Validation of FACBC as an early indicator of sub-clinical metastatic disease among high-risk or unfavorable intermediate-risk prostate cancer patients with presumed localized disease

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Early Detection of Occult Metastatic Disease in High-Risk Primary or Unfavorable Intermediate-risk Prostate Cancer Patients

1. Abstract

Approximately 50-80% of patients who are considered high-risk or unfavorable intermediate-risk experience recurrent disease after being treated with definitive radical prostatectomy, often because of undetected extra-prostatic metastatic spread. In addition, there is increasing evidence that performing radical prostatectomy in patients with high-risk disease or locally advanced disease is feasible and has potential benefit in terms of local control, overall survival, and quality of life [1-3]. Thus, improved imaging approaches for early detection of occult metastatic prostate cancer at the time of presentation could inform a directed treatment approach that would significantly improve patient outcome, including use of extended lymphadenectomy as well as postoperative radiation therapy planning.

Amino acid transport is up-regulated in prostate and other cancers. *Anti*-1-amino-3-[18F]fluorocyclobutyl-1-carboxylic acid (FACBC) is a synthetic amino acid analog positron emission tomography (PET) radiotracer that has demonstrated promising results in the staging and restaging of prostate carcinoma, with high positive predictive value (PPV) in the identification of extraprostatic malignancy [4, 5]. Most of the prior studies of FACBC were in post-primary treatment recurrence, and this proposed trial will be the first comprehensive study to evaluate FACBC PET in detecting occult metastatic disease at initial diagnosis in patients with negative or equivocal conventional imaging with the objective of developing a more effective primary treatment plan.

The goal of this study is to determine if FACBC PET will detect significant occult metastatic disease in patients with high risk or unfavorable intermediate-risk primary prostate carcinoma who have negative or equivocal conventional imaging such as CT, MR and bone scan. In addition, amino acid regulation has been implicated in mTOR pathway signaling; therefore, we believe that FACBC may also play a complementary role with other biomarkers of aggressive or metastatic disease. Therefore, a secondary goal is to leverage the utility of FACBC as a biomarker of the upregulation of amino acid transport and to correlate FACBC uptake parameters with tissue RNA signatures of prostate cancer, and levels of novel serum and urine biomarkers (urine RNA and serum phi) as an adjunct to another ongoing study.

Our hypothesis is that FACBC PET imaging will detect occult metastatic prostate cancer at the time of presentation, especially nodal disease, in patients with newly diagnosed high risk or unfavorable intermediate-risk primary prostate cancer who have negative or equivocal conventional imaging. In addition, we hypothesize that FACBC as an imaging biomarker may play a complementary role to tissue RNA signatures of prostate cancer, as well as urine RNA and serum phi.

2. Background and Significance:

Most patients with prostate cancer present with clinically localized disease, yet after curative radical prostatectomy, over 30-50% of patients eventually present with biochemical failure and recurrence [6-8]. This is especially so in patients with high or very high risk prostate cancer in which failure rates may approach or exceed 50% [8-10]. While this higher failure rate is in part due to the biologic aggressiveness of disease, it is also likely that at the time of the initial treatment that metastatic disease was present but not appreciated. Despite advances in surgery, cryosurgery and radiation therapy of localized and hormonal treatment of extra-

prostatic disease, nearly all of prostate cancer deaths result from progressive metastatic disease. Thus, the presence or absence of extra-prostatic disease will change the therapeutic approach [8]. Imaging is central to the differentiation of prostatic from extraprostatic disease. In addition, with locoregional spread or even instances of metastatic disease, radical prostatectomy may still have benefit in regards to general health-related quality-of-life (HRQOL) and overall survival (OS) in this population [11]. Imaging may then play an even greater role in formulating individualized therapy plans.

Conventional imaging such as routine CT and MR has demonstrated relatively poor performance in the staging of high risk prostate cancer especially in terms of locoregional nodal spread and distant disease [12-16]. While FDG PET has been useful in patients with more aggressive castration resistant disease it also has suboptimal performance in the routine staging of patients with prostate cancer [17, 18]. FDG-PET is not accurate in the differentiation of cancer from inflammation, and generates suboptimal images in the pelvis where small lesions can be masked by the accumulation of FDG metabolites from urine accumulation in the bladder [17]. Other molecular imaging techniques such as the FDA approved ^{111}Indium-capromab-pendetide radiotracer (ProstaScint) also have reported poor diagnostic performance [19-23]. Though newer PSMA ligands are promising, they are still early in their translation to routine clinical use [24].

