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Amendment E

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Study Sponsor: National Cancer Institute, Cancer Imaging Program

IND #: 122053

NCI-Supplied Agent(s): ^{18}F-DCFBC
Other Agent(s): ^{18}F NaF

Manufacturer: Leidos Biomedical Research, Inc.

Précis

Background

- Prostate cancer is the second leading cause of cancer deaths in American men
- Current methods of imaging advanced prostate cancer (CT and bone scan) are non-specific and new, more specific molecular imaging probes are sought.
- Many prostate cancers express the prostate specific membrane antigen (PSMA) a transmembrane protein with NAALADase enzymatic activity. PSMA is also expressed in angiogenesis but otherwise has limited expression in normal tissue.
- ^{18}F-DCFBC is a radiolabeled PET agent which binds with high affinity to PSMA and through whole-body non-invasive functional imaging, may provide new information on the expression of PSMA.

Primary Objective

- To assess the ability of ^{18}F-DCFBC to differentiate between tumorous and non-tumorous tissues in localized, recurrent (based on rising PSA post treatment) and metastatic prostate cancer

Eligibility

- Subject is ≥18 years old
- ECOG 0-2 with adenocarcinoma of the prostate and fits criteria for one of the following:
- ARM 1
    - Patients with known localized prostate cancer with a soft tissue lesion at least 6mm or greater.
        - A multiparametric MRI (standard of care at the NIH Clinical Center) must be performed within 4 months of ^{18}F-DCFBC injection with findings suggestive for prostate cancer and confirmed with histopathology.
- ARM 2
    - Patients with biochemical prostate cancer relapse after definitive treatment
        - For patients status post radiation therapy for prostate cancer, any PSA increase from post radiation therapy nadir

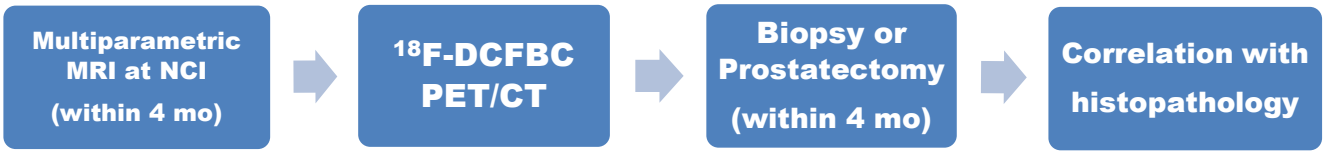
      OR
        - For patients status post prostatectomy, a PSA >/=0.2 ng/ml
    - Nonspecific or no evidence for disease on standard imaging modality
- ARM 3
    - Patients with identifiable metastatic disease on a conventional imaging modality. If only soft tissue metastasis, one lesion must measure 6mm or greater. Patients must have confirmation of prostate cancer prior to ^{18}F-DCFBCimaging.

Design

This is a single site 3-arm study enrolling a total of 110 evaluable patients: Arm 1 will include 12 patients with presumed localized prostate cancer scheduled to undergo prostatectomy or biopsy within 4 months of enrollment; Arm 2 will include 78 patients with biochemical recurrence without evidence of metastasis on conventional imaging; and Arm 3 will include 20 patients with known metastatic disease who may or may not be on or/scheduled to begin therapeutic intervention. Patients with presumed localized disease will undergo a standard of care, clinical multiparametric endorectal coil MRI in the NCI Molecular Imaging Clinic within 4 months of screening. Patients in Arm 3 will undergo 2 imaging sessions: baseline and 4-6 month follow-up. Clinical records (including PSA) and treatment (if any) that occurred in the imaging interval must be available. All patients in Arm 3 will also undergo $Na^{18}F$ PET/CT for evaluation of bone metastases as part of this protocol. In order to allow for a small number of nonevaluable patients, the accrual ceiling will be set at 125.

Imaging Schema

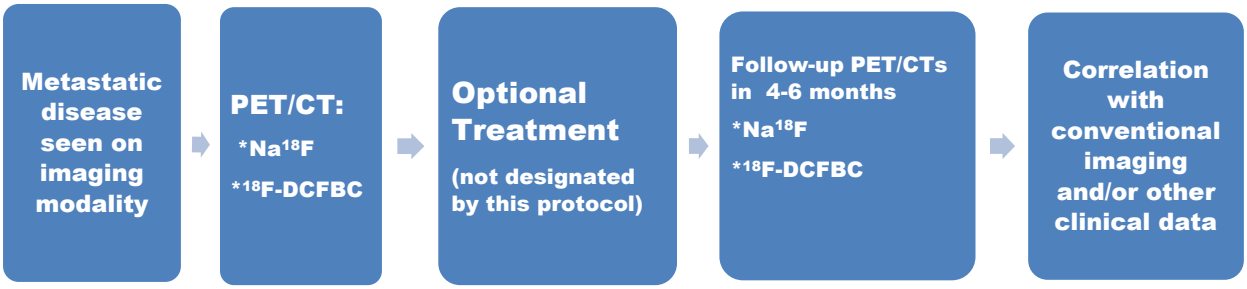
ARM 1 Suspected localized prostate cancer



*Biopsy is standard of care at NCI, prostatectomy will only be performed if clinically indicated and patient wishes to pursue this form of treatment

ARM 2 (biochemical recurrence)

ARM 3 (known metastasis)



Each set of Na^{18}F PET/CT and ^{18}F-DCFBC PET/CT will be done within 3-weeks of each other.

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1 Study Objectives

1.1 Primary Objective

- To assess the ability of ^{18}F-DCFBC to differentiate between tumorous and non-tumorous tissues in localized, recurrent (based on rising PSA post treatment) and metastatic prostate cancer

1.2 Secondary Objectives

- Compare the distribution ^{18}F-DCFBC with multiparametric MRI and whole mount histopathology in patients undergoing prostatectomy
- Evaluate the distribution ^{18}F-DCFBC uptake in prostate cancer patients with biochemical relapse (site of recurrence unknown)
- Compare focal ^{18}F-DCFBC uptake with focal abnormalities identified on standard of care imaging
- Compare the uptake of ^{18}F-DCFBC in bone with respect to Na^{18}F PET/CT in patients with metastatic disease (the emerging gold standard, for detection of bony metastases).
- Evaluate the change over time in ^{18}F-DCFBC distribution in patients with known metastatic disease with clinical follow-up data 4-6 months post baseline ^{18}F-DCFBC PET/CT (e.g. understand the effect of androgen deprivation therapy (ADT) on ^{18}F-DCFBC uptake)

1.3 Exploratory Objective

- If PET/MRI is obtained, findings will be compared with other acquired imaging studies.

2 Background and Rationale

2.1 Prostate Cancer

The lifetime risk of developing prostate cancer for men is 1 in 6. In 2013, it is estimated that 238,590 men will be diagnosed with and 29,720 men will die of cancer of the prostate according to the National Cancer Institute. Many therapeutic options are dependent on the cancer stage at diagnosis and after treatment, recurrent malignancy and accurately defining these stages can be diagnostically challenging. Especially complex is the patient with biochemical recurrence who has no other evidence for cancer except for a suspiciously rising PSA. Accurate assessment at all levels of the disease is critical to guide the best therapy and minimize morbidity related to treatment. Non-invasive methods to detect and monitor this malignancy are limited to PSA for biochemical relapse and CT, US and MRI for standard anatomic morphology. Nuclear medicine has the potential to capture physiologic function but is currently limited to conventional ^{99m}Tc MDP bone scintigraphy or^{18}F NaF PET/CT, which is restricted to visualizing bone changes; however the findings can be nonspecific, occur from metastatic disease or benign causes. The only FDA approved molecular imaging radiotracer to detect soft tissue prostate cancer metastasis, ^{111}In Prostascint, has proven to be suboptimal for many reasons and is not routinely used in most clinical settings. Improving molecular imaging capabilities in prostate cancer is crucial to battling this illness.

Much interest has centered on prostate specific membrane antigen (PSMA) as a target for imaging and therapy. Also known as Glutamate Carboxypeptidase II (GCPII) in the central nervous system, PSMA is a type II cell surface membrane glycoprotein receptor found in almost all prostate cancers, especially in advanced, hormone-independent and metastatic disease. It can also be found in the neovasculature of nearly all solid tumors. [1, 2] It is also seen in normal prostate, small bowel, proximal renal tubules, salivary glands and brain but at 100 to 1000 fold lower expression. [3] This normal expression appears to occur within luminal sites which is advantageous in formulating specialized antibodies because they do not need to cross intact basement membranes and tight junctions to bind. Another attractive feature of PSMA is that it does not appear to be secreted in serum, unlike PSA [4]; therefore imaging background due to organ perfusion will be less of an issue. Important to drug development, PSMA bound antibodies undergo internalization through clathrin coated pits. [5] This would give time for targeted imaging once any background activity and non-specific binding clears. These unique characteristics make PSMA a desirable target.

