliomas. One study in rats using an alternate TSPO binding PET tracer suggested increased uptake in tumors[12] where as another human study showed a lack of TSPO expression in microglial associated with high grade gliomas.[13] The rat study did not specify which cells expressed TSPO. Importantly, these studies were not designed to test the response of human gliomas to treatment or changes in TSPO expression that may occur *during* treatment. Thus, there is a rationale to further study the role of this tracer in human brain tumors to better characterize its utility in measuring inflammation.

One goal with including both glioma patients and metastatic brain tumor patients is to determine if there are differences in PBR28 uptake based on type of cancer which may suggest differences in TSPO expression within different tumor microenvironments and in inflammatory response to treatment. Given the limited data on this tracer in cancer, it may be more useful in one type of cancer rather than another because of the different underlying biology of tumors. There is a high number of patients with metastatic melanoma to the brain and immunotherapy is commonly used for this patient population so we elected to start with this cohort of patients but are now amending the protocol to include all cancer types as there are now immunotherapy options and clinical trials of immunotherapy for more than just melanoma patients.

Thus, we will evaluate [11C]PB28 PET as a tool for measuring inflammation associated with the response to immunotherapy or chemoradiation in patients with brain tumors. Having such a tool that distinguishes active tumor from inflammation will be an incredibly useful tool in the management of patients. If this tracer shows potential utility in this pilot study, we will examine

it further in separate planned phase II glioma vaccination studies at our center, in an effort to correlate PET findings with outcome.

One limitation of PBR PET is that certain people can be classified as low binders because of a genetic polymorphism.[14] These "low binders" have negligible binding to the PBR28 tracer so would not be informative to include in our study and will be excluded. Only about 10% of human subjects are low affinity binders based on prior data.[14] As part of the screening process, after informed consent has been obtained, a simple blood test will be performed to determine binding affinity of consented patients. Those who are low-affinity binders will be not be enrolled.

In summary, we our simple goal is to perform two PBR PETs in patients with metastatic brain cancer undergoing treatment with immunotherapy and one PBR PET in patients with GBM to measure inflammation. This is similar to performing FDG PETs in these patients but uses a different PET tracer than FDG. Since PBR28 was first used at the Martinos Center, there have been 11 clinical trials approved using this tracer and no adverse events reported.

2.5 Correlative Studies Background

In addition to PET imaging, MRI scans will be acquired. MRI is a very useful tool to non-invasively probe tumor response to treatment and is already part of the routine management of patients with GBM. The complicated relationship between tumor perfusion, vascular permeability, and tumor cellularity can be assessed by MRI. Dynamic susceptibility contrast (DSC) and dynamic contrast enhanced (DCE) MRI can measure vascular parameters such as cerebral blood volume (CBV), blood flow, mean transit time, vessel size, and permeability - all of which are impacted by immunotherapy and chemoradiation. These will be exploratory analyses to see if changes in tumor vasculature/cellularity can help interpret changes in PBR uptake.

PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have evidence of metastatic cancer to the brain for Cohort A or histologically confirmed GBM for Cohorts Band C.

3.1.2 Those with GBM but suspected to have pseudoprogression at any time after completion of chemoradiation can enroll in Cohort C.

3.1.3 Participants must have measurable brain disease, defined as at least one lesion that is 10 mm in diameter.

3.1.4 Age > 18 years.

3.1.5 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

3.1.6 Life expectancy of greater than 3 months.

3.1.7 Participants must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– creatinine	within normal institutional limits
	OR
– creatinine clearance	≥55 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.

3.1.8 For Cohort A, only patients with metastatic cancer to the brain for whom their treating physician has planned to give immunotherapy as monotherapy are eligible for this study. This can be in the setting of a clinical trial or not.

3.1.9 For Cohort B, only patients with GBM for whom their treating physician has planned to give immunotherapy are eligible for this study. This can be in the setting of a clinical trial or not.