Recent studies suggest that utilizing more advanced imaging such acetate and choline PET has the potential to improve early detection of occult metastatic prostate cancer of presumed locally confined primary and recurrent prostate carcinoma. Though there is suboptimal sensitivity for microscopic disease, added value has been described in higher risk prostate cancer to improve staging, especially in the detection of distant disease [25-30]. Schiavina has reported that while not sensitive enough to replace pelvic nodal dissection, imaging with choline PET demonstrated better diagnostic performance than clinical nomograms [31]. Yet, the isoform of the choline PET radiotracer that is available in the United States is based on carbon-11, which has a 20 minute half-life and is impractical without an on-site cyclotron. Though fluorocholine (FCH) with a longer half-life is available outside of the United States, intellectual property issues will limit its availability in the US until 2021. In addition, FCH has high bladder excretion which may be a limiting factor in image interpretation.

Amino acids are involved in a variety of biologic processes including protein synthesis, and amino acid transport is up-regulated in many neoplasms [32-35]. Consequently, radiolabeled amino acids, both natural and synthetic, have been utilized for oncologic molecular imaging. FACBC is an investigational synthetic non-metabolized amino acid analogue positron emission tomography (PET) radiotracer [4, 5, 36-43]. Transport is primarily mediated by sodium dependent amino acid transporters, specifically system ASC, with contribution by sodium independent system L [44, 45]. FACBC PET has been studied at multiple centers, primarily in the restaging of recurrent prostate carcinoma where it has demonstrated significantly better diagnostic performance than conventional imaging [4, 5, 39, 46, 47].

FACBC has characteristics that are advantageous in the imaging of prostate carcinoma including little renal excretion, and longer half-life of the fluorine-18 radioisotope. Most importantly, FACBC is FDA approved for recurrent prostate cancer detection. Thus, FACBC is an ideal PET radiotracer candidate to conduct a study determining if advanced molecular imaging provides significant value in the early detection of occult metastatic prostate cancer in high risk or unfavorable intermediate-risk patients before radical prostatectomy who have negative or equivocal conventional imaging, with the goal of informing a targeted treatment approach including extended pelvic nodal dissection and potentially postoperative radiotherapy and/or systemic therapy.

3. Objectives

Primary Aim- To validate FACBC as an early indicator of occult metastatic disease among high risk or unfavorable intermediate-risk prostate cancer patients with presumed localized disease.
After completion of FACBC PET, detection rate for extraprostatic disease will be determined. In addition, after surgery and review of histology, correlation will be made to histologic findings for extraprostatic disease, as well as definitive skeletal imaging to determine diagnostic performance as a secondary analysis noted in the statistical analysis plan. Reference standards as to ground truth for extraprostatic disease will be established with histologic analysis of nodes harvested in extended nodal dissections, extrapelvic and/or skeletal biopsy and/or correlation with definitive imaging findings. Thus, for this aim: 1) positivity rate will be calculated for

FACBC PET for extraprostatic disease as the primary analysis; 2) diagnostic performance of FACBC in the detection of extraprostatic disease as confirmed with histology and/or correlative imaging will be determined as a secondary analysis.

Secondary Aim- to evaluate the correlation of FACBC uptake in the prostate with presence of FACBC-detected metastasis.

With data obtained from the trial we will correlate uptake within known tumor in the prostate to the frequency of FACBC extraprostatic positivity. We will use various indices such as SUVmax, SUVpeak, SUVmean, total lesion activity, and retention indices of the primary tumor to determine if degree of uptake and uptake characteristics of FACBC PET as an imaging biomarker in itself indicate the propensity of the primary prostate cancer to metastasize as correlated with the reference standards of this trial.