Monoclonal antibodies have been developed against PSMA, but the first agent, ^{111}In Prostascint, targets an intracellular epitope that is inaccessible in viable tumor cells which is one factor contributing to its lack of clinical utility.[6] More promising antibodies have been engineered with binding sites to the extracellular domain such as J591 and IgG monoclonal antibodies such as ^{64}Cu-3/A12. [7]

J591 is the first humanized monoclonal antibody targeting the extracellular domain of PSMA to be tested in humans. In one trial, 29 patients received ^{111}In-J591 for imaging followed by ^{90}Y-J591 for therapy. In the parallel trial, 24 patients were treated with ^{177}Lu-J591, an isotope that can be imaged directly. Overall, of the 43 evaluable patients J591 accurately targeted bone and/or soft tissue lesions in 42 patients (98%). J591 accurately targeted bone lesions in 32 of 34 (94%) and soft tissue lesions in 13 of 18 (72%) evaluable patients. [8] Nargund et al used PSMA scintigraphy with ^{99m}Tc labeled J591 to show usefulness in detecting prostate bed recurrence and distant micrometastasis but not in identifying tumors of the capsule, seminal vesicles or bladder neck.[9] Imaging through PET has been accomplished using ^{64}Cu -J591. Evans et al demonstrated that the androgen receptor (AR) is required for androgen repression of PSMA and can be quantitatively imaged with PET. [10] Androgen deprivation therapies, such as MDV3100, increase ^{64}Cu -J591 uptake. Illustrating AR signaling changes from pharmacologic intervention in human prostate cancer xenograft models suggests this radiotracer's potential as an imaging biomarker of AR activity.

Disadvantages of radiolabelled antibodies include their large size which slows clearance from the blood pool producing high background radioactivity. The bulky size could also prevent contact with all available binding sites of a heterogeneous tumor. Consequently, binding to target tumor is not quick and can take several days. Small molecule PSMA inhibitors have been created to address this shortcoming. Low-molecular weight compounds have better pharmacokinetics with faster clearance from nontarget tissues and short circulation times in

the blood pool. Typically, these compounds bind to zinc and attach to a glutamate form and belong to 3 different classes- (1) phosphonate-, phosphate-, and phosphoramidate, (2) thiols or (3) ureas.

Urea based scaffolds have yielded the most promising results for molecular imaging. Foss et al first synthesized urea-based small molecule PSMA ligands for PET, ^{11}C-DCMC, and SPECT, ^{125}I-DCIT, and showed specific binding to PSMA in prostate cancer xenograft rodent models.[11] The PET agent has limited clinical use due to the short half-life of 20 minutes for^{11}C. ^{125}I is produced by nuclear reactor and, with a long half-life (59.4 days) and low energy emissions (27keV) it is suboptimal as an imaging agent. Substitution with ^{123}I (cyclotron produced, primary emission 159keV, half-life of 13.2 days), while imagable with a gamma camera/SPECT, given current limitations SPECT camera yields non-quantitative images with high count loss. ^{68}Ga PSMA ligands to urea compounds have also been produced with good PSMA affinity and tumor-to-background ratios.[12] and can be imaged by PET/CT. A valuable feature of ^{68}Ga-PSMA compounds is that it is a generator produced radiotracer with a reasonable half-life (68 minutes), eliminating the need for a cyclotron and therefore could be more widely available for use.

A significant urea platform for radiolabelling is a lysine glutamate urea molecule and its tri-esters. SPECT agents have been produced from these foundations (^{123}I-MIP-1072 and ^{123}I-MIP-1095), that have good affinity for PSMA and are able to detect metastatic lesions. [13] Structurally similar, Mease et al expanded initial work with carbon-11–labeled compound N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]- S-[^{11}C]methyl-L-cysteine (^{11}C-DCMC) to developing fluorine-18, N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4- [^{18}F]fluorobenzyl-L-cysteine (^{18}F-DCFBC) as the first agent designed specifically for clinical PET imaging of prostate cancer.[14]

2.2 ^{18}F DCFBC (CIP # 122053)

^{18}F DCFBC is a small molecule targeting an external binding domain of PSMA. Mease et al described the synthesis, in vivo behavior and human dosimetry estimates using mouse biodistribution data for ^{18}F DCFBC.[14] Mice were implanted with PSMA+ and PSMA – prostate cancer cell lines and injected with ^{18}F DCFBC. PSMA has N-acetylaspartyl-glutamate (NAAG) peptidase activity which was utilized to determine ^{18}F DCFBC's inhibitory capacity for PSMA through the NAAG peptidase inhibition assay. Findings of 13.9 nmol/L for IC50 value were consistent with other compounds of this class. At 60 minutes after radiotracer injection, rodents had the highest uptake in the kidneys and urinary bladder as well as in the PSMA+ tumor. Little to no uptake was noted in PSMA- cells. Physiologic

excretion occurred through the kidneys and bladder and by 2 hours, renal radioactivity was confined to the cortex. Target to muscle background ratio of 10:1 at 60 min and 20:1 was seen at 120 min after injection. Clearance from non-target tissue was faster than from target sites. Low uptake in normal bone was noted indicating no significant defluorination of ^{18}F DCFBC, which will allow visualization of bone metastasis.

Their human dosimetry estimates based on the animal model [14] calculate the highest absorbed dose to the kidneys at 0.0487 mGy/MBq (0.2 rad/mCi). The mean absorbed dose to the liver was 0.009 mGy/MBq and .0005 mGy/MBq to the brain. The effective dose equivalent was .005 mSv/MBq and the effective dose was .003 mSv/MBq. Administering a dose of 185 to 370 MBq (5-10 mCi) ^{18}F DCFBC yields acceptable absorbed dose estimates for nuclear medicine diagnostic procedures.

Cho et al followed up with initial clinical experience with ^{18}F DCFBC in metastatic prostate cancer patients.[15] Five patients with metastatic disease were injected with 370 MBq (10 mCi) of ^{18}F DCFBC and serial PET/CTs obtained for 2 hours after injection. Based on visual and quantitative assessment, the highest ratio of tumor activity to background was seen at the 2 hour scan. PET images were considered positive if focal radioactivity was above adjacent background tissue or blood pool for lymph nodes or bone. Lean body mass maximum standardized uptake values (SUV_{max}) were obtained for regions-of-interest (ROIs) for quantitative measurements. Focal abnormal PET uptake was seen in 32 metastatic lymph nodes and bone lesions with median SUV_{max} of 5.6 for lymph nodes, and 3.6 for bone. Conventional imaging was concordant with PET findings in 21 sites, 5 of them bone. Discordant positive PET findings were attributed to possible early bone metastases or subcentimeter lymph nodes. All 10 positive sites on conventional imaging that were negative on PET, were in bone and considered indeterminate for malignancy or due to trauma. One true metastatic bone lesion that was PET negative could have been related to antiandrogen therapy.

Metabolite analysis was also done in 2 patients with high performance liquid chromatography with essentially no metabolism or defluorination of ^{18}F DCFBC in plasma at approximately 1 and 2 hours after injection. Radioactivity remained almost entirely within the blood plasma.

Surprisingly, blood pool activity remained moderately persistent through imaging. Possible explanations include binding to a free form of PSMA circulating in the blood. They tested the inhibitory capacity of unlabeled DCFBC to prevent PSMA from hydrolyzing N-acetylated aspartyl-glutamate in normal human plasma and found 3nM was the 50% inhibitory concentration.

Dosimetry calculations showed a mean effective dose of 19.9 $\pm$ 1.34 uSv/MBq. The highest mean absorbed dose (uGy/MBq) was the urinary bladder wall (32.4) then the stomach wall

(30.2), heart wall (29.2) and kidneys (28.4). Similar to preclinical findings, ^{18}F DCFBC, cleared through urinary excretion with PSMA-mediated uptake in normal renal tissue. No significant brain uptake was noted consistent with the radiotracer's hydrophilic nature (and resultant inability to cross the blood-brain barrier). Effective dose estimates are comparable to ^{18}F FDG (used in clinic routinely) which is 1.90 x 10^{-2} mSv/MBq and ^{18}F DCFBC averages 1.99 x 10^{-2} mSv/MBq per administered dose. Their dosimetry calculations are below.

Organ	Average
Adrenals	1.85E−02
Brain	4.21E−03
Breasts	8.51E−03
Gallbladder wall	1.79E−02
Lower large intestine wall	2.47E−02
Small intestine wall	2.36E−02
Stomach wall	3.02E−02
Upper large intestine wall	2.34E−02
Heart wall	2.92E−02
Kidneys	2.84E−02
Liver	2.46E−02
Lungs	2.45E−02
Muscle	9.69E−03
Ovaries	1.32E−02
Pancreas	1.92E−02
Red marrow	1.70E−02
Osteogenic cells	1.82E−02
Skin	7.30E−03
Spleen	1.72E−02
Testes	1.54E−02
Thymus	1.10E−02
Thyroid	1.17E−02
Bladder wall	3.24E−02
Uterus	1.34E−02
Total body	1.09E−02
Effective dose	1.99E−02

Figure 1: Average Organ-Absorbed Dose (mGy/MBq) and Estimated Effective Dose (mSv/MBq) **[15]**

In this study, none of the 5 patients experienced any severe adverse events. There were 3 minor adverse events that were classified as either unrelated or unlikely to be attributable to the radiopharmaceutical. Two patients experienced grade 3 blood pressure events using the Common Terminology Criteria for Adverse Events (National Cancer Institute) on routine vital sign assessment after administration of the radiopharmaceutical (patient 1 unrelated; patient 2 unlikely), both of which resolved on 7-d follow-up assessment. Several days after administration of the radiopharmaceutical, a third patient experienced lower back pain that began during physical exertion and was considered unrelated to the radiopharmaceutical.

