Imaging Brain Tumors with FACBC and Methionine

THERAPEUTIC/DIAGNOSTIC PROTOCOL

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SUMMARY AND/OR SCHEMA

The purpose of this research is to: 1) perform both 3-[18F]-FACBC and [11C-methyl]-L-methionine brain tumor PET imaging studies in patients with primary brain tumors who have previously been treated and are now suspect for having recurrence or progression of disease (a pilot study, n=20); 2) perform only 3-[18F]-FACBC PET imaging studies on an additional set of patients with primary brain tumors who have previously been treated and are now suspect for having recurrence (n=10) . 3) obtain organ/tissue and body radiation dosimetry information following i.v. injection of 3-[18F]-FACBC; 4) look for potential correlations between the scan results obtained from those patients enrolled to 03-028 and the patients' past medical treatment;

The first set of 20 patients will agree to two PET studies. One study will involve the i.v. administration of a fluorine-18 labeled amino acid analogue, 3-fluoro-aminocyclobutane carboxylic acid (3-[18F]-FACBC) with sequential brain and body PET imaging. The second study will involve i.v. administration of [11C-methyl]-L-methionine and head imaging only.

The additional set of 10 patients will undergo one PET study which will consist of the i.v. administration of fluorine-18 labeled amino acid analogue, 3-fluoro-aminocyclobutane carboxylic acid (3-[18F]-FACBC) with one brain scan and one body scan only.

The 3-[18F]-FACBC PET studies (n=30) will be performed under the Radioactive Drug Research Committee (RDRC) guidelines as defined and established by the Federal Drug Administration (FDA). [11C-methyl]-L-methionine is in the hospital formulary and is approved for imaging brain tumors at MSKCC.

Our hypotheses include: 1) [18F]-FACBC has equal or better brain tumor imaging characteristics compared to [11C]-methionine; 2) [18F]-FACBC is not metabolized, and radiolabeled metabolites will not confound the interpretation of the images as can be the case with [11C]-methionine; 3) imaging recurrent brain tumors with [18F]-FACBC will be enhanced by lower brain (background) activity as compared to corresponding [11C]-methionine images; 4) the biodistribution of [18F]-FACBC and radiation dosimetry following i.v. administration of a 370 MBq (10 mCi) dose is safe and within FDA guidelines; 5) a 370 MBq (10 mCi) dose of [18F]-FACBC is sufficient for imaging brain tumors in a clinical setting; 6) the accumulation of [18F]-FACBC will correlate with the patients response to prior treatment and will provide prognostic information with respect to tumor progression and survival.

The results of this study will be used to support the submission of an investigational new drug (IND) application to the Food and Drug Agency (FDA).

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Demonstrate in a pilot study (n=30) that [18F]-FACBC has equal or better brain tumor imaging characteristics compared to [11C]-methionine.

2.2 Determine the biodistribution and clearance of 3-[18F]-FACBC in different tissues/organs of the body using PET, and calculate body and critical organ radioactivity exposure (dosimetry).

2.3 The results of this study will be used to support the submission of an investigational new drug (IND) application to the Food and Drug Agency (FDA).

2.4 Look for potential correlations between subsequent MR and PET scan results obtained from those patients enrolled to 03-028 and the patients' subsequent medical treatment, progression of the tumor and survival.

3.0 BACKGROUND AND RATIONALE

3.1 A frequent question that neurooncologists and neurosurgeons must address in the management of post-treatment primary brain tumors, is whether a new or expanding brain lesion observed on CT or MR imaging represents recurrent tumor, treatment effects or tissue necrosis **[1-6]**. This is of particular concern in the management of patients with previously treated low-grade or anaplastic gliomas. Frequently, a patient may have little or no change in clinical neurological status on follow-up clinical visits, but changes in the pattern of contrast enhancement or an expansion of T2, FLAIR or diffusion abnormalities are observed on routine MRI. The question of recurrent disease vs. treatment effect is frequently raised by clinicians in this setting. This question often leads to further studies or a surgical procedure (e.g., needle or open biopsy) to resolve this issue or to confirm the diagnosis of recurrent tumor. The number of needle biopsy specimens is usually limited in surgical practice (due to the risk of hemorrhage) and it is not uncommon for the pathology of the biopsy sample(s) to be read as nonspecific "gliosis" or "inconclusive".