Exploratory Aim- to evaluate tissue RNA signatures of prostate cancer, as well as urine RNA and serum phi parameters that are associated with higher rate of FACBC positivity in this cohort.
Urine, tissue and serum samples will be obtained from all study participants for urine and tissue RNA, and serum Phi parameters through the Prostate Satellite Tissue Bank (IRB 00045859). With data obtained through the trial and in conjunction with other ongoing studies:
1) We will correlate tissue RNA signatures of prostate cancer, urine RNA and serum phi parameters with the detection rate of FACBC studies for extraprostatic disease.
2) We will also correlate FACBC uptake parameters within the prostate/primary tumor (such as but not limited to SUVmax, SUVpeak, SUVmean, total lesion activity, and retention indices as available) with tissue RNA signatures of prostate cancer, as well as urine RNA and serum phi parameters.
3) We will therefore determine if FACBC PET may be used as an adjunct imaging biomarker in combination with the novel tissue RNA signatures of aggressive prostate cancer, as well as urine RNA and serum phi biomarkers in the detection of more aggressive or metastatic disease.
4) We will also, at a later time point, correlate uptake within the prostate itself to pathology from Emory standard histologic processing, likely on a sextant basis. Specifically, we will correlate presence or absence of tumor, inflammation, and BPH with uptake parameters.

4. Study Design

We will undertake a clinical trial with 88 patients who have been diagnosed with primary prostate carcinoma who are considered at least unfavorable intermediate-risk (Grade Group 2 (Gleason score 3+4) with either PSA 10-<20 or clinical stage T2b-c, OR Grade Group 3 (Gleason 4+3) with PSA < 20) or high risk per standard guidelines (clinical T3a, or Gleason score 8-10, or PSA greater than 20 ng/ml; and/or recurrence probability of ≥50%) as per clinical assessment, without definitive findings of systemic metastasis on conventional imaging, and who are candidates for potentially curable radical prostatectomy and extended pelvic nodal dissection. We will employ the Kattan nomograms and other standard instruments as appropriate in making this determination [48]. Subsequently, patients will undergo whole body FACBC PET-CT. Typically patients will then undergo radical prostatectomy and extended nodal dissection, but if disease is detected preoperatively outside of the prostate, this will inform a discussion between the surgeon and patient as to an individualized treatment plan which may include targeted nodal dissection and use of postoperative radiotherapy and/or systemic therapy. Primary analysis will be centered on detection of occult extraprostatic disease by FACBC PET in high or very high-risk patients without definitive findings of systemic metastasis on conventional imaging. While the primary endpoint will be FACBC PET occult extraprostatic disease detection, as a secondary analysis we will cross-tabulate the agreement between FACBC classifications versus extraprostatic disease status as identified by extended pelvic nodal dissection and other extraprostatic truth verification. Patients will also be followed for long-term outcome, but that is beyond the scope of this current trial.

FACBC radiolabeling: Production will be accomplished by the GE FastLab cassette system. Alternatively by automated synthesis developed by J. McConathy and M.M. Goodman [49]. We have prepared greater than 200 batch productions for tumor imaging in volunteer subjects. Imaging will be performed under the IND held by Dr. Schuster and FDA mandated monitoring will be completed.

Standard of Care Procedures

1. Conventional imaging: Prior to enrolment in this study, all patients will undergo standard of care preoperative bone scan and/or NaF PET, as well as nodal staging with diagnostic CT and/or MR per institutional standards. The official report is an important part of the initial evaluation and will serve as the basis for recording findings of extraprostatic disease since this will duplicate standard practice. Equivocal findings and/or non-definitive findings of systemic metastasis will be considered as negative for extraprostatic disease since management is typically not changed unless definitive radiologic findings are evident. The interpreter of the conventional imaging will have no access to FACBC imaging (and typically will be performed before FACBC). It is anticipated that all the conventional imaging will be reimbursed by third party payers.

2. Radical Prostatectomy and Extended Lymph node dissections: Patients will undergo standard of care radical prostatectomy and extended or super-extended pelvic node dissection. The surgical plan will generally involve nodal dissection of right and left obturator, right and left external iliac, right and left internal iliac, right and left common iliac, right and left pre-sciatic, and central pre-sacral with optional para-aortic and para-caval regions subject to clinical exigencies. Each group of nodes will be removed as a packet, labeled separately and sent to pathology for routine histopathologic examination. If either conventional imaging or the FACBC scan demonstrates potential other pelvic or extrapelvic nodal disease, the surgeon may choose to extend the nodal dissection to other sites. If this is done, the additional nodes will be labeled to indicate the site and they will be also be submitted for pathology review. It is noted that some patients with extrapelvic disease may still undergo surgery after a discussion between patient and surgeon as to risks, advantages, and disadvantages since there is solid evidence that patients may still benefit from this approach [1-3, 11]. Burden of disease will likely be an important factor in this decision. In addition, since patient safety is paramount, an individual patient may have surgery stopped or altered due to clinical judgement, which will modify nodal basins sampled.