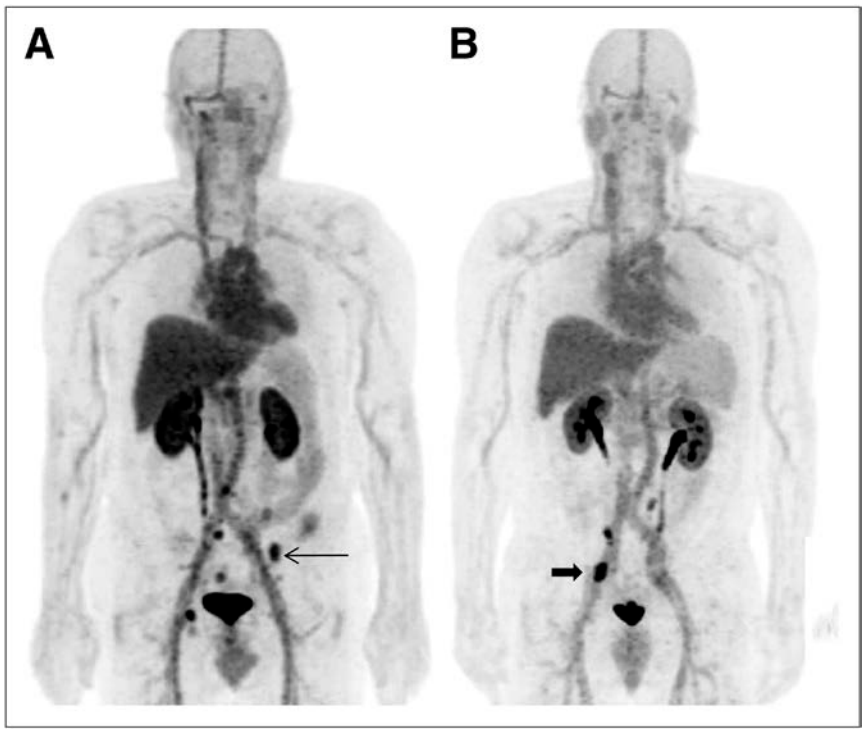

Figure 2 ^{18}F-DCFBC PET anterior projection maximal-intensity-projection images at 2 h after injection in patient 1, with several bone metastases (arrow) (A), and patient 5, with LN metastases (arrow) (B), as confirmed by correlation to CT portion of PET/CT exam. [15]

2.2.1 Toxicity and Pharmacology

2.2.1.1 Toxicity in animals

A toxicity report "Single Dose Toxicity Study of ^{19}F-DCFBC (NSC-743104) in Rats" was prepared by Bridge GPS, Inc. (Study No. 1535-07015). The following summary is taken from that report.

This study was designed to determine target organ toxicity of 19F-DCFBC (NSC-743104) and its reversibility in rats treated with a single intravenous dose.

Sixty Fischer 344 rats (30/sex) were randomly assigned to one of three dose groups(10/sex/group) based on body weight and physical examination. Five rats/sex/group were designated to the main phase of the study, and five rats/sex/group were designated to the recovery phase of the study. All animals were dosed once on Study Day (SC) 1 via intravenous injection (tail vein) with either the control article (5% dextrose) or 19F-DCFBC (NSC-743104) at nominal dose levels of 0.1 or 0.5 mg/kg. Terminal sacrifice necropsies were performed on SD 4; recovery sacrifice necropsies were performed on SD 15.Parameters evaluated during the study included mortality, clinical and cage side observations, body weights, body weight changes, clinical pathology parameters (clinical chemistry and hematology), gross pathology and histopathology. Mortality, clinical and cage-side observation, body weight and body weight changes, clinical pathology, gross pathology and histopathology were unaffected by treatment.

Based on the results of this study, a single intravenous injection of 18F-DCFBC (NSC-743104) at doses up to 0.5 mg/kg to male and female Fischer 344 rats was well tolerated.

2.2.1.2 Toxicity in Humans

Cho et al [15] studied five patients with metastatic prostate cancer and none experienced any severe adverse events. There were 3 adverse events that were classified as either unrelated or unlikely to be attributable to the radiopharmaceutical. Two patients experienced grade 3 blood pressure events using the Common Terminology Criteria for Adverse Events (National Cancer Institute) on routine vital sign assessment after administration of the radiopharmaceutical (patient 1 unrelated; patient 2 unlikely), both of which resolved on 7-d follow-up assessment. Several days after administration of the radiopharmaceutical, a third patient experienced lower back pain that began during physical exertion and was considered unrelated to the radiopharmaceutical.

2.2.2 Safety

Cho et al [15] demonstrated that radiation doses to patients with ^{18}F DCFBC are comparable to other PET radiopharmaceuticals such as ^{18}F FDG with the overall effective dose for ^{18}F-DCFBC averaging 1.99×10^{-2} mSv/MBq per administered dose (vs. ^{18}F-FDG, estimated at 1.90×10^{-2} mSv/MBq).

2.2.3 Catheter Placement

DCFBC is physiologically excreted through the bladder making visualization of surrounding tissue, (primarily the prostate bed in our situation) extremely challenging. In Arm 2 patients specifically, we are looking for possible recurrence within the region that may be very small and often overshadowed by the adjacent high urine activity. Mertens et al., described using a catheter during FDG imaging that significantly improved visualization and quantification of primary bladder cancer [17]. Other groups have also shown better evaluation of gynecologic tumors using catheter irrigation [18]. We are hoping to similarly optimize our ability to accurately find disease by reducing bladder activity with the catheter.

2.3 Rationale

We propose to further expand upon initial clinical work with ^{18}F DCFBC and evaluate its usefulness in three different categories of prostate cancer- localized, metastatic and biochemical recurrence. In the case of localized disease ^{18}F DCFBC distribution will be compared with endorectal coil multiparametric MRI at 3T. In the case of potentially recurrent or metastatic disease ^{18}F DCFBC will be compared with CT, bone scan and/or Sodium Fluoride PET/CT bone scan. This study should offer insights into how and when ^{18}F DCFBC could be used in the clinical setting to direct proper management. Moreover, by monitoring ^{18}F DCFBC uptake in metastatic disease over time, one may better understand how useful this agent may be in monitoring responses to therapy.

Amendment C Addendum:

The agent has shown some preliminary promising results. In Arm 2, we have had patients with questionable uptake only near the bladder. We have noted that bladder activity may obscure possible prostate bed recurrence, so a recent amendment was approved for urinary catheterization with possible bladder irrigation. We have only been able to scan a limited

number of patients using this technique and have been able to locate areas suspicious for recurrence in some. Additional patients will help to determine if the technique is beneficial in visualization, potentially improving detection rates for early local recurrence. In Arm 3, we have noted a mixed response in tracer uptake for hormone sensitive patients, which contradicts what other PSMA research groups are reporting. They assert that uptake is always positive in patients on anti-androgen treatment. Our findings could be due to the heterogeneous evolution of lesions to castrate resistance, but currently our numbers are small. More patients to this arm will allow better characterization of the relationship between 18F DCFBC uptake and androgen deprivation therapy.

Amendment E Addendum:

To date 31 patients have been scanned on Arm 2. All are assumed to have recurrent disease based on rising PSA. There have been 20 positive scans (9 in the prostate bed, 8 outside the prostate bed (nodes or bone) and 3 both in and out of the prostate bed. Biopsy is only available in 7 but clinical information is supportive (i.e. response to therapy) in 4 more. Thus, the results are still preliminary. In the range of PSA 0.2-0.5ng/ml the scan is 25% positive, 0.5-1.0 ng/ml 50% 1.0 to 2.0ng/ml 40% and >2.0ng/ml 85%. However, the first 10 patients were done without irrigation catheters and this undoubtedly explains some of the findings. The first expansion request for Arm 2 was to get more patients with bladder irrigation catheters after we recognized that bladder-urethra activity was probably hiding some lesions. We now have over 20 patients in that category. Having shown some promising results, the purpose of this expansion cohort is to better define the sensitivity of DCFBC as a function of serum PSA. This should be a useful metric for comparing DCFBC with the next agent, DCFPyl which is reputed to have higher sensitivity. Thus, the basis of our request is to obtain more accurate assessment of the sensitivity of this agent as a function of PSA in patients with biochemical recurrence.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Subject is ≥18 years old

3.1.2 Platelet count > 50,000/mm^3

3.1.3 Eastern Cooperative Oncology Group (ECOG) Performance score of 0 to 2.

3.1.4 Ability to provide informed consent. All subjects must sign an informed consent form indicating their understanding of the investigational nature and risks of the study before any protocol-related studies are performed.

3.1.5 Categories

3.1.5.1 ARM 1 only

3.1.5.1.1 For patients with presumed localized disease (any T, N0, M0), a multiparametric MRI (standard of care at the NIH Clinical Center) must be performed within 4 months of the ^{18}F-DCFBC injection with findings suggestive for prostate cancer and a prostate lesion at least 6mm or greater. Must have histopathologic confirmation of prostate cancer prior to ^{18}F-DCFBC imaging.

3.1.5.2 ARM 2 only:

3.1.5.2.1 For patients status post radiation therapy for prostate cancer, any PSA increase from post radiation therapy nadir

OR

3.1.5.2.2 For patients status post prostatectomy, a PSA >/=0.2 ng/ml

3.1.5.2.3 Nonspecific or no evidence for disease on standard imaging modality

3.1.5.3 ARM 3 only:

3.1.5.3.1 Patients must have identifiable metastatic disease on at least 1 clinically indicated imaging modality. If only soft tissue metastasis, one lesion must measure at least 6mm or greater. Patients must have confirmation of prostate cancer prior to ^{18}F-DCFBCimaging.

Note: A patient who is eligible for one arm, subsequently may cross-over into a different arm.

3.2 Exclusion Criteria

3.2.1 Subjects for whom participating would significantly delay the scheduled standard of care therapy.

3.2.2 Subjects with any coexisting medical or psychiatric condition that is likely to interfere with study procedures and/or results.