3.2 The "functional" imaging capabilities of PET can provide important additional information that will facilitate making patient management decisions. [18F]-fluoro-2-deoxyglucose ([18F]FDG) PET imaging has been used to distinguish recurrent tumor from treatment effects and tissue necrosis for almost two decades. More recently, the advantages of [methyl-11C]-methionine ([11C]MET) PET imaging of brain tumors have been documented in Europe and Japan **[7-10]**. Functional information, such as glucose utilization and amino acid transport, can be obtained from PET imaging, and these functional/metabolic/transport images are now routinely compared to the abnormal CT or MR images. This comparison is particularly robust following digital registration of the PET and MR/CT images (see below), and provides very useful information for making timely patient management and treatment decisions.

3.3 The current medical management of brain tumor patients with inconclusive changes on MRI usually involves repeating the MRI in three months. Serial MRI comparisons are performed to determine whether there is significant progression in the abnormalities. Monitoring changes in serial MRI's is considered to be the standard of care for the neurological and neurosurgical management of patients with primary brain tumors. However, such changes can be subtle and occur over an extended period of time, particularly for low or intermediate (anaplastic) grade gliomas. The several month

interval required to document a significant change on MRI can delay initiating a new treatment or the surgical resection of a recurrent tumor. The assessment of recurrent disease is a frequent quandary in the management of patients with primary brain tumors.

3.4 Alternatively, a patient may undergo a biopsy or surgical procedure to address the question of recurrent disease. We suggest that many surgical procedures could be avoided based on a negative functional PET scan, or the surgical resection or biopsy could be targeted to the site that is identified in the functional PET scan most likely to represent recurrent tumor. As a consequence, the management of patients with suspected recurrent gliomas frequently involves multimodality imaging assessments at MSKCC. We have found that multimodality imaging assessments result in more rapid patient management decisions for initiating new treatments as well as sparing some patients a surgical procedure (e.g., needle biopsy or craniotomy.

3.5 [18F]-FACBC PET studies in human subjects have been performed at Emory [**11**]; the images from this study are shown in Figure 1.