   After the FACBC scan described below, and before surgery the diagnostic imager and the surgeon will communicate to review findings and to ensure consistency in correlation of findings to nodal packet nomenclature. In addition, patients with abnormal though non-definitive findings on conventional imaging and/or abnormal and/or equivocal and/or discrepant on FACBC PET-CT in extraprostatic or especially extrapelvic locations may also have those sites sampled as clinically appropriate through a combination of percutaneous image guided needle biopsy and/or laparoscopic techniques.

3. Serum, urine, and tissue samples will be collected for RNA and other genomic analysis.

Study Specific Experimental Procedures

1. **Fluciclovine PET-CT imaging:** PET-CT images will be acquired on a state-of-the-art scanner. All studies will use measured attenuation correction (routinely acquired through the initial CT portion of the scan). All subjects will fast for 4 hours to normalize their neutral amino acid levels. Within 1 hour prior to scanning, the patient (if able) will drink up to 450 ml of standard oral contrast. IV contrast will not be used. After completion of the CT scan, approximately 10 mCi *anti*-[^{18}F]FACBC will be injected into an antecubital vein as a bolus and flushed with normal saline. Scanning will commence immediately as technically possible starting with the pelvis at 2.5 min/bed for 2 bed positions (from just below ischium to approximately bifurcation); this sequence will be designated, early 0-5 minutes. At 5 minutes, 7 consecutive 2.5 minute/frame acquisitions will be obtained from the pelvis (below ischium) to approximately the skull base. At 22.5 minutes, a delayed 2 bed similar pelvis will then be acquired from the 22.5 to 27.5 mins. Thus, we will have early (effectively 10 min multi-time point imaging of the pelvis) and 10-22.5 min imaging from pelvis inlet to skull base. This acquisition is similar to a successful protocol with FACBC for primary prostate cancer staging employed at Aleris Medical Center in Oslo, Norway (personal communication, F Willoch), but also allows us to cover the entire pelvis to the bifurcation and also obtain an exploratory final 5 minutes delayed acquisition of the pelvis. The whole body acquisition itself is similar to that employed clinically. Scanning will preferably be undertaken arms above the head if possible for the patient.

Image Analysis of FACBC PET-CT:

1) Images will be reconstructed with iterative technique and interpreted on a MimVista or similar workstation.
2) Visual inspection of the PET-CT images by a board certified nuclear medicine imager, blinded to other imaging, will then occur and results recorded on a case report form. (It is possible that as part of clinical duties, the research reader may have interpreted one of the patient's earlier clinical exams. This type of situation is impossible to avoid, but it is highly unlikely that recall of an individual exam would be possible with our institutional workflow. Therefore, this situation is still considered as *blinded* for the purpose of this study.)
3) Uptake will be defined according to the following criteria in relation to background structures: mild (above blood pool but less than marrow), moderate (above or equal to marrow but less than liver), and intense (equal to or above liver). Visual analysis will aided by quantitative criteria of SUV_{max} lesion/SUV_{mean} background. Maximum and mean SUV of each focus of abnormal uptake and background will be recorded. SUV (mean, maximum, peak, total lesion activity) will also be documented for the prostate primary lesion(s) as a whole gland ROI at all time points to calculate uptake and retention indices. For extra-prostatic sites such as lymph nodes and bone, abnormal moderate or intense focal uptake which are present on 5-27.5 minute images will be considered prospectively positive (allowing for partial volume effect). Analysis will be supplemented by data from early and delayed time point acquisitions of the pelvis and is most useful to increase sensitivity for small lesions subject to partial volume effect on PET and also increase specificity. These criteria were successfully used in our studies of FACBC in recurrent disease [4, 50]. The multi-time point data of the pelvis will also be used for future analysis of uptake in comparison to the reference histologic standard likely on a sextant basis. If possible. we will use a segmentation algorithm under development to assist with this analysis.
4) A final review of the images by the nuclear medicine imager and the urologist will occur to ensure that nodal regions are understood in a similar manner and determine if areas of uptake will be in the field of operation. For example that internal iliac means the same to the imager and the surgeon.

Histologic Assessment:

The histologic examination of the nodal tissue will be done using standard clinical protocols. The surgical specimens will be submitted with each of the nodal groups separately identified with appropriate labels. This will ensure that the pathology reports will be evaluable for the presence of positive nodes in each of the nodal groups, and that it will be feasible to correlate the pathology data with the imaging data.