3.2.3 Subjects with severe claustrophobia unresponsive to oral anxiolytics

3.2.4 Other medical conditions deemed by the principal investigator (or associates) to make the subject unsafe/ineligible for protocol procedures.

3.2.5 Subjects weighing > 350 lbs. (weight limit for scanner table), or unable to fit within the imaging gantry

3.2.6 Serum creatinine > 2 times the upper limit of normal

3.2.7 Total bilirubin > 2 times the upper limit of normal

3.2.8 Liver transaminases (ALT, AST) greater than 3 times the upper limit of normal

3.3 Screening Evaluation

Subjects will be seen by their treating NCI physician and be scheduled to undergo a multiparametric 3T MR in the NCI Molecular imaging center as standard of care for Arm 1. Confirmation of disease will be made following standard of care biopsy or prostatectomy (not part of this protocol) and slides must be reviewed by the Pathology staff at NIH. For presumed biochemical recurrence (Arm 2) or metastatic disease (Arm 3) conventional imaging studies and pathology confirmation of the diagnosis of adenocarcinoma of the prostate are required. Outside imaging studies can be used to include/exclude metastatic disease; however the images must be made available in DICOM format for review by MIP staff.

A screening visit will be performed within 21 days before administration of ^{18}F DCFBC. Subjects will be permitted to continue taking any routine or necessary medication.

All subjects must satisfy all the inclusion criteria and none of the exclusion criteria listed in Section 3.1. Signed, dated and timed informed consent must be obtained from all subjects before any study-specific procedures are performed.

The following data will be collected:

- Date of birth
- Weight
- Height
- Prior and concurrent medications
- Medical history and concurrent diseases
- Results of screening tests: physical examination; vital signs; PSA test

Personal data (including contact information) will be collected with the subject's permission and only to the extent that is necessary for the purposes of the study. Blood samples for clinical laboratory tests will be drawn and include a CBC, Acute Care Panel, Hepatic Panel and PSA. Vital signs (BP, HR, RR and Temperature) will be recorded. Temperature will only be recorded at baseline, and following the completion of each PET/CT. A limited physical examination will be performed (if not performed within 30 days of ^{18}F DCFBC injection).

3.4 Inclusion of Women and Minorities

Members of all races and ethnic groups are eligible for this trial. Women are excluded from this trial as prostate cancer does not occur in females.

3.5 Registration Procedures

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to 301-480-0757. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

4 STUDY IMPLEMENTATION

4.1 Study Design

This is an open-label, 3-armed single-center pilot study. 110 evaluable subjects will be enrolled into the study (12 evaluable patients in arm 1; 78 evaluable patients in arm 2, and 20 evaluable patients in arm 3). An evaluable patient is defined as a patient who completes all required study procedures according to the assigned study arm. In order to allow for a small number of nonevaluable patients, the accrual ceiling will be set at 125.

Informed consent will be obtained prior to study enrollment. All subjects will undergo ^{18}F DCFBC injection and PET/CT imaging.

Patients in Arms 1 and 2 will undergo a single ^{18}F DCFBC PET/CT.

Patients in Arm 1 will have undergone a standard of care biopsy or clinically indicated prostatectomy. Specimens will be whole mounted on glass slides and regions of malignant tumor will be marked by the pathologist.

When possible, uptake of ^{18}F DCFBC depicted on PET/CT in Arms 2 and 3 will be validated with biopsy.

Patients in Arm 2 will be followed for clinical, imaging or pathologic data that may be obtained by their medical team within 12 months of imaging to determine if associations with ^{18}F DCFBC PET/CT can be seen.

Subjects in the metastatic disease arm (Arm 3) (as well as individuals who cross over into Arm 3) will undergo 2 separate ^{18}F DCFBC PET/CT imaging sessions, one at initial enrollment, and a second upon clinical follow-up (4-6 months after baseline ^{18}F DCFBC).

Patients in Arm 3 will also undergo a whole body Na^{18}F PET/CT scan within 3 weeks of each ^{18}F DCFBC to assess for potential early bone metastases. Changes in distribution of each radiotracer over the 4-6 month period will be compared with clinical data and imaging (obtained as standard of care) at that time. Each ^{18}F DCFBC PET/CT will be compared with the corresponding Na^{18}F PET/CT scan when obtained.

4.2 Stratification Procedures

4.2.1 Categories

- ARM 1
    - For patients in the localized disease arm, a multiparametric MRI (standard of care at the NIH Clinical Center) with findings suggestive for prostate cancer must be performed in the NCI Molecular Imaging Clinic (MIC) within 4 months of enrollment and histopathologic confirmation of prostate cancer must be done
- ARM 2

  Patients enrolling into the biochemical relapse arm:
    - For patients status post radiation therapy, any PSA increase from post radiation therapy nadir
      OR
    - For patients status post prostatectomy, a PSA >/=0.2 ng/ml
    - Nonspecific or no evidence for disease on standard imaging modality
- ARM 3
    - Patients in the metastatic monitoring arm must have identifiable metastatic disease on at least 1 imaging modality.

4.3 Drug Administration

4.3.1 ^{18}F DCFBC

See Section 7.1.5.

4.3.2 ^{18}F NaF Injection

See section 7.2.4

4.4 ^{18}F DCFBC PET/CT Imaging

All images will have personal subject identification removed and will be assigned unique subject identification.

Patients will be instructed to maintain good hydration for the 24 hours prior to the ^{18}F DCFBC PET/CT (recommended 1-2 liters of fluid, unless medically contraindicated).

Patients will report to the NCI Molecular Imaging Clinic (MIC) on the day of their ^{18}F DCFBC PET/CT imaging sessions and peripheral venous access will be obtained. The patient will be encouraged to void prior to positioning in the PET/CT scanner.

Patency of the venous access will be demonstrated with a saline flush and the patient will then receive 8 mCi of ^{18}F DCFBC as an IV bolus.

Dynamic PET/CT imaging of a single bed position (including the prostate bed) will be performed for 45-min for patients in Arm 1 and 2 then, at 60 minutes post injection of ^{18}F DCFBC. A static whole body PET/CT will be performed then repeated again at 2hrs post injection. Only a single injection of ^{18}F DCFBC is required. The initial 45 minutes dynamic regional scan will be used to determine the kinetics of ^{18}F DCFBC in the tumor as compared with normal prostate and other background.

Patients in Arm 3 will only have static whole body PET/CTs performed at 60 minutes post injection and again at 2 hrs post injection. As previous studies have suggested, increased T:B uptake is seen at 2 hours compared with 1 hour after radiotracer injection. After 5 patients are imaged in each arm, an interim analysis will be done to determine the utility of imaging at 2 hrs.

Patients in Arm 2 who have had a prostatectomy may have a 2 or 3 lumen urinary catheter inserted to improve visualization of the bladder and adjacent anatomy during imaging. The urinary catheter is inserted prior to injection and is removed once all scans are completed. The 3 lumen catheter will be used to irrigate and empty the bladder during the scan. One lumen is used to inflate the balloon to secure the catheter in the bladder, the second lumen allows for continuous drainage of urine from the bladder during imaging and the third lumen allows for inflow of fluids. The catheter will be attached to an irrigation system that will allow for better visualization of the bladder and adjacent anatomy.

After the patient is injected with the radiotracer, the bladder will be filled with up to 500cc of saline via the third inflow arm of the urinary catheter. The outflow arm is attached to the drainage bag which has a clamp. The clamp on the drainage bag will closed to allow for collection of the urine in the bladder. Approximately ten minutes before the patient is scanned the clamp on the drainage bag will be opened to allow for drainage of the bladder. The clamp will remain open during the imaging session to allow for continuous drainage of the bladder. This procedure will be repeated prior to the 2 hrs post-injection scan. Once all scans are completed the catheter will be removed.

A 2 lumen catheter will be used in lieu of the 3 lumen catheter to keep the bladder empty, if the patient cannot tolerate the insertion of a 3 lumen catheter.

If a patient is not able to tolerate catheter placement, they will be asked to empty their bladder frequently during the PET uptake phase and immediately prior to whole body PET/CT imaging.

A corresponding low dose CT scan for attenuation correction and co-registration purposes will be performed prior to each PET image (i.e. 1-single bed position including the prostate bed, and 2 whole body (1 each for the 1-hr and 2 hr images). All whole body ^{18}F DCFBC PET/CT images will be obtained from the top of the skull down to the thighs.

4.4.1 Summary of scanning procedure:

1. IV placement
2. If not previously drawn within 30 days of ^{18}F DCFBC, blood will be drawn for PSA measurement
3. Subject asked to void (Arm 2 patients will receive a urinary catheter which will be removed once all imaging is completed).
4. Administration of ^{18}F DCFBC; begin AE monitoring
5. Initial positioning in the scanner and single bed position low dose transmission CT
6. For Arm 1 and Arm 2 patients: 45-minute dynamic imaging of the pelvis
7. Subject asked to void
8. 1 hour following ^{18}F DCFBC injection, whole body PET/CT imaging will be performed (~45 minutes in duration)
9. Another whole body PET/CT scan will be performed (~45 minutes) at 2 hours post-injection of ^{18}F DCFBC
10. Follow-up AE query ~1-3 days post-injection

4.5 ^{18}F NaF PET/CT Imaging

^{18}F NaF PET/CT Imaging (only in ARM 3 subjects, may be performed as clinical standard of care in this or other arms)

Patients undergoing ^{18}F NaF PET/CT Imaging at NCI/MIC are instructed to maintain good hydration for the 24 hours prior to the ^{18}F NaF PET/CT (recommended 1-2 liters of fluid, unless medically contraindicated). Patients will report to the NCI MIC on the day of their ^{18}F NaF PET/CT imaging sessions and peripheral venous access will be obtained (most commonly via IV in the antecubital fossa). The patient will be encouraged to void prior to positioning in the PET/CT scanner. A low dose non-diagnostic transmission CT will be performed. Patency of the venous access will be demonstrated with a saline flush and the patient will then receive 3mCi of ^{18}F NaF IV bolus.