3.1.10 For Cohort C, patients with GBM who have completed standard temozolomide + radiation and have suspected pseudoprogression can enroll. There is no time frame from completion of chemoradiation as pseudoprogression is increasingly recognized at later time points.

3.1.11 Patient must be able to undergo MRI and PET scans.

3.1.12 Patient must be maintained on a stable corticosteroid regimen for 5 days prior each MR-PET scan.

3.1.13 High or mixed affinity binders (Ala/Ala or Ala/Thr) based on genotyping result from PBR affinity test. This blood test will be performed as part of the screening process after consent has been obtained.

3.1.14 The effects of PBR on the developing human fetus are unknown. For this reason and because radiopharmaceuticals agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Radiopharmaceutical agents are known to be teratogenic.

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

3.2 Exclusion Criteria

3.2.1 History of allergic reactions attributed to compounds of similar chemical or biologic composition to PBR.

3.2.2 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.3 Pregnant women are excluded from this study because PBR is a radiopharmaceutical agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to exposure of the mother to PBR, breastfeeding should be discontinued. These potential risks may also apply to other agents used in this study.

3.2.4 HIV-positive participants are excluded because their immune system is compromised and may affect the interpretation of the imaging data.

3.2.5 Patients who are not suitable to undergo MRI or PET or use gadolinium contrast due to:

- Claustrophobia
- Presence of metallic objects or implanted medical devices in body (i.e. cardiac pacemaker, aneurysm clips, surgical clips, prostheses, artificial hearts, valves with steel parts, metal fragments, shrapnel, tattoos near the eye, or steel implants) The craniotomy patients will all have titanium but this is MRI compatible
- Sickle cell disease
- Renal failure
- Reduced renal function, as determined by creatinine clearance < 30 mL/min based on a serum creatinine level obtained within 28 days prior to registration

3.3 Inclusion of Women and Minorities

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

REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of any imaging. 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 QACT 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. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the QACT registration line at [redacted] and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

  Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for a treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at [redacted]

[redacted]. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

4.3 General Guidelines for Other Investigative Sites

NA

4.4 Registration Process for Other Investigative Sites

NA

5. IMAGING PLAN

5.1 Treatment Regimen

This study does not add any additional treatment to enrolled patients. All treatment decisions will be at the discretion of the treating physician. There will be no change in the diagnosis or management of the patient based on any procedures or tests carried out as a part of this study.

There are no expected toxicities and potential risks for PBR. All scans will be performed at the Martinos Center for Biomedical Imaging in Charlestown on the combined MR PET scanner.

For GBM patients with suspected pseudoprogression, MR-PET will be performed at the time of suspected pseudoprogression.

For GBM patients treated with immunotherapy, MR-PET will be performed prior to start of the immunotherapy and then 2 cycles later.

For metastatic cancer patients treated with immunotherapy, MR-PET will be performed prior to start of the immunotherapy and then 3 cycles later.

5.2 Pre-MR-PET Scan Criteria

5.2.1 Genotyping for the Ala147Thr TSPO polymorphism in the TSPO gene (rs6971). Venous blood (up to 50 ml) will be drawn during the Screening Visit for this purpose and sent Partners HealthCare Personalized Medicine Translational Genomics Core located at 65 Landsdown street at Cambridge. This lab performs this testing for all other current PBR PET studies conducted at MGH.

5.2.2 Stable dose of corticosteroids for 5 days prior to MR-PET scan as change in steroids can affect interpretation of the MRI scan.

5.2.3 Creatinine clearance >30 mL/min based on a serum creatinine level obtained within 30 days.

5.2.4 β-HCG in woman of childbearing age (prior to each MR-PET scans). Please see http://healthcare.partners.org/phsirb/Guidance/Pregnancy_Testing_in_Research_Involving_Radiation.1.09.pdf for Pregnancy Testing guidelines)

5.3 MR-PET Scan Procedure

5.3.1 MRI Scan

Image Acquisition Details:

MR scans will be performed including T1- and T2-weighted volumetric images, fluid attenuated inversion recovery (FLAIR), contrast agent enhanced T1-weighted permeability, diffusion imaging, T2/T2*-weighted perfusion scans, and MR Spectroscopy. The "Autoalign" package available from the manufacturer will be used to achieve the same slice prescription in the same patient at each visit. Each MRI will last 60-75 minutes versus 45 minutes for standard brain MRIs.