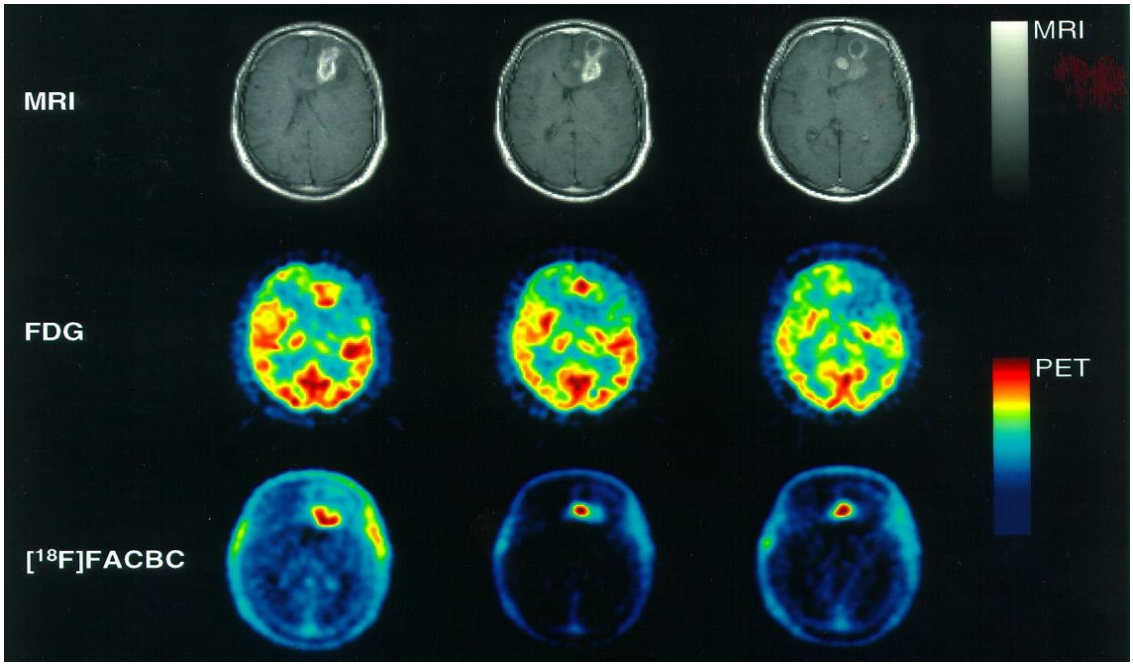

Figure 1

Although [18F]-FACBC PET studies in patients have yet to be performed at MSKCC, [11C]-methionine and [18F]-FDG are in clinical use for evaluating patients with suspected recurrent brain tumors, as well as patients who are noted to have a new but inconclusive changes in their MR scans. PET imaging with these two tracers (along with Gd-DTPA T1, T2 and FLAIR MR images for the brain) are currently being used to further assess these patients and address clinical management issues. The proposed [18F]-FACBC PET imaging studies will be integrated into this established framework for clinical brain tumor assessment.

3.6 Significant points and rationale for imaging brain tumors with FACBC. FDG and methionine imaging of brain tumors have some significant limitations that are likely to be addressed by imaging with FACBC. First, the interpretation of FDG images of solid tumors is often confounded by the multiplicity of factors that increase glycolysis (factors other than cell proliferation), such as tissue hypoxia and the infiltration of inflammatory cells. Second, FDG images of brain tumors are often difficult to interpret because of the relatively "high" metabolic activity of surrounding brain tissue; this results in relatively "low" tumor-to-brain activity ratios (contrast), particularly when compared to the activity ratios (contrast) observed in FDG body images of systemic tumors and metastases (e.g., lung, colon, etc.). Third, the relatively "low" tumor-brain contrast in the FDG images frequently requires PET-MR image registration to more clearly identify the tumor margins; FDG-MR image registration has become a standard procedure in the clinical evaluation of FDG PET scans of brain tumor patients at MSKCC and other institutions. Fourth, FDG images, in contrast to methionine images, are not useful for identifying tumor infiltration of adjacent brain tissue (beyond the margin of contrast enhancement). Fifth, the interpretation of methionine images (and images of other naturally occurring amino acids) are confounded by the presence of radiolabeled metabolites that contribute to the image; ACBC, ACPC and AIB are not metabolized in mammals and are excreted unchanged in the urine. Sixth, amino acid imaging of tumors benefits from the up-regulation of "A" transporter expression in the cell membranes of transformed and malignant tumor cells. Seventh, the amino acid transport carriers (both "L" and "A" transport systems) and transport carrier kinetic parameters (Bmax) across cell membranes in vitro and endothelial cells (BBB) in vivo favor FACBC over methionine (see Tables 1 and 2, and related discussion). Eighth and most important for routine clinical applications, tumor imaging with [18F]-FACBC would have substantial logistical and cost-effective benefits in a busy nuclear medicine department in comparison to imaging with [11C]-methionine

4.0 STUDY DESIGN

4.1 The first set of 20 patients will consent to two PET studies. One study will involve the i.v. administration of a fluorine-18 labeled amino acid analogue, 3-fluoro-aminocyclobutane carboxylic acid (3-[18F]-FACBC) with sequential brain and body PET imaging. The second study will involve i.v. administration of [11C-methyl]-L-methionine for a head imaging study only. An additional set of 10 patients will consent to one type of PET study which will involve administration of [18F]-FACBC only for one brain scan and one body scan.

4.2 ~~All~~ The first set of 20 patients will first undergo a [11C-methyl]-L-methionine PET study. Whenever possible, approximately two hours later, the same patient will undergo the [18F]-FACBC PET study.

4.3 For the first 20 patients, we will attempt to complete both studies on the same day; if this is not possible, the two PET studies will be completed within 1 week of each other.

4.4 The 3-[18F]-FACBC and [11C-methyl]-L-methionine PET images will be digitally registered to each other and to corresponding contrast enhanced and FLAIR MR images (from the most recent MR study obtained as part of the patient's standard medical care). Region of interest (ROI) measurements of 3-[18F]-FACBC and [11C-methyl]-L-methionine activity in tumor and remote brain tissue will be obtained from the two data sets and paired comparisons will be performed.

4.5 The study will also provide data to determine body and critical organ radioactivity exposure (dosimetry) following 3-[18F]-FACBC administration. These calculations will be based on the biodistribution and clearance of radioactivity from the tissues and organs of the body as determined by sequential PET imaging.