4.5.1 Whole body PET/CT

A whole body PET/CT will be performed beginning 1 hour post ^{18}F NaF injection.

Good hydration is recommended in order to reduce excessive radiation exposure. The patient should void one-half hour after the administration of ^{18}F NaF Injection and as frequently thereafter as possible.

4.6 Additional Imaging

1. For subjects with known metastatic disease (Arm 3), additional $Na^{18}F$ PET/CT and ^{18}F DCFBC PET/CT will be performed, within 3 weeks of each other and within 4-6 months following the initial scans.

2. Additional PET/MR imaging may be done if scheduling allows, and the subject does not have any MR incompatible conditions or implants) immediately after F18 DCFBC PET/CT in all arms to explore visibility of anatomic correlates to tracer uptake between the two modalities. No additional radiation risk is involved.

Patients who will undergo additional PET/MR will first complete the PET/CT portion in the Molecular Imaging Clinic (MIC). They will then be escorted to the Clinical Center Radiology Department for PET/MR imaging. Arm 2 patients with urinary catheters will have them removed prior to leaving MIC.

MRI image acquisition will follow with sequences acquired with standard MRI imaging in order to spatially correlate findings, which may include T2W, diffusion, and MRSI. Simultaneous PET emission data will be acquired with MRI images. This portion of the study will last approximately 1 hour. MR contrast will not be used to this portion of the visit, and no additional radiotracer will be injected.

4.7 Pathology

4.7.1 Surgical Pathology (Standard of care, for ARM 1 only)

Specimens will undergo standard preparation and sectioning in the Department of Surgical Pathology for pathological diagnosis. Additional sectioning and IHC staining may also be conducted by an approved outside pathology laboratory. Prostatectomy specimens will be processed by patient specific MRI based specimen molds to provide geometric and spatial alignment between MRI, PET and histopathology. The specimen results will be correlated with ^{18}F DCFBC PET/CT results and MRI imaging results.

4.8 Biopsy

Biopsy of abnormal sites of uptake will not be required by this protocol; however if a suspicious focus of uptake is identified, this information will be communicated to the referring physician, who may choose to evaluate the site further with biopsy or clinical follow-up. In such a case any follow-up information obtained (including pathology) will be collected as clinically needed.

4.9 Correlative Studies

4.9.1 Imaging Correlation

A volume of interest (VOI) will be drawn over the target lesion on the PET/CT and PET/MRI (if PET /MRI is obtained) images for each subject and Standard Uptake Values (SUVs) will

be recorded. Focal areas of abnormal uptake will be compared with any abnormalities on standard of care imaging.

4.9.2 Pathologic and Imaging Correlation

NIH Clinical Center prostatectomy or standard of care biopsy is planned for subjects enrolled in ARM 1 (localized disease). The specimen results will be correlated with ^{18}F DCFBC PET/CT and MRI results.

Following radical prostatectomy, surgical specimens will undergo standard preparation and sectioning in the Department of Surgical Pathology for pathological diagnosis. Urologists from the UOB at the NIH Clinical Center have extensive experience with laparoscopic prostatectomy. The surgical specimen obtained with the laparoscopic procedure is preserved at least as intact as in open laparotomy procedures. To date, the UOB has performed over 250 MRI/pathology correlations after laparoscopic prostatectomies.

At resection, the specimen is painted with three different colored inks (anterior right with blue, anterior left with red and urethral side with yellow) for correct orientation, and the gland is left to dry for 1-2 minutes. The gland is divided into two equal parts in the axial plane; from one of these parts, a rectangular sample of 2x1x0.2 cm is taken for DNA analysis – it is understood that this sample may contain cancer tissue and may not be reported. The DNA analysis is for research interest of the NCI and is not a component of this protocol. The two cut parts are re-glued for fixation. Fresh prostate gland is hard to hold and cut, so slicing after fixation is better and easier. The glued and combined gland is kept in formalin for 24 to 48 hours at room temperature for fixation. After fixation, the seminal vesicles are removed and then the gland is sliced via a custom-made mold based on the 3D imaging information from high resolution T2W MR images. The molds are equipped with slots spaced 6 mm apart. The gland only shrinks by approximately 3% after the first fixation and prior to slicing. A single-blade steel knife is used for one prostate. In this manner, attempts will be made to cut the specimens in the same plane as the imaging was performed. The sliced gland is kept within formalin for as long as a week at room temperature. The tissue is processed into paraffin blocks and sectioned by standard methods. The gland shrinks by 10-15% after all of these procedures.

Slide specimens will be stained for morphology and regions with malignant tumor, non-malignant pathologies, and normal tissue will be marked by the pathologist. The resultant pathologic specimen is cut transversely using the same alignment as the T2W MR images. Thus, the MRI and PET/CT scans are approximately aligned with the prostate specimens.

Tumor extent, Gleason Score and presence of BPH, and inflammation on tissue sections will be evaluated and correlated with uptake of ^{18}F DCFBC.

4.9.3 PET: MR comparison (Arm 1 or other MR available)

The distribution of uptake of ^{18}F DCFBC depicted by PET/CT will be compared with tumor indicators observed on the MR image data (T2W MRI, DCE MRI, MR DWI, and MRSI) on a per-subject and per-lesion basis.

In case the new imaging agent shows an unexpected finding, this may be correlated with conventional imaging.

4.10 Off-Study Criteria

In cases where a subject withdraws or is withdrawn from the study after administration of ^{18}F DCFBC and before surgery or biopsy is performed, a replacement subject will be enrolled.

Should a subject withdraw after administration of ^{18}F DCFBC, or should the investigators decide to withdraw the subject, all efforts will be made to complete and report the protocol-stipulated observations up to the time of withdrawal as thoroughly as possible. A final evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing or being withdrawn from the study. The reason and date and time of withdrawal must be recorded. If the reason for withdrawal is a clinical AE, monitoring will continue until the outcome or stabilization is established.

Patients will be taken off treatment upon completion of all study procedures. The patients will be taken off study one year after the follow-up period. During this one year time period, the patient's PSA levels and prostate cancer related medical history, biopsy results, imaging studies and will be collected.

4.10.1 Criteria for Removal from Protocol

- Investigators have the right to withdraw subjects from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of co-operation.
- Subject completes a one year follow-up period upon completion of all study procedures
- Subjects can be taken off study at the discretion of the Investigator.
- Patient requests to be taken off study
- Patient non-compliance with protocol guidelines
- A serious or intolerable adverse event related to the study drug occurs
- Patient may not be taken off study until intolerable adverse event has stabilized or resolved.

4.10.2 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site

(http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and faxed to 301-480-0757.

4.11 Follow-up

All subjects will be contacted by phone ~1-3 days post injection and will be asked a non-leading question to determine whether any new AEs have occurred and to follow up on any ongoing AEs since completion of PET imaging. If the patient is being evaluated in person 24 hours post-injection then a phone call will not be necessary.

Within 4-6 months following PET imaging the clinically indicated surgery or biopsy procedure will be performed.

5 Dose Modifications

Due to potential unpredictable delays and the short half-life of ^{18}F, the total dose of ^{18}F DCFBC administered may be reduced at the discretion of the principal investigator or her designee.

6 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.1.1.1) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

6.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

> **NOTE**: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously via CTEP-AERS. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Please note that a CAEPR has not been developed for ^{18}F DCFBC to-date. However, once available, the protocol will be updated to include this information.

6.1.1.1 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 that are ***bold and italicized*** in the CAEPR should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **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.

6.2 Expedited Adverse Event Reporting to CTEP

Expedited AE reporting for this study must use CTEP Adverse Event Reporting System (CTEP-AERS), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section **6.2.1**).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

6.2.1 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 0 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1 and 2 Timeframes	Grade 3-5 Timeframes
10 Calendar Days	24-Hour 5 Calendar Days

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur **more than** 30 days after the last administration of investigational agent/intervention require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for **ALL** Grade 4 and 5 AEs and Grade 3 AEs with at least a possible attribution.

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

6.3 Routine Adverse Event Reporting to CTEP

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through** CTEP-AERS **must also be reported in routine study data submissions.**

6.4 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

6.5 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

7 PHARMACEUTICAL INFORMATION

7.1 18F DCFBC (CIP # 122053)

7.1.1 Classification:

Radiopharmaceutical for imaging

7.1.2 Chemical Name:

N-[N-[(S)-1,3-Dicarboxypropyl]carbamoyl]-4-[^{18}F]fluorobenzyl-L-cysteine

7.1.3 C.A.S Number:

564482-79-7

7.1.4 How supplied:

^{18}F DCFBC is a sterile, IV injectable solution with a volume of ≤ 15 mL containing normal saline: 6.7% ethanol (V:V)

7.1.5 Route of Administration:

Subjects will receive ^{18}F DCFBC under the direct supervision of study personnel. Each subject will receive a single i.v. dose of ^{18}F DCFBC by bolus injection at a rate of approximately 1 ml/3-5 sec. The maximum amount of injected active drug will be 50 μg. The injection will be followed by a 10-ml saline flush (sodium chloride iv infusion 0.9% w/v) over ~10sec.