Gadolinium-diethylenetriaminepentaacetic acid (or gadopentetate dimeglumine, Gd DTPA) will be used as a contrast agent. The maximum contrast dose that could be given is 0.3 mmol/kg per visit, in line with the FDA-approved dosing for this class of contrast agents.

Image Analysis Details:

MRI data will be analyzed per our usual techniques as have been reported previously.

Image Interpretation Details:

Interpretation will be performed at the Martinos Center for Biomedical Imaging. The results will not be automatically relayed to the patient or treating physician as it is unclear how these scans should be interpreted so should not influence patient management. If requested, we will share the data with the patient's physician but again, should not

influence patient management. Patients and treating physicians may be curious to see the images so we want to allow for sharing of the images. The detailed analysis required for interpretation of the data will not be in real time so will not be able to influence treatment decisions. Moreover, we do not want lack of communication to be a barrier to accrual.

5.3.2 PBR PET Scan

Image Acquisition Details:

During each visit, [11C]PBR28 (up to 15mCi, which results in ~3.7 mSv) will be injected intravenously with a slow bolus over a 30s period. The catheter will be flashed post-injection of with 0.9% saline solution. Dynamic data will be collected over approximately 90 minutes in list mode, and framed post-collection.

At the beginning of the scan session, an intravenous catheter will be placed for tracer injection. A second line will be placed in the opposite arm from the injection site and will be used to draw 2mL or 12mL blood samples throughout the test, for at most 200mL of blood. The blood draws will be used to assess the radioactivity levels in the blood necessary for dynamic imaging. The catheters will be removed at the end of the study.

Image Analysis Details:

PET volumes will be reconstructed using the ordinary Poisson ordered subsets expectation maximization (OP-OSEM) 3D algorithm. Corrections will be applied for variable detector dead time and efficiency, random coincidences, photon attenuation and scatter, and decay.

Image Interpretation Details:

Interpretation will be performed at the Martinos Center for Biomedical Imaging.

5.4 General Concomitant Medication and Supportive Care Guidelines

NA

5.5 Criteria for Taking a Participant Off Protocol Therapy

Patients may remain on study (i.e. continue with MR-PET imaging) until one of the following criteria applies:

- Intercurrent illness that prevents further participation in the imaging studies
- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the documentation requirements or imaging studies.
- Participant decides to withdraw from the protocol (i.e. does not want to undergo further imaging studies)
- General or specific changes in the participant's condition render the participant unacceptable for further imaging studies in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, *Elizabeth Gerstner*, at [redacted].

5.6 Duration of Follow Up

Participants will be followed for 3 years after removal from protocol therapy or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A QACT Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

DOSING DELAYS/DOSE MODIFICATIONS

No dose modifications will be made to the PBR dosing.

ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

Per NCI Adverse Event Reporting Requirements related to PET tracers, adverse events related to the PET imaging are reportable up to 3.5 hours after injection (i.e. 10 half-lives of the C11 tracer).

7.1 Expected Toxicities

7.1.1 Adverse Events List

7.1.1.1 Adverse Event List for PBR

There are no known adverse events related to PBR.

7.1.1.2 Adverse Event List(s) for Other Agent(s)

NA

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event

varies in nature, intensity or frequency from the expected toxicity information which is provided.
- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

There are no known adverse events related to PBR28 but any event thought related to PBR28 that is CTCAE grade ≥3 will be considered a serious adverse event and should be reported to the Overall PI and RDRC per the DFCI IRB reporting policy.

7.3 Expedited Adverse Event Reporting

Per NCI Adverse Event Reporting Requirements related to PET tracers, investigators **must** report to the Overall PI any serious adverse event (SAE) related to the PET imaging up to 3.5 hours after injection (i.e. 10 half-lives of the C11 tracer). Thus, by 3.5 hours after injection the tracer should be out of a patients system and not responsible for any adverse events. Any SAEs related to the PET imaging will also be reported to the RDRC.