4.6 Look for potential correlations between the MR and PET scan results obtained from those patients enrolled to 03-028 and the patients' past medical treatment, as well as the patients' subsequent medical treatment, progression of the tumor and survival. _

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Routine production of fluorine-18 labeled FACBC and [11C]-labeled methionine will be produced by the Cyclotron-Radiochemistry Core at MSKCC for human administration [Appendix A].

F-18 labeled FACBC is prepared stereo-specifically in a semi-automated, NCA procedure utilizing the General Electric FDG MicroLab, a system employing a quaternary 4-aminopyridinium resin to effect F-18 fluorination. The triflate species is displaced with F-18 fluoride in the MicroLab, and then the 1-t-butyl carbamate-3-trifluoromethane sulfonoxy-1-cyclobutane-1-carboxylic acid methyl ester is hydrolyzed with 1 N HCl. The final product is isotonic and sterile, and has been utilized in animal experiments. The product was obtained in 30% radiochemical yield after 65 minutes from EOB. The radiochemical purity was greater than 95% and no preparative HPLC was required. The procedure could be considered routine, and is performed on the FDG synthetic module without changes either to the programming or to the cassettes.

Because of the deliberately closed design of the MicroLab, the only variables readily changeable include the contents and concentrations of the four reagent vials feeding into the system, and the makeup of the final purification columns attached to the cassettes. The MicroLab features a single-use, disposable cassette (see Appendix 2) in which the starting syntheton is slowly passed through a small heated column of a quaternary 4-aminopyridinium resin on which has been absorbed the F-18 anion. As the fluorination occurs on the resin, it is carried in an organic solvent to the hydrolysis vessel, where in subsequent steps, the hydrolytic deprotection occurs. Finally, the pH is adjusted with buffer, and the whole mixture is filtered, in succession, through various filtration cartridges. The fluorine-18 labeled trans-FACBC passed testing for toxicity, radiochemical purity, radionuclidic purity, sterility and apyrogenicity.

5.2 L-[methyl-11C]-methionine is prepared in the Cyclotron Facility at MSKCC according to the method reported by Comar [**12**]. Approximately 60% radiochemical yield (decay

corrected to methyl iodide reaction) has been obtained with radiochemical purity approaching 100% as determined by HPLC and radio TLC. No chemical impurity associated with the starting L-homocysteine thiolactone could be detected. The measured specific activity of the product was 250-350 mCi/umole decay corrected to start of synthesis. Routine synthesis time is approximately 45 minutes. The finished radiopharmaceutical has successfully passed testing for general safety, sterility and apyrogenicity.

6.1 CRITERIA FOR PATIENT/SUBJECT ELIGIBILITY

The criteria for patient selection will include patients registered at Memorial Hospital with a diagnosis of a primary brain tumor and are suspect for having recurrent disease. Patients will be nonpregnant, have a Karnofsky score of 60 or more, and have no known medical contraindications to MRI and PET scans. The total number of patients expected to enter the protocol is 30. There will be no exclusions based on age, sex or ethnic background; a pregnancy test will be required of women of child-bearing age. Pregnant women will be excluded from this study.

6.2 PATIENT/SUBJECT INCLUSION CRITERIA

- Registered patient at MSKCC.
- Child-bearing age females must be non-pregnant, non-lactating, and must be using adequate contraception or surgically sterile.
- Karnofsky score of 60 or greater.
- Children that can sit still for 60-90 minutes, without sedation, will be included in this protocol.

6.3 PATIENT/SUBJECT EXCLUSION CRITERIA

- Patient cannot tolerate lying still for 90 minute sessions in the PET tomograph.

7.0 RECRUITMENT PLAN

7.1 Recruitment of patients will be through the participating investigators and referrals from staff physicians at Memorial Hospital. 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 senior investigators of this research proposal.

7.2 The signed IRB consent form will be brought to the patient protocol accrual (PPA) system in the Data Management Resource Group of the Dept. of Biostatistics and Epidemiology at MSKCC for registration at MSKCC, and the imaging study requisition for the imaging protocol will be brought to the Department of Nuclear Medicine.