The target administered activity will be 8 mCi; dose variations will be in accordance with the Nuclear Regulatory Commission (NRC) standard dose variation (i.e. 20%) permitted for diagnostic clinical studies. The administered activity has been based upon the results of dosimetry analysis on data from ^{18}F DCFBC prior pre-clinical and human studies.

The administration site should be evaluated just before, during and after injection, to assess for extravasation and/or for the presence of signs of local irritation.

A member of the Molecular Imaging Program clinical team will be in attendance during the injection. In the event of an emergency, such as an allergic reaction, immediate treatment will be initiated using emergency medication available in the Molecular Imaging Clinic. If the subject requires admission due to the severity of the reaction, the subject will be admitted to the appropriate service for observation as the clinical situation dictates.

Any administration complication of the drug (e.g., overdose, observable extravasation, medication error) is a protocol related event and will be reported.

Due to potential unpredictable delays and the short half-life of ^{18}F, the total dose of ^{18}F DCFBC administered may be reduced at the discretion of the principal investigator or her designee.

7.1.6 Adverse Events and Potential Risks:

A list of the adverse events and potential risks associated with ^{18}F DCFBC can be found in Section 2.2.1.2.

7.1.7 Production of the Radiopharmaceutical:

The ^{18}F DCFBC used in this study is prepared locally by the Leidos Biomedical Research, Inc. radiopharmacy, Frederick, MD.

Manufacture of ^{18}F DCFBC drug substance and formulation, sterilization and filling of ^{18}F DCFBC Injection drug product, is a continuous process whereby the drug substance is never isolated or held. Immediately upon completion of the radiosynthesis reaction that forms ^{18}F DCFBC drug substance, the reaction mixture is purified by high performance liquid chromatography and formulated in a solution of Sodium Chloride Injection (0.9%) containing ethanol. A sample is removed for analytical testing under septic conditions for chemical and radiochemical quality control analysis, and bacterial endotoxin and sterility testing. This completes the manufacture of ^{18}F DCFBC Injection. The batch consists of about 15 mL of formulated drug product contained in a single 20 mL vial. It is held in quarantine pending completion of required quality control testing and release.

7.1.8 Agent Ordering:

^{18}F DCFBC will be ordered from the Leidos Biomedical Research, Inc. Radiopharmacy using the form supplied in Appendix B; orders should be placed 5 business days prior to the scheduled ^{18}F DCFBC scan date and time.

George Afari, PharmD, BCNP
Clinical Radiopharmacist
Applied/Developmental Research Directorate,
Leidos Biomedical Research, Inc.
National Cancer Institute-Frederick
Phone: 301 846 7391
Fax: 301 846 5935
E-mail: george.afari@nih.gov

7.1.9 Agent Returns:

If for any reason the study imaging is unable to be completed, sites will allow the radioactivity of the ^{18}F DCFBC solution to decay and then discard it appropriately per site's policies and procedures, making a record of the event as required. A copy of the policy should be available upon request.

7.1.10 Source

^{18}F DCFBC will be prepared and handled by Leidos Biomedical Research, Inc., Radiopharmacy according to the chemistry and manufacturing described in the IND. A delivery sheet/protocol will be provided with each delivery of ^{18}F DCFBC which will contain

the batch number, time of preparation, radioactive concentration (mCi/ mL) at a stated time, and shelf-life information. The delivery sheet/protocol will include the expiration date and time (hh:mm), based on the chemical stability of the synthesized compound.

Before administration, the suitability of each preparation will be assessed by a number of QC tests ran by the manufacturer, which may include radioactivity content by well-counting, radiochemical purity by thin-layer chromatography, chemical content, and pH measurement, according to approved methods provided by in the IND. A document attesting to the passing of these quality control (QC) processes will be provided to the Molecular Imaging Clinic.

Dr. Liza Lindenberg or an appropriate designee will review the documentation provided to ensure that the product quality meets the criteria for clinical use defined within the IND, and to certify (verbally, in writing or via email) that ^{18}F DCFBC is released for clinical use. The medically responsible person at the PET imaging site will ensure that the correct dose is present in the injection syringe and that the product is used within the stability period of time stated on the delivery sheet/protocol prior to injection. A lower amount of radioactivity (potentially due to an unpredictable delay in delivery or injection time) may be administered at the discretion of Dr. Liza Lindenberg or an appropriate designee, and will be documented.

7.1.11 Agent Inventory Records –

The CIP regulatory staff will inform the commercial radiopharmac(y/ies) that your NCI protocol is authorized to use the IND agent under NCI's IND. The IND agent can then be purchased from a NCI CIP AUTHORIZED commercial vendor under the NCI IND. The vendor must be specifically authorized within the NCI IND. The investigator or appropriate investigator-designee will order subject doses of the IND agent for this specific trial. The investigational radiopharmaceutical will be shipped to the site by the day the participant is to be injected, taking into account varying radioactive half-lives for different radioactive imaging agents.

7.1.12 Stability and Storage

The in-use shelf-life of ^{18}F DCFBC will be specified on the label. Although from a chemical perspective, the product remains stable beyond 6 hours, due to the short 109.8-minute half-life of ^{18}F, the low level of activity present after 6 hours renders it unsuitable for positron imaging tomography studies. ^{18}F DCFBC is stored in the original container at 4 °C under inert atmosphere.

7.1.13 Supply and Packaging

^{18}F DCFBC for each study patient will be received in individual patient doses from the manufacturer. Containers that are radioactive or contain radioactive products will be disposed of per NIH Radiation Safety Guidelines.

7.2 ^{18}F NaF Source:

^{18}F NaF will be obtained from Cardinal Health, Beltsville, MD, IBA, Sterling VA, PETNET Solutions Inc., Philadelphia, PA, or other commercial vendor according to the DMFs filed with the FDA respectively.

7.2.1 Toxicity

Fluoride is a normal body constituent. The amount of fluoride ions in ^{18}F NaF Injection at the indicated dose is expected to have minimal effect on normal human physiology. When ^{18}F NaF Injection was approved for marketing in 1972, no adverse reactions were noted in over 400 patient studies reported in the medical literature [16]. In a 1999 review of the published literature, publicly available reference sources and adverse drug reaction reporting systems indicated that no adverse reactions have been reported for ^{18}F NaF Injection[16].

The safety and effectiveness of ^{18}F NaF Injection has not been established in pediatric patients, and prudence suggests limiting exposure in growing children; carefully selected pediatric use has been reported.

7.2.2 Formulation and preparation

Supplied as a unit dose, 300-450 MBq (8.0 to 12.0 mCi) or as a multi-dose vial containing 370–14,800 MBq/mL (10–400 mCi/mL) of no-carrier-added sodium [^{18}F] fluoride at the end of synthesis (EOS) reference time in aqueous 0.9% sodium chloride solution. If supplied as a multi-dose vial, a unit dose (3-5 mCi) will be aseptically drawn from the multi-dose container for intravenous injection.

7.2.3 Stability and storage

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F). Use the solution within 12 hours of the EOS calibration time printed on the label.

7.2.4 Administration procedure

IV bolus followed by saline flush. ^{18}F NaF Injection preparations containing particulate matter or discoloration will not be administered. To maintain sterility, aseptic technique will be used during all operations involved in the manipulation and administration of ^{18}F NaF Injection.

The patient should be instructed to ingest copious amounts of fluid 1-2 hours prior and following ^{18}F NaF PET/CT imaging. The patient should void just prior to imaging and maintain hydration and as frequently thereafter as possible.

8 Study Calendar

All measurements obtained during the course of the study are summarized in the Study Calendar 8.1.1.

The timing of study events in the following descriptions is relative to the administration of ^{18}F DCFBC.

8.1.1 Study Calendar

	Screening [a]	**PET/CT Imaging** [a, b]					**Post- PET Imaging** [d]	
	Up to -30 days (screening)	**F-18 DFBC I.V. injection**	**+15 min**	**+30 min**	**+1 hours** [b]	**+2 hours**	**+1-3 days post dose administration**	**Arm 1 patients: Within 4-6 months following PET/CT imaging**
Informed consent	•							
Study entry criteria	•							
Demographic information	•							
Medical history and concurrent diseases	•							
Prior/concomitant medication	•							
Limited physical examination [c]	•							
Injection site monitoring		•	•	•	•			
Vital signs	•		•	•	•	•		
Blood samples for PSA	•							

	Screening [a]	PET/CT Imaging [a, b]					Post- PET Imaging [d]	
	Up to -30 days (screening)	F-18 DFBC I.V. injection	+15 min	+30 min	+1 hours [b]	+2 hours	+1-3 days post dose administration	Arm 1 patients: Within 4-6 months following PET/CT imaging
AE Monitoring/Query		•	•	•	•	•	•	
^{18}F DCFBC administration		•						
Tissue Sample [e]								•
PET/CT Imaging					•	•		

8.1.2 Procedures conducted during Follow-up

Occurs 4-6 months after initial scans

	Follow-Up Imaging [f]
Vital signs	•
AE Monitoring/Query	•
^{18}F DCFBC administration	•

	Follow-Up Imaging [f]
PET/CT Imaging	•

NOTE: Shaded areas depict continuous measurement or monitoring.

a. Timing of events is relative to administration of ^{18}F DCFBC.
b. At the investigator's discretion, subjects with safety concerns noted during the post-injection period may remain at the site or be asked to return to the site to undergo further safety assessments at the1-3 days post-injection time point.
c. If not performed within 30 days of ^{18}F DCFBC injection on H&P or SOAP note
d. All subjects will be contacted by phone at ~1-3 days post-injection and will be asked non-leading questions (i.e., such as "How are you doing", "Are you having any problems?") to determine whether any new AEs have occurred and to follow up on any ongoing AEs.
e. Pertains to subjects in ARM 1.
f. Performed in subjects with known metastasis (ARM 3). Subjects in this arm will also receive an ^{18}F NaF PET/CT Imaging. Each set of Na^{18}F PET/CT and ^{18}F DCFBC PET/CT will be performed within 3 weeks of each other.