7.3.1 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.3.2 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

NA

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.** Any AEs related to the PET imaging will also be reported to the RDRC.

IMAGING AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1 PBR

8.1.1 Description

The chemical name is: N-acetyl-N-(2-methoxybenzyl)-2-phenoxy-5-pyridinamine.

8.1.2 Form

PBR is an intravenous injection. The radiopharmaceutical product, PBR, is the only active ingredient and it is dissolved in a solution of ≤10 mL of 95% isotonic saline: 5% ethanol (v:v). PBR is provided as a ready to use isotonic, sterile, pyrogen-free, clear, and colorless solution. PBR is typically packaged in a glass vial and does not contain any preservatives.

8.1.3 Storage and Stability

The PBR will be produced onsite the day of the scheduled PET scan at the Martinos Center under the auspicious of the Radiation Drug Review Committee (RDRC). Proper transportation will take place according to Martinos Center policies. The Martinos Center policies include standard operating procedures for the tracer. These SOP's have been developed by radiochemist, nuclear medicine experts and the MGH RDRC that oversees all studies using novel PET tracers. Following synthesis and quality control, the radiopharmaceutical will be used within 2 hours of the end of synthesis.

8.1.4 **Compatibility**

NA

8.1.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment. These personnel have undergoing training and certification in the handling of radiolabeled tracers (ex. qualified nuclear medicine technicians).

8.1.6 **Availability**

PBR will be produced onsite.

8.1.7 **Preparation**

PBR will be produced onsite as a fully prepared agent ready for intravenous administration. Radioactivity dose can be adjusted by modifying the injection volume. No other changes in constitution should be made. Preparation will follow the SOPs of the Martinos center that have been developed by radiochemist, nuclear medicine experts and the MGH RDRC that oversees all studies using novel PET tracers. All personnel involved have undergoing training and any necessary certification in the handling of radiolabeled tracers.

8.1.8 **Administration**

PBR will be administered by intravenous injection by bolus by a qualified nuclear medicine technician.

8.1.9 **Ordering**

PBR will be prepared on a single injection basis as dictated by MR-PET scheduling of studies at the Martinos Center.

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 **Destruction and Return**

At the end of the study, unused supplies of PBR should be decayed in storage according to institutional policies. This will be documented in the PBR individual batch record and scan log.

BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

NA

9.2 Laboratory Correlative Studies

NA

STUDY CALENDAR

Screening evaluations are to be conducted within 4 weeks prior to start of protocol therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

GBM Patients with suspected Pseudoprogression

	Pre-Study		**Post-chemoradiation**
PET + MRI			X[a]
Informed consent	X		
Medical History	X		
Physical exam	X		

(Ht, Wt, VS)			
Steroid dose	X		X[b]
KPS	X		
Genotyping for Ala/Ala or Ala/Thr status[c]	X		
CBC with diff	X		
CMP[d]	X		
B-HCG[e]	X		X
Adverse event evaluation[f]			3.5 hours post-PET scan
Follow-up[g]			

a – at any point during therapy that a GBM patients has suspected pseudoprogression but within 4 weeks of consent

b- Record steroids dose at time of PET scan

c – this test will be performed as part of screen after informed consent is obtained. The blood will be sent to Partners HealthCare Personalized Medicine Translational Genomics Core located at 65 Landsdown street at Cambridge. This lab performs this testing for all other current PBR PET studies conducted at MGH.

d - Sodium, potassium, chloride, glucose, BUN, creatinine, calcium, total protein, albumin, total bilirubin, SGOT [AST], SGPT [ALT], alkaline phosphatase.