8.0 PRETREATMENT EVALUATION

Primary pre-treatment evaluation will be based on the evaluation performed as part of the patient's regular medical care at MSKCC. No additional pre-treatment evaluation will be performed.

9.0 TREATMENT/INTERVENTION PLAN

9.1 All subjects will be pre-registered at MSKCC and will have signed the consent form prior to participation in this study.

9.2 The morning of the PET imaging studies, all patients will be asked to avoid high protein foods (meat, fish, poultry, cheese, eggs, beans and nuts) and to record the types and servings of the foods they eat. Some patients may also be asked to avoid high protein foods the day prior to imaging. These same patients will also be asked to refrain from eating lunch on the day of the study to reduce muscle uptake of the FACBC. All patients will also be urged to drink several glasses of water to attain good hydration and urine output. Patients will be placed comfortably on the couch and positioned in the GE Advance PET scanner. The first 20 patients will first receive 185 MBq (5 mCi) of: [11C-methyl]-L-methionine by i.v. infusion over approximately 1 minute. Whenever possible, approximately 1.5 to 2 hours later, the same patient will receive 370 MBq (10 mCi) [18F]-FACBC by i.v. infusion over approximately 1 minute. In cases where both studies cannot be obtained on the same day, they will be obtained within one week of each other.

9.3 For the first 20 patients, the [11C-methyl]-L-methionine study will involve a 45-minute emission dynamic scan of the head. Previous studies have shown that [11C-methyl]-L-methionine accumulation in tumor and brain tends to reach a plateau value within 15-30 minutes following administration. The [18F]-FACBC study will involve a 45-minute emission dynamic scan of the head to obtain kinetic information on tumor uptake for modeling. After the initial dynamic scan, the patient will void completely; the volume of urine will be recorded and a urine sample will be assayed for urine radioactivity. Up to three [18F]-FACBC body scans will be performed following the completion of the dynamic scan to obtain data for calculating body and organ specific dosimetry. The last 10 patients will undergo a [18F]-FACBC 45-minute emission dynamic scan of the head followed by one body scan.

9.4 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 "warmed arterialized" venous blood sampling. For the first 20 patients, a blood sample will be obtained just prior to the injection of [11C-methyl]-L-methionine and [18F]-FACBC to measure plasma amino acid concentration at the time of each study. Sequential blood samples will be obtained following [18F]-FACBC infusion and assayed for whole blood and plasma radioactivity, to check for radiolabeled metabolites by HPLC, and to measure plasma amino acid concentration at the time of the study. All catheters will be removed at the end of the day.

9.5 After the [18F]-FACBC head scan and ~10-15 min break period, patients will be placed comfortably on the couch and positioned in the GE Advance PET scanner for sequential body imaging. The total time in the scanner for each imaging sequence will be up to 45 minutes. For the first 20 patients, this sequence of scans will be repeated a maximum of three times over a four hour post injection period (approximately two 18-F half lives). The first body scan sequence will commence ~60 min after [18F]-FACBC injection. The second and third sequences will commence at ~2 and ~3 hours post-injection of [18F]-FACBC, respectively, with a break between scans. During the intervals between scans, the patient will come out of the scanner, exercise and will be asked to void completely. To assist correct re-alignment in the scanner for repeat scans, the patient's skin will be "marked" to identify the plane defined by the PET laser during the first scan set. On the second and third scans, the technologist will position each patient field of view so as to align the laser with the skin markings.

9.6 Venous blood will be sampled before the methionine and FACBC scans to measure plasma amino acid concentrations. Blood samples (1/2 teaspoon per sample) will be drawn during the FACBC scans to measure the radioactivity level in your blood. Total blood sampled for the two PET studies will be less than 6 tablespoons (less than 90 ml). Whole blood and plasma will be assayed for radioactivity and for radiolabeled metabolites by HPLC.

9.7 The volume of urine voided between scans will be recorded and a urine sample will be assayed for urine radioactivity and radiolabeled metabolites by HPLC. This frequent urination will reduce bladder exposure and provide a brief "relaxation" period between sequential sets of scans, and will facilitate individual patient acceptance and compliance during the study.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Reconstructed images will be obtained from the PET data; corrections will be made for randoms, scatter, dead-time, detector inhomogeneity and attenuation. Image data will be calibrated to nCi/cc and decay corrected to the time of injection. Comparisons will be made with the most recent MRI study obtained as part of the patient's standard radiographic assessment. The PET and MRI scans will be digitally co-registered using established methods at MSKCC to facilitate this comparison.