8.1.3 Study Periods

8.1.3.1 Screening Period

Refer to section 3.3

8.1.3.2 ^{18}F DCFBC PET/CT Imaging Period

Refer to section 8.1.1

Monitoring of AEs will start when ^{18}F DCFBC is administered. Study personnel will remain vigilant for the occurrence of AEs, particularly those that may be life-threatening. Personnel trained in the acute management of anaphylaxis and other emergencies and who have access to appropriate clinical supplies will be immediately available for no less than 30 minutes to observe for possible anaphylactic reactions after dosing. Treatment of serious AEs should be primarily supportive of vital functions. The subjects will be closely observed and questioned for any kind of AE during the study procedures with non-leading questioning (e.g., "How do you feel?"). The subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

Vital signs will be taken prior to injection, 15 and 30 minutes after injection and following completion of each PET/CT scan.

At the end of the last PET/CT scan, the following safety assessments will be conducted: injection site monitoring, vital signs, and AE query. At the investigator's discretion, subjects with safety concerns noted during the post-injection period may remain at the site or be asked to return to the site to undergo further safety assessments at the 1-3 day follow-up time point.

8.1.3.3 Vital Signs

Vital signs will be measured at various pre- and post-injection time points described in the Study Calendar. Vital sign parameters include measurements of systolic and diastolic BP, heart rate and respiratory rate.

The interpretation and follow-up of abnormal vital signs results should be conducted on a case by case basis in conjunction with the individual clinical situation.

8.1.3.4 Physical Examination

Qualified study personnel will conduct all physical examinations. Limited physical examination will be performed as described in the Study Calendar.

In the event that new and worsening abnormal physical examination findings are encountered during the study, these terms are defined as follows: a new abnormal physical examination finding is defined as one that occurs when a subject's normal baseline physical examination becomes abnormal post-baseline, based on clinical grounds. A worsening abnormal physical

examination finding is defined as one that occurs when a subject's abnormal baseline physical examination becomes worse post-baseline, also based on clinical grounds. In both cases, observations will be collected as AEs.

8.1.3.5 Injection Site Monitoring

Injection site monitoring will be performed prior to administration of the imaging agent and at various time points post-injection described in the Study Calendar. Any abnormal findings during this period will be recorded as an AE on the research record. Abnormal injection site findings include, but are not limited to, radiopharmaceutical extravasation, bleeding, hematoma, redness and infection.

Any abnormal finding that is new or represents a worsening from baseline is an AE. Once AE notification is decided upon, investigators are required to follow the procedure described for AE notification and document the abnormal finding in the subject's research record.

8.1.3.6 Pre-Administration Events

The presence of any pre-administration event (baseline signs and symptoms present just before ^{18}F DCFBC administration) will be recorded in C3D.

The following information will also be recorded:

- The date and time of evaluation
- The onset time
- The resolution time or duration
- Action taken
- Status of symptom
- Intensity

8.2 Surgical Guidelines

No surgical procedures will be dictated by this protocol. However, if any such procedures do occur, the results will be documented.

In the event that the ^{18}F DCFBC PET/CT scan demonstrates an unexpected finding, it may be correlated with conventional imaging. The referring physician will use best clinical judgment in determining the risks and benefits of changing the surgical procedure in light of the new findings based on the correlation with conventional testing.

8.3 Radiation Therapy Guidelines

Any sites of radiation therapy must be documented (site, date began, duration, dose, and technique). Radiation therapy will not be dictated by this protocol.

9 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 6 (Adverse Events: List and Reporting Requirements).

9.1 Data Reporting

9.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via the monitoring method identified above.

9.1.2 Responsibility for Data Submission

N/A

10 Cooperative Research and Development Agreement (CRADA) / Clinical Trials Agreement (CTA)

N/A

11 CONCOMITANT MEDICATION/MEASURES

In the event that a subject has a reaction (allergic) to the radiotracer, all appropriate medical measures will be taken immediately. In rare instances, this may entail admission to the hospital for observation.

12 DATA COLLECTION AND EVALUATION

12.1 Data Collection

12.1.1 Clinical Data

All data will be kept secure. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number.

Clinical data including summary and demographic data will be collected and entered into NCI CCR Database, C3D. Adverse events occurring during any scanning session will be recorded. Adverse events which are designated possibly, probably or definitely related to ^{18}F DCFBC will also be recorded.

Imaging data will include storage of the reconstructed images and image derived parameters on a secure, password protected lab imaging database. Images may also be stored in the clinical

center PACS. The lab imaging database will be stored and maintained in the Molecular Imaging Program facilities. Personal identifiers will not be used when storing data.

NCI Molecular Imaging Program may exchange anonymized clinical data with working groups, and qualified investigators. The anonymized image data will be stored in an existing secure off-site imaging database (EXEC PACS) and these images may be shared with researchers at other institutions.

During the one year follow-up period, the patient's PSA levels and prostate cancer related medical history, biopsy results, imaging studies and will be collected (reports and CD copies of the imaging studies).

12.1.2 Safety Data

The following safety data will be collected and evaluated according to the Study Calendar (Section 8.1.1):

- Clinical laboratory variables: CBC, acute care panel, hepatic panel
- Vital signs: systolic and diastolic BP, heart rate, body temperature, and respiration rate
- Physical examination
- Injection site monitoring
- Pre-administration events (baseline signs and symptoms)
- AEs

SAEs will be recorded if they occurred as follows:

- After a subject first received ^{18}F DCFBC and throughout the subject's follow-up period,
- During the subject's follow up period, and for which a causal relationship to ^{18}F DCFBC cannot be ruled out.

Interpretation and follow-up of abnormal results will be done on a case by case basis in conjunction with the individual clinical situation. Any clinically significant abnormal finding, or change in one that represents a worsening from baseline, is an AE. Once a decision is reached to report a finding as an AE, the investigator is required to follow the procedure described for AE notification.

12.1.3 Imaging Data

Extracted imaging data include:

(1) PET imaging data will include SUV for each region of interest

(2) All image data will be stored on a secure server, with access limited to credentialed users. This will permit flexible numeric raw data extraction for quantitative analysis and creation of summary data reports.

(3) Anonymized image data from this study will be stored in a secure database that it is administered by the Cancer Imaging Program, NCI. The data may be shared with research collaborators to improve upon current methods of image analysis. The database is password protected and access is only given to qualifying collaborators.

Imaging findings for $Na^{18}F$ PET/CT will be dictated into the PACS system similar to other clinical radiologic studies, but dictations for ^{18}F DCFBC PET/CT will only reflect the radiotracer dose, injection site and a statement indicating that the scan is for research purposes only.

12.2 Toxicity Criteria

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. 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#ctc_40).

13 Biospecimen Collection

13.1 Tissue Samples (Arm 1)

All tissue specimens (slide specimens) will have been obtained during the standard of care radical prostatectomy or biopsy under the NIH routine clinical protocol (part of the eligibility criteria for Arm 1) which includes: barcoding and labeling as follows:

Tissue samples will be shipped to a core biomarker laboratory analysis of PSMA expression by immunohistochemistry. Additional exploratory biomarker assessments may be conducted on tissue specimens to provide further information regarding correlation of tumor hypoxia and uptake of ^{18}F DCFBC depicted by PET/CT.

Following completion of the core biomarker laboratory assessments, the PI, lead associate PI, one of the associate PIs or an appropriate designee will be responsible for collection of tissue specimens from the laboratories and return of specimens to NCI.

Upon return of specimens to the NCI and following completion of this study, samples will remain in storage at NCI. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a subject withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Patient Sample Data Management System (PSDMS). It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

13.2 Blood Samples

Blood samples will be collected for screening and on-study clinical laboratory safety assessments. All blood samples will be processed and handled in accordance with standard laboratory procedures. All samples will be analyzed at the NCI Clinical Center laboratory.

14 STATISTICAL CONSIDERATIONS

14.1 Primary Analysis

This is a single site three-arm pilot study, where prostate cancer patients are enrolled into different arms according to their disease types: localized (Arm 1), recurrent (Arm 2) or metastatic (Arm 3). The primary objective of this study is to assess the ability of ^{18}F-DCFBC to identify sites of localized, recurrent and metastatic prostate cancer. To achieve this goal, ^{18}F-DCFBC PET/CT and conventional imaging will be used to identify positive suspected sites, and the proportion of positive concordance will be used to assess the performance of ^{18}F-DCFBC. In a recent study (Cho et al., 2012), 32 positive suspected sites in five prostate cancer patients with metastasis were identified by ^{18}F-DCFBC PET/CT with 21 concordant on both ^{18}F-DCFBC PET/CT and conventional imaging. At the individual level, the number of positive suspected sites ranged from 2 to 12 with the patient-specific concordance rate ranging from 0 to 100%. The overall concordance rate which was the average of individual-specific estimates across patients equaled 64% with corresponding standard deviation equal to 43%. For the new study, assume that for patients in Arm 1 and Arm 3, the mean concordance rate is 70% with 43% standard deviation as observed in Cho et al. With 12 evaluable patients in Arm 1, the 90% expected confidence interval for the mean concordance rate is (0.50, 0.90). With 20 evaluable patients in Arm 3, the 90% expected confidence interval for the mean concordance rate is (0.54, 0.86). For patients in Arm 2 (recurrent disease), it is unlikely to identify suspected lesions by conventional imaging at the baseline. These patients will be followed according to the protocol.