e – Serum pregnancy test (for women of childbearing potential) to be performed at baseline and prior to each PET. See http://healthcare.partners.org/phsirb/Guidance/Pregnancy_Testing_in_Research_Involving_Radiation.1.09.pdf

f – Per NCI Adverse Event Reporting Requirements related to PET tracers, the window to collect adverse event is 3.5 hours post PET scan (i.e. 10 t½ of radiotracer). Patient will be contacted by phone call or clinic visit within 24 hours of scan to assess for adverse event during this window.

g – Follow-up every 3 months will assess subsequent treatments, tumor response to treatment, and survival

For patients undergoing immunotherapy

	Pre-Study	**Pre-Immunotherapy**	**During-Immunotherapy**
PET + MRI		X[a]	X[b]
Informed consent	X		
Medical History	X		
Physical exam (Ht, Wt, VS)	X		
Steroid dose	X	X[c]	X[c]
KPS	X		

Genotyping for Ala/Ala or Ala/Thr status[d]	X		
CBC with diff	X		
CMP[e]	X		
B-HCG[f]	X	X	X
Adverse event evaluation[g]		3.5 post-PET scan	3.5 post-PET scan
Follow-up[h]			

a – 1-7 days prior to surgery or immunotherapy
b – 0-5 days prior to cycle 4 of immunotherapy for metastatic brain cancer patients or prior to cycle 3 of immunotherapy for GBM patients
c- Record steroids dose at time of PET scan
d– This test will be performed as part of screen after informed consent is obtained. The blood will be sent to Partners HealthCare Personalized Medicine Translational Genomics Core located at 65 Landsdown street at Cambridge. This lab performs this testing for all other current PBR PET studies conducted at MGH.
e - Sodium, potassium, chloride, glucose, BUN, creatinine, calcium, total protein, albumin, total bilirubin, SGOT [AST], SGPT [ALT], alkaline phosphatase.
f – Serum pregnancy test (for women of childbearing potential) to be performed at baseline and prior to each PET. See http://healthcare.partners.org/phsirb/Guidance/Pregnancy_Testing_in_Research_Involving_Radiation.1.09.pdf
g– Per NCI Adverse Event Reporting Requirements related to PET tracers, the window to collect adverse event is 3.5 hours post PET scan (i.e. 10 t½ of radiotracer). Patient will be contacted by phone call or clinic visit within 24 hours of scan to assess for adverse event during this window.
h – Follow-up every 3 months will assess subsequent treatments, tumor response to treatment, and survival

MEASUREMENT OF EFFECT

Measurement of effect will be determined by the treating physician per standard of care. The following is only included as reference for the treating physician.

11.1 Antitumor Effect – Solid Tumors

RANO criteria are recommended to assess response.[15]RECIST is recommended for the metastatic brain tumor patients.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Per RANO or RECIST guidelines as appropriate.

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.*

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported

as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Per RANO or RECIST guidelines as appropriate.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

RANO Criteria (JCO 2010; 28:1963-1972)

Complete Response: a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. b) No new lesions. c) Stable or improved non-enhancing (T2/FLAIR) lesions d) Patients must be on no corticosteroids. e) Stable or improved clinically. Note: 1) Patients with non-measurable disease only cannot have a complete response. The best response possible is stable disease.
Partial Response: a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. b) No progression of non-measurable disease. c) No new lesions. d) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. e) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan. f) Stable or improved clinically. Note: 1) Patients with non-measurable disease only cannot have a partial response. The best response possible is stable disease.
Stable Disease: a) Does not qualify for complete response, partial response, or progression. b) The designation of Stable Disease requires a minimum of 4 weeks duration, determined by a confirmatory scan. c) 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. d) Stable clinically.
Progression: a) > 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids and/or b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects). c) Any new lesion d) 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 treating physician but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less, for at least 7 days, be considered, unless attributable to co-morbid events. e) Failure to return for evaluation due to death or deteriorating condition

11.1.4.2 Evaluation of Non-Target Lesions

Per RANO or RECIST guidelines as appropriate.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not	No	SD	Documented at least once ≥4 wks from baseline**

	evaluated			
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.7 Response Review

NA

11.2 Antitumor Effect – Hematologic Tumors

NA

11.3 Other Response Parameters

NA

DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT.