1) The FACBC readings for nodal groups in each patient will be compared against the histologic results. To ensure proper correlation of both FACBC and histologic results, FACBC nodal reads will be labeled according to the packets listed in #2 above. This will also guide nodal dissection and labelling of nodal tissues for pathologic analysis.
2) The readings for skeletal disease will also be compared to biopsy and definitive correlative imaging as appropriate. Criteria for skeletal metastasis are considered more well established than for lymph nodes and therefore biopsy may not be needed in the case of skeletal metastasis if two separate conventional imaging modalities such as MR, CT, and/or bone scan are concordant in probability for skeletal malignancy [51].
3) At a later time point the prostate sextant histologic data will be compared to best matching imaging sextant based on automatic or manual segmentation and correlation of uptake indices made with tumor, Gleason grade, inflammation, and BPH as well as other potential imaging and histologic analysis.

Tissue and Data Management:

1) Tissue specimen obtained from participants will be formalin fixed and paraffin embedded by the Emory Pathology Department, preserved for future intra-patient genomic comparisons between primary and metastatic disease.
2) Radiological data of participants will be stored on a secured password protected database for future retrieval and follow-up as indicated.
3) Experience from this trial will be used to plan a multicenter trial in cooperation with ECOG-ACRIN, SNMMI-CTN and Blue Earth Diagnostics (corporate developer of FACBC in the US and the EU) to potentially obtain expanded FDA approval of the modality in early detection of occult metastases before primary treatment.
4) Patients will also be followed for long term outcome measures correlating FACBC findings with PSA and clinical recurrence. Though this endpoint is beyond the scope of the current trial, patients will therefore be consented for 10 year follow-up through the medical record and via selected contact.

5. Participant selection

1) Inclusion criteria
    a. High-risk or very-high risk prostate cancer eligible for standard of care surgery
        i. At least clinical T3a disease, and/or Gleason ≥8, and/or PSA>20, as per clinical assessment and routine guidelines
    b. Unfavorable risk intermediate prostate cancer eligible for standard of care surgery
        i. Grade Group 2 (Gleason score 3+4) with either PSA 10-<20 or clinical stage T2b-c, OR Grade Group 3 (Gleason 4+3) with PSA < 20.
    c. 18 or years of age or older
    d. Undergone standard of care conventional imaging (CT and/or MR; bone scan and/or NaF PET)

2) Exclusion criteria
    a. Definitive findings of systemic metastasis on conventional imaging.

3) Recruitment: Any attempt to recruit a large cohort of subjects is always a possible limitation. We believe with the typical numbers of patients for this clinical question seen at Emory hospitals including ESJH hospital per year (approximately 50), we will be able to achieve our target goal of 18 patients per year at a conservative 36% recruitment rate. We have an on-site cyclotron and radiopharmacy staff with a proven ability to manufacture FACBC. Thus, we have the capacity to scan these subjects. If accrual is lagging, we also have the capability to open this trial at our sister institutions, Grady Hospital and the Atlanta VA.

4) Dropout**:** We have factored in an extra 2 scans for unforeseen difficulties, but since the endpoint of the study is FACBC imaging, even if a patient does not undergo surgery, sufficient data will have been obtained for the primary analysis. Therefore patient dropout is not considered to be highly relevant in this design. We will seek IRB approval of sufficient patients to allow for screening failures, but these patients will not have undergone FACBC imaging.

6. Informed Consent Process

Informed consent is required prior to participation in the study. Patients will sign the written informed consent, if possible, at the time of enrollment. In instances where this is not possible, verbal informed consent will be first obtained in order to instruct the patient to fast in preparation for the PET scan. However final written informed consent will be obtained before the PET scan. Participants will also be assigned an identification number for screening purposes; data collected during the screening process will also be recorded using that number. Consent would also be obtained for RNA, DNA and other genomic analysis on urine and other indicated biofluids.

7. Incidental Findings

a. All incidental findings noted by the imager will be discussed with the attending urologist who is a co-investigator, and documented in the electronic medical record.
b. Incidental findings (such as incidental lung nodule for example) will be disclosed to the patient who

will then formulate a follow-up plan with the attending urologist including any referrals.

c. The urologist will educate the patient about the nature of the incidental finding, how to seek care from a clinician or specialist, obtaining health insurance to secure treatment, and/or referral to a clinical specialist, if one is required.
d. Language to this effect is present in the consent form.