10.2 The registered image sets will be displayed simultaneously, facilitating the identification of the correspondence between the lesion(s) in each modality. Volumes of interest created on one modality will be applied to the other modalities, thus enabling direct quantitative comparisons.

10.3 Two levels of image analysis will be performed. One level will involve two Nuclear Medicine physicians (or one Nuclear Medicine physician and one Neurologist) who will independently view the full set of registered images. The analysis will involve assessment for the presence or absence of disease using a five point visual scoring system. These assessments will be blinded to the clinical and pathologic results pertaining to the patient, although all imaging studies (including MRI) will be available

(which is standard clinical practice). We chose a five point scale rating disease from 0-4 in terms of probability for the presence of disease (0=no evidence of tumor, 1=probably no evidence of tumor, 2=equivocal for the presence of tumor, 3=probably tumor present, 4=definitely tumor present).

10.4 The second level of analysis will be quantitative. Volumes of interest (VOI) will be drawn on the lesions that are positive on the 3-[18F]-FACBC scan; VOI's on remote normal white and gray-matter regions of the brain will also be drawn. The mean of the voxel values within each VOI will be determined for each of the dynamic frames of the 3-[18F]-FACBC study. Profiles will be generated in units of: 1) standard uptake value [SUV = (% dose/g) * body weight] versus time, and 2) the brain tumor-to-gray or white matter ratio versus time. These curves will be evaluated to determine a single, near "optimal" tumor imaging time, for each of the patients. The criteria used in making this assessment will be target to background contrast, robustness (i.e. time insensitivity) and image noise level. The SUV and ratio values at this "optimal" time point will then be compared to similar SUV and lesion to background values determined for the corresponding location within the [11C]-methionine scan..

10.5 Radiolabeled metabolites of 3-[18F]-FACBC, if any, in plasma and urine will be assayed by HPLC and % parent compound vs. time profiles will be constructed for plasma and urine, and compared to the tissue radioactivity concentration vs. time profiles calculated above and used for calculating the kinetic parameters.

10.6 The absorbed tissue radioactivity dose estimates for 3-[18F]-FACBC will be calculated in the standard manner. Attenuation corrected PET images provide information for the tumor and organ activities directly in units of activity per cubic centimeter. Regions of interest will be drawn within identified normal organs e.g. brain, lung, liver, bladder etc. This data will be plotted versus time post injection and used for determining organ residence times. These organ residence times will be entered into MIRDOSE for determination of the organ dosimetry. MIRDOSE is a personal computer software package for internal dose assessment from tracers used in nuclear medicine [**13**]. This program calculates the radiation dose to each organ from the activity residing within that organ, as well as the contribution of the penetrating photon emissions from other body organs accumulating significant levels of radioactivity, according to the methodology laid out by the Medical Internal Radiation Dose (MIRD) Committee [**14**] (MIRD PRIMER 1988).

The plasma and urine radioactivity concentration data (nCi/cc) will be plotted vs. time after injection. The integral of activity-time curve will be calculated from zero to infinity and multiplied by the equilibrium dose constant for 18F to obtain the absorbed dose to blood. The dose to the bladder wall will be determined using the dynamic bladder model of Cloutier et al. [**15**], as implemented in MIRDOSE using measured clearance data from urine samples.

The dose estimates described above incorporate estimates of the biological clearance of the tracer. Companion calculations will also be performed using the assumption of no biological clearance, i.e. only physical decay from the organ maximum. This is a

conservative "worst case" scenario and does not depend on the accuracy of the organ clearance fits.

10.7 Look for potential correlations between the MR and PET scan results obtained from those patients enrolled to 03-028 and the patients' past medical treatment, as well as the patients' subsequent medical treatment, progression of the tumor and survival.