12.2 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.

12.3 Multicenter Guidelines

NA

12.4 Collaborative Agreements Language

NA

STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a pilot study to test the potential utility of PBR28 PET in measuring treatment related inflammation . We will measure if increased uptake of PBR28 in the tumor during treatment is associated with longer time to progression (i.e. suggesting that the response to therapy is inflammatory rather than tumor growth).

13.2 Sample Size, Accrual Rate and Study Duration

Total sample size is anticipated to be 40 patients: 15 patients in cohort A (metastatic brain tumor patients) and 15 in cohort C (GBM patients suspected of having pseudoprogression) and 10 in cohort B (GBM patients treated with immunotherapy).

Several factors influence the sample size for this study. This is a non-therapeutic study in a patient population which typically chooses to enroll in therapeutic trials if they are going to participate in a clinical trial at all so this trial will be less appealing to patients. In addition, since PBR PET remains investigational it is a very expensive test so budgetary constraints limit accrual.

In order to assess if PBR PET helps to assess tumor inflammation, we will quantitate PBR uptake in the tumor and correlate that with tumor progression as determined by the treating physician or tissue histology if obtained. The hypothesis is that if tumor PBR retention is high, this would be consistent with a strong response to immunotherapy and should be associated with prolonged progression free survival. If PBR retention is low, indicating an immunosuppressive, active tumor microenvironment, PFS should be short. We selected 9 months because by this time, we should know who has true progression since treatment related inflammation has peaked by this time.

The aim of this study is to demonstrate higher levels of PBR uptake in the non-progression group. Therefore the sample size calculation is based on two group means comparison and the test used is a one-sided two-sample equal variance t-test (with mean and SD estimates as cited below). Since there is no a priory indication for the breakdown between progression and non-progression, we assumed equal group sizes.

With 15 patients in cohort A (metastatic brain tumor patients) and 15 in cohort C (GBM patients suspected of having pseudoprogression), the study will have at least 80% power to detect a 60% difference in PBR uptake between those progression free at 9 months and those not progression free at 9 months using a one-side hypothesis test with a 0.1 significance level. By 9 months, we should know who has true progression and who has pseudoprogression. Patients who die before nine months will be considered true tumor progression. Given this conservative approach we will have the power to detect a smaller difference in PBR uptake.

For the patients who have baseline and mid treatment PET (cohort A), we will use the change in PBR uptake. There is limited data on PBR28 in brain tumors so this calculation assumes a baseline of 125 ml/cm^3 and equal variance of 100 ml/cm^3 (based on literature reported rates from healthy brain).[9] PFS at 9 months was selected as most patients would have progressed at 9 months. All patients will also be followed for 3 years after study completion for progression and survival. Time to event analysis will be used to incorporate other potential prognostic factors such as age and functional status.

Given the small number of patients anticipated to accrue to cohort B (GBM patients treated with immunotherapy), these patients will be analyzed with descriptive statistics alone. This accrual is anticipated to be low because of the small number of GBM patients currently treated with immunotherapy. We anticipate enrolling a maximum of 10 patients in this cohort.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	2	=	4
Not Hispanic or Latino	3	+	8	=	11
Ethnic Category: Total of all subjects	5	+	10	=	15
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	1	=	1
Black or African American	0	+	1	=	1
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	5	+	8	=	13
Racial Category: Total of all subjects	5	+	10	=	15

13.3 **Stratification Factors**

NA

13.4 **Interim Monitoring Plan**

NA

13.5 **Analysis of Primary Endpoints**

As above

13.6 Analysis of Secondary Endpoints

Given the small sample size, any secondary endpoint analysis will be exploratory and reported as descriptive.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

Patients will be evaluable for toxicity related to PBR PETs within 3.5 hours of the PET scan.

13.7.2 Evaluation of the Primary Efficacy Endpoint

NA

PUBLICATION PLAN

Dr. Gerstner will have sole responsibility for publishing results of this study.

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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.