It is possible that nodes may be missed that are FACBC positive even with nodal dissection leading to an overestimation of false positivity of FACBC. If this is suspected, patients may be followed with conventional imaging as per routine to clarify the ground truth in specific situations. Also, a patient could then be enrolled in an ongoing clinical trial at Emory for PSA failure after prostatectomy (R01 CA169188) to undergo repeat FACBC study to determine if abnormality persists. Yet, since the PPV of FACBC has already proven to be high for extraprostatic disease and FACBC detection in itself is the primary endpoint, this potential limitation would only affect secondary analyses.

FACBC findings will be used for research purposes within the context of the clinical trial as noted above. All incidental findings will be recorded in the clinical research form and emergent incidental findings will be communicated to the patient's physician who is also the principal investigator on this study.

8. Compensation for time and effort:

Each patient will be compensated $50 as per diem for travel expenses for the FACBC scan.

9. Statistical Analysis and Power Calculation

In calculating statistical power we have taken realistic suppositions. The prevalence estimate of occult metastatic disease, FACBC sensitivity and specificity is extrapolated from reported large series and nomograms, as well as data culled from our previous trials and clinical experience [4, 5, 48, 52, 53].
The primary goal of the study is to estimate the rate of positive FACBC studies in this population for occult extraprostatic metastasis. We therefore assumed a 50% prevalence of occult metastasis (metastases not definitively evident on routine clinical imaging), 95% specificity, and a conservative sensitivity of 40%. They translate to 22.5% FACBC scans to be positive (note that FN included) and 89% PPV. We plan to enroll 88 patients to have 0.8 power for detecting the rate of positive FACBC to be at least 10%. The number of patients with positive FACBC is expected to be 20, and the number is between 12 and 28 with 0.95 probability. In addition to the point estimate, 95% CI will be calculated for the rate of positive FACBC and a statistical test will be conducted against the null hypothesis of a rate of 10%.

As part of the secondary analysis, we will cross-tabulate the FACBC classification versus extraprostatic disease status as detected by extended pelvic nodal dissection as outlined above. Note that the latter is not regarded as a gold standard for extraprostatic disease detection since it may still results in substantial false negatives. Nevertheless, the percent of positive FACBC among patients with extraprostatic disease detected by extended pelvic nodal dissection provides a reasonable estimate of the sensitivity for FACBC. We will calculate the corresponding exact 95% confidence interval. In addition, we will evaluate the extent to which the FACBC and extended pelvic nodal dissection agree with each other using kappa statistic. This analysis of concordance will help guide design of analyses of tissue-imaging concordance in the subsequent, Phase III Validation Trial (ECOG-ACRIN), to comprehensively evaluate the diagnostic characteristics of FACBC.

For Aim 2, we will assess associations between FACBC uptake parameters in the prostate and rate of extraprostatic disease detection using standard associative statistical tools including logistic regression and ANOVA as applicable.

For Aim 3, we will evaluate the association of the tissue RNA signatures of prostate cancer as well as urine and serum biomarkers with the rate of FACBC positivity using standard associative statistical tools including logistic regression and ANOVA as appropriate. Finally we will correlate FACBC uptake parameters in the primary prostate tumor to the tissue RNA signatures of aggressive prostate cancer and urine and serum biomarkers using Spearman's correlation coefficients.

10. Data and Safety Monitoring and Reporting:

See http://irb.emory.edu/documents/DSMB-DSMPGuidance.pdf for guidance.

This study is being performed under the auspices of FDA IND 72,437. Patients will be monitored by the technologists and study nurse before and after the studies for any adverse events/reactions. They will be given contact phone numbers to call if they experience any problems (i.e. problems with the IV site, any allergic reaction symptoms). They will be followed routinely by their referring physician with clinical exams, and the PI will work with the co-investigators and referring physicians to ensure that the patients continue to follow up as scheduled. The GU Oncology Working Group will serve as the Data and Safety Monitoring Board (DSMB) only if a drug related serious adverse event has been reported.