Amendment E Addendum:

Sensitivity of ^{18}F-DCFBC uptake in prostate cancer patients in Arm 2 is evaluated by its ability in differentiating mean values of PSA between PET-CT positive and PET-CT negative patients. To this end, the current study with sample size 35 for Arm 2 is under-powered to detect a sizeable mean difference in PSA between the two groups. Based on the preliminary data of the study, log-transformed PSA is approximately normally distributed with standard deviation equal to 1.3. Assume 1:2 allocation of PET-CT negative vs. PET-CT positive

patients. The current study has only 48% power to detect a 2.5-fold geometric mean ratio in PSA between the two groups at the 5% significance level using a two-sided Wilcoxon test. To achieve 80% power, 26 PET-CT negative and 52 PET-CT positive patients are required. These results are based on 2000 Monte-Carlo samples from the normal distributions. Under the alternative hypothesis, log (PSA) is assumed to follow a normal distribution with mean (SD) equal to 0.06 (1.3) and 0.98 (1.3) for the PET-CT negative and PET-CT positive group, respectively. The mean difference of 0.92 (=0.98-0.06) in log scale of PSA corresponds to a 2.5-fold geometric mean ratio in the original scale.

In order to allow for the possibility of a small number of unevaluable patients, the accrual ceiling will be set at 15, 85 and 25, yielding a target ceiling of 125 patients for this study.

14.2 Secondary Analysis

For patients with localized disease, the diagnostic accuracy of ^{18}F-DCFBC PET/CT will be compared with multiparametric MRI using the sector-based analysis. Patient-specific sensitivity and specificity will be estimated and differences in sensitivity and specificity between different modalities will be tested by the Wilcoxon signed-rank test. Change of ^{18}F-DCFBC uptake for patients with metastatic disease over time will be estimated by the linear mixed effect model where random intercept will be used to account for the intra-patient correlation of longitudinal ^{18}F-DCFBC uptake. In addition, in patients with metastatic prostate cancer to bone, the uptake of ^{18}F-DCFBC will be correlated with the uptake of the emerging gold standard, ^{18}F Sodium Fluoride PET/CT by the Spearman rank correlation.

14.3 Interim Futility Analysis and Early Stopping Rule

To avoid excessive expense and radiation exposure, if ^{18}F-DCFBC PET/CT is not successful in identifying lesions, we implement the following interim futility analysis and early stopping rule.

We plan to stop the protocol if the first 5 patients with soft tissue lesions greater than 1 cm have negative uptake (defined as tumor uptake less than adjacent background soft tissue, or blood pool for lymph nodes). Otherwise, a separate interim analysis for Arm 1 and Arm 3 will be carried out after 8 patients in each arm have been accrued. These will be independent interim analyses for each arm and only affect the given arm. If the mean PET-positive rate, defined as the average of patient-specific PET-positive rate among the positive sites identified by the conventional imaging, is less than 60%, the study would be declared futile, otherwise the study would proceed with accrual. Assuming the standard deviation of patient-specific PET-positive rate is 0.30, the probability of stopping for futility is 83% when the true PET-positive rate is 0.5 and 17% when the true PET-positive rate is 0.70. Since Arm 2 will by criteria not have lesions on conventional imaging, they are excluded from this interim analysis and early stopping rule.

14.4 Sample Size and Accrual Rate

The sample size for this single site pilot three-arm study is targeted at 12, 78 and 20 evaluable patients in Arm 1, Arm 2 and Arm 3, respectively. In order to allow for a small number of

nonevaluable patients, the accrual ceiling will be set at 125. Assuming the accrual rate is 5-6 patients per month, the total length of accrual period for this study will be about 24 months.

15 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN for NCI IRB

15.1 Definitions

15.1.1 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

15.1.2 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

15.1.3 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

15.1.4 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

15.1.5 Disability

A substantial disruption of a person's ability to conduct normal life functions.

15.1.6 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

15.1.7 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

15.1.8 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

15.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

15.2 NCI-IRB Reporting

15.2.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All serious non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

15.3 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

15.3.1 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

15.4 Data and Safety Monitoring Plan

15.4.1 Principal Investigator/Research Team

The principal investigator or appropriate designee and research nurse will monitor the study for AEs.

This study will not have a formal data safety monitoring plan (DSMP), however, the principal investigator and Lead Associate Investigator will re-evaluate the protocol after each patient.

The principal investigator reserves the right to terminate the study on safety grounds. If 3 study subjects experience ≥ grade 2 ^{18}F DCFBC –possibly or definitely related SAEs then the study will be terminated. Before terminating the study, the investigator will ensure that a review of the overall risk/benefit analysis confirms the balance to be no longer acceptable. Should termination be necessary, the PI will arrange the relevant procedures, which will include informing the IRB, and the FDA and other relevant local and national authorities. On termination of the study, the investigator will assure that adequate consideration is given to the protection of enrolled subjects' interests. Termination of the study will be considered in the event of significant safety findings occurring at any time during the performance of the study.

Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

16 HUMAN SUBJECTS PROTECTION

16.1 Rationale for Subject Selection

The patient population in whom this disease occurs is adult males. All ethnic groups/ race categories would be represented as they are represented in the disease as a whole. Cognitively impaired individuals will not be included in this study if they are unable to understand the informed consent. Physically impaired persons who otherwise satisfy eligibility criteria will be included in this study. This study is considered more than minimal risk to subjects and no direct benefits to the patient are expected. We anticipate that a thorough discussion of the study at the time informed consent is obtained will minimize any susceptibility to undue influences and unnecessary risks to research subjects.

16.2 Participation of Children

Children will not be considered as research subjects for this study as this disease has never been documented to occur in children.

16.3 Evaluation of Benefits and Risks/Discomforts

Risks and discomforts of the experimental procedure are expected to be low and related to the risks of ^{18}F DCFBC, and PET/CT imaging. Most complications are expected to be minor and require no treatment.

Risks and discomforts associated with ^{18}F DCFBC PET/CT imaging are discomfort of an IV placement and the theoretical effects of the amount of additional radiation exposure. The maximum effective dose is 2.4 rem for Arm 1 and for Arm 2 and 5.9 rem for Arm 3, which exceeds the NIH Radiation Safety Committee's guidelines of 5.0 rem per year for adults. The benefits of the study for this group with metastatic cancer outweigh the potential radiation risks. The higher dosage for Arm 3 is due to the inclusion of F-Na PET/CT at baseline and follow-up. A follow-up ^{18}F DCFBC PET/CT image also accounts for Arm 3's higher dose. The activity of F18 FDCFBC is 8 mCi and the activity of F18 NaF is 3 mCi. In this study, the subject will be required to lie still on his back for up to 45- minutes at a time, and this might produce some discomfort.

16.4 Risks/Benefits Analysis

The risks of participation are low based on the very low doses used and prior knowledge of a low rate of AEs for ^{18}F DCFBC. No direct benefits to the subject are anticipated; however, the knowledge derived from the study could have broader implications in the field. As the significance of a ^{18}F DCFBC-depicted lesion is uncertain, treatment decisions will not be based on ^{18}F DCFBC PET/CT findings. Further evaluation with standard of care diagnostic imaging and/or biopsy will be performed at the discretion of the referring physician. The decision to pursue further imaging or pathological confirmation and the methods of doing so will be left to the referring clinician and is not dictated by this imaging protocol.

16.5 Consent and Assent Process and Documentation

The subject will be informed of the study by a member of the study team. Written and oral information about the study in a language understandable by the subject will be given to all subjects. The study will be explained in detail and the consent form and protocol (if requested) will be provided to the subject to take home (if desired) for consideration. If the subject has any questions they will be answered at the time of initial protocol discussion or later by telephone. Each subject's willingness to participate in the study will be documented in a signed and dated informed consent form before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record and the investigator will sign, and date the informed consent form after the subject and/or legal representative has signed and dated it. The investigator(s) will keep the original consent forms and copies will be given to the subjects. Informed consent may be obtained from the patient by the PI, an associate PI or any clinical designee credentialed to obtain informed consent for any procedure.

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18 APPENDICES

18.1 APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

18.2 Appendix B: F18 DCFBC Order Form

leidos
Leidos Biomedical Research, Inc.

F^{18} DCFBC Order Form

1. Site Section – Complete and fax to Leidos, Inc at Fax - 301-228-4624		
Site	**Subject / Patient ID**	**Date of Request *** DD MMM YYYY
Scheduled F^{18} DCFBC Scan DD MMM YYYY	**Time** *24 hr clock*	**Dose Activity** mCi

*Please place orders 5 business days prior to Scheduled F^{18} DCFBC scan date and time

Site Contact Information	
Site Name:	
Principal Investigator:	
Study Coordinator:	
NCI Protocol Number:	
Shipping Information	
Account Name:	
Contact Name:	
Contact Phone & Email or Fax:	
Shipment Address:	

2. Leidos Radiopharmacy Section – Confirm receipt of Request Form and fax or email to Clinical Site

Request Form received on _____ _____ _____ by _____
DD MMM YYYY Print Name

3. Leidos Radiopharmacy Section		
Date request received:	*Leidos Radiopharmacy Shipment Number:*	
Tracking Number:	*Mode of Transportation:*	
Batch Number:	Attachements: **Dosage Instruction + Release Document**	
Please affix copy of the vial label below		
Checked by:	*Packed by:*	*Date Shipped:*