11.0 TOXICITIES/SIDE EFFECTS

11.1 PET Scanning. Potential risks to the patient are small, and present more of an inconvenience (multiple scans on consecutive days). The GE Advance tomograph has a large bore (92.7 cm in diameter) to accommodate the whole body and the environment is much less confining than the head cage of the General Electric Signa 1.5 Tesla MR tomograph. For the first 20 patients, the length of time in the PET scanner will be ~45 min for the [11C-methionine head scan; for the [18F]-FACBC scan, an initial scanning period of the head will be ~45 min, followed by ~45 min for each of the up to three subsequent body scan periods (maximum total time in the scanner for the [18F]-FACBC imaging series will be ~180 minutes). The last 10 patients will be scanned for a maximum of ~90 minutes (an initial [18F]-FACBC scanning period of the head will be ~45 min, followed by a ~45 min body scan). This is long and could produce some discomfort because movement and changes of position will be discouraged. However, there will be substantial breaks between each of the [18F]-FACBC imaging sequences where the patient will come out of the scanner. Many studies on patients have been performed for this length of time and longer.

11.2 Radiation Exposure. The radiation exposure from diagnostic 3-[18F]-FACBC or [11C-methyl]-L-methionine PET studies is expected to be within acceptable limits as established by FDA Guidelines (Code of Federal Regulations, Section 361.1). Dosimetry estimates of [11C-methyl]-L-methionine to critical organs have been reported [16 and Appendix B]. Preliminary measurements of 3-[18F]-FACBC dosimetry performed Emory have been reported [11 and Appendix B] and will be extended by results obtained in this study.

11.3 The dosimetry estimates in Appendices B have led us to select a conservative 185 MBq (5 mCi) dose of [11C-methyl]-L-methionine and a 370 MBq (10 mCi) dose of 3-[18F]-FACBC for this study. This will maintain the radioactivity exposure to all normal tissue (including whole body, blood forming organs and gonads) well below the annual radiation dose limit of 5 cSv established by the FDA (Code of Federal Regulations, Section 361.1) (see Appendix B). In the event that our measurements and dosimetry estimates for 3-[18F]-FACBC exceed the annual radiation dose limit of 5 cSv established by the FDA, we will reduce the administered dose of 3-[18F]-FACBC to insure that the annual radiation dose limit of 5 cSv is not exceeded.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUT COME ASSESSMENT

Evaluation of therapy is not the focus of this proposal.

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1 If the patient is no longer able to participate in the protocol and imaging schedule.

13.2 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.

13.3 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

14.1 This is a pilot study involving only ~~20~~ 30 patients initially. Basic measurements (biodistribution, clearance, radioactivity exposure) will be summarized as means, ranges and standard deviations.

14.2 Published data in humans and our own prior laboratory experience indicate that statistical analyses of measurements of the type we propose to study would benefit from first applying a logarithmic transformation. For example, cumulated activities per unit of administered activity in Table 3 of [**17**] had nearly constant coefficients of variation (CoV) within subgroups of organs: 24.7% average CoV for brain, heart, kidneys and liver and 11.9% average CoV for lungs, pancreas and spleen. (Note that we corrected the published calculations of standard deviations to the unbiased estimate using divisor = n-1.) Our own preliminary animal data had an average CoV of 24.4%. This suggests that mean organ values could be estimated with 95% confidence to within +/- 16% from a sample of size 10, and within +/- 11% from a sample of size 20.

14.3 Randomization of the sequence of studies will not be performed because of our objective to perform both studies on the same day; the [11C-methyl]-L-methionine study must be performed first because 11-C has the shorter physical half-life (20 minutes vs. 110 min for 18-F). A 3 or more hour interval will separate the [11C-methyl]-L-methionine and 3-[18F]-FACBC studies to allow for near complete 11-C decay.

14.4 Data may be compared to FDG scans, when available.

15.0 SUBJECT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 RESEARCH PARTICIPANT REGISTRATION

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

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

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

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

15.2 RANDOMIZATION

Randomization of the sequence of studies will not be performed because of our objective to perform both studies on the same day; the [11C-methyl]-L-methionine study must be performed first because 11-C has the shorter physical half-life (20 minutes vs. 110 min for 18-F). A 3 or more hour interval will separate the [11C-methyl]-L-methionine and 3-[18F]-FACBC studies to allow for near complete 11-C decay.

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. Source documentation will be available to support the computerized patient record.

16.2 QUALITY ASSURANCE

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and 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.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

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

Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

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.

19.1 Reference(s)

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20.0 APPENDICE(S)

Appendix A. Radiopharmaceutical Preparation of [11C-methyl]-L-methionine and 3-[18F]-FACBC