Patient safety, study efficacy and compliance will be reviewed at the Urology working group meeting. Urology Department Clinical Research Unit Director of Clinical Trials, Mersiha Torlak or a designee will serve as the independent internal monitor and will oversee the conduct of this study. The independent internal monitor will review pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy. The independent internal monitor will review the charts of 10% of patients enrolled to the study. At a minimum, review is required annually. The independent internal monitor reserves the right to conduct additional audits if necessary. The Principal Investigator (PI) or designee is responsible for notifying the independent internal monitor about ongoing patient accrual at a minimum on a monthly base.

Any study specific experimental (not standard of care) procedure related serious adverse event will be communicated by the PI to the Emory IRB and the sponsor to the FDA using standard adverse event reporting forms. Yearly safety reporting will also be forwarded to the FDA. A formal DSMB, except as noted above, will not be utilized as this is a diagnostic study with minimal risk to the patient. In addition, Blue Earth Diagnostics, Ltd, will receive data on safety since they supply FACBC cassettes.

11. Adverse Event Reporting

Halting a clinical trial due to adverse events is a possibility that must always be considered in any trial. Though we have a system in place for adverse event reporting and evaluation, it is extremely unlikely such adverse events will occur. The radiotracer is administered in trace pharmacologic amounts like all PET radiotracers. Our experience with extensive animal testing and with over 1000 human subjects has failed to demonstrate any serious adverse events due to the radiotracer. This lack of adverse events is similar to general experience with other PET radiotracers. FACBC is FDA approved for recurrent prostate cancer. But since we will be conducting research off-label and to potentially change drug labelling, we will administer the radiotracer drug under our existing IND after manufacture at our CSI radiopharmacy. **An event greater than 7 days post scan will not be considered an AE or SAE since 95% of ligand is eliminated by 7 days.**

However, in the event of patient death that may be due to the study procedure (i.e. severe radiotracer reaction), unanticipated problem, would be promptly reported to the Emory IRB office. Additionally any patient death not associated with the study procedure or serious unanticipated event(s) (i.e. radiotracer allergy) will be reported to the Emory IRB and FDA upon continuing review. Protocol deviation/non-compliance will be reported according to IRB Policies & Procedures. This radiotracer is studied under IND 72437 and monitoring will be performed per already agreed upon FDA guidance. Over 1000 patients in multiple centers have been studied without attributable serious adverse events.

A serious adverse event is any medical occurrence which is fatal, is immediately life threatening, requires hospitalization (or prolongs an existing hospitalization), results in persistent significant disability or incapacity, is a congenital abnormality or a birth defect, or is considered medically significant by a physician.

The Investigator will report all Serious Adverse Events occurring in a subject on the day of or within 28 days following the Agent administration to Pharsafer® Associates Ltd (“Pharsafer”) by telephone (+44 1483 212151), FAX (+44 1483 212178) or e mail (drugsafety@pharsafer.com). Events should be reported to

Pharsafer within 24 hours of the investigator becoming aware of the events occurrence. Pharsafer will prepare an individual single case report (ISCR) in compliance with applicable regulations. A copy of the ISCR will be sent by Pharsafer to the Investigator. The Investigator is responsible for informing the ethics committee of serious events occurring during the study in compliance with local regulations. Pharsafer will report the event, if appropriate, to the regulatory authority in compliance with local regulations. The sponsor will also report SAEs to the FDA per regulations as noted in Section 10 above.

12. Medical Record and Confidentiality

To maintain patient confidentiality, medical records will be accessed only by IRB approved study personnel (e.g. CRC). Partial HIPAA waiver will be obtained to allow screening of provider schedules for identification of potentially eligible research subjects. Upon medical record review and identification of a potentially eligible research subject, patient's full name, MRN, EMPI, and full dates (e.g. DOB, procedure dates, admission dates, etc.) will be stored on a screening log and used by study coordinators for the subsequent study activities. The screening log will be kept on the HIPAA compliant shared folder and will be accessible only to limited IRB approved study personnel (e.g CRC). Sensitive data will be stored on the HIPAA compliant shared folder at all times and should never be stored on any local or portable drives.

Each study participant will be assigned a unique study identification (ID) number at the time that informed consent is given. Personal identifying information, study data, including the unique study ID, will be entered in the Microsoft Access Database that will be kept on the HIPAA compliant shared folder accessible to approved study personnel only. Only de-identified data will be shared with those outside the study team to ensure adequate protection of sensitive data.

Study identifiers will be kept indefinitely.

To maintain participant confidentiality, no identifying information about any of the study participants will be published. Any data published (including demographic information about the study sample as a whole) will be in aggregate/summary form only.

13. References

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