Scientific Protocol
For

\(^{68}\text{Ga-PSMA PET/CT for detection of recurrent prostate cancer after initial therapy}\)

UCLA IRB # 16-001095
UCLA clinical trials registry: NCT02940262
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1. Preliminary information

Data from the American Cancer Society suggests that for 2015 in the United States prostate cancer will continue to be the leading non-cutaneous cancer diagnosis in males with 220,800 estimated new cases, and has the second highest mortality (after lung) with 27,540 estimated deaths (1). Subsequent treatment is multifaceted and may involve observation, surgery (prostatectomy), radiation therapy (external beam or brachytherapy), hormonal therapy, chemotherapy, or a combination of these (2-4).

Up to 40% of the patients with prostate cancer develop biochemical recurrence within 10 years after initial treatment (5). Usually an increase of the PSA-level precedes a clinically detectable recurrence by months to years (6). However, it cannot differentiate between local, regional or systemic disease with the necessary precision that is essential for further disease management (7). Morphological imaging methods exhibit considerable limitations: sensitivity ranges between 25% and 54% for the detection of local recurrence by transrectal ultrasound (TRUS) or contrast-enhanced CT and is moderately improved by using functional MRI techniques (7-9). The sensitivity for detection of lymph node metastases of CT or MRI is reported to be 30-80% (10). Ultra-small particles of iron oxides (USPIOs) proved to be very effective, but are yet to be approved by regulatory authorities (11). Bone metastases presenting as osteoblastic lesions can be effectively detected by bone scintigraphy, PET, CT and MRI (12, 13).Various targets have been addressed by molecular imaging to improve the detection of recurrent prostate cancer. PET tracers such as $^{18}$F- or $^{11}$C-labeled choline and $^{11}$C-acetate have been investigated for the diagnosis of recurrent (14-16) prostate cancer. Their feasibility in primary diagnosis is limited because of uptake in benign tissue such as benign prostatic hyperplasia or inflammatory lymph nodes (17, 18). In addition, fluorinated versions are not available in the United States, while $^{11}$C-labeled tracers cannot be widely used due to the requirement for an on-site cyclotron due to the short half-life. $^{18}$F-FACBC, a new synthetic amino acid, might be superior when compared to $^{11}$C-choline PET/CT (19). However, recent work indicates that $^{18}$F-FACBC uptake in prostate cancer is similar to that in BPH nodules (20). Prostate-specific membrane antigen (PSMA) continues to elicit high interest. This cell surface protein is significantly overexpressed in prostate cancer cells when compared to other PSMA-expressing tissues such as kidney, proximal small intestine or salivary glands. It therefore provides a promising target for prostate cancer-specific imaging. Recently methods have been developed to label PSMA ligands with $^{68}$Ga and $^{18}$F. Initial experience suggests that these novel tracers can detect prostate cancer relapses and metastases with high contrast by binding to the extracellular domain of PSMA, followed by internalization (21, 22). However, these promising agents do not detect all recurrences.
Although choline based PET/CT is widely used outside the US for imaging prostate cancer, there have been numerous studies reporting a low sensitivity and specificity, especially at low prostate specific antigen (PSA) levels (23, 24). Consequently, improved imaging of prostate cancer is necessary. One novel promising method is PET imaging with \(^{18}\text{F}-\text{FACBC}\), a new synthetic amino acid. Recent evaluations by Nanni et al. indicate that this tracer might be superior when compared to choline PET/CT (19). However, recent work indicates that \(^{18}\text{F}-\text{FACBC}\) uptake in prostate cancer is similar to that in BPH nodules (20).

In addition, prostate-specific membrane antigen (PSMA) recently has received increased attention (25). This cell surface protein is significantly overexpressed in prostate cancer cells when compared to other PSMA-expressing tissues such as kidney, proximal small intestine or salivary glands (26). It therefore provides a promising target for prostate cancer-specific imaging (27). Recently methods have been developed to label PSMA ligands with \(^{68}\text{Ga}\) enabling their use for PET imaging and therapy (28). Initial experience with PET/CT using Glu-NH-CO-NH-Lys-(Ahx)-[\(^{68}\text{Ga}\)(HBED-CC)] (\(^{68}\text{Ga}-\text{PSMA}\)) as a \(^{68}\text{Ga}\)-labelled PSMA ligand suggests that this novel tracer can detect prostate cancer relapses and metastases with high contrast by binding to the extracellular domain of PSMA, followed by internalization (29). Improved detection of occult metastatic disease will improve treatment efficacy by enabling better patient selection for treatment and prompting more extended pelvic node treatment with surgery or radiation for patients with evidence of nodal metastases outside the normal lymph node treatment area.

**Study Agent**

We will use \(^{68}\text{Ga}-\text{PSMA}\) as the PET radiopharmaceutical.

**Rationale**

In this study, we propose to use a well-established PET isotope, Gallium-68 (\(^{68}\text{Ga}\)), bound to a PSMA ligand, \(^{68}\text{Ga}-\text{PSMA}\), which has high affinity for prostate specific membrane antigen. \(^{68}\text{Ga}-\text{PSMA}\) has been shown to be superior to other PET tracers used in prostate cancer such as \(^{18}\text{F}\) Fluoroethylcholine (FECH) and \(^{18}\text{F}\) Fluoromethylcholine (30, 31). Therefore, we propose the following aim:

To evaluate \(^{68}\text{Ga}-\text{PSMA}\) PET/CT for detection of recurrent prostate cancer after initial therapy in patients with elevated PSA.

A prior first-in-human study investigated the biodistribution of \(^{68}\text{Ga}-\text{PSMA}\) and its ability to detect lesions. Thirty-seven men with prostate cancer underwent whole-body PET/CT after an intravenous injection of \(^{68}\text{Ga}-\text{PSMA}\) (median 121.0 MBq, range 52–212 MBq). Within healthy organs, kidneys and salivary glands demonstrated the highest radiotracer uptake. Lesions suspicious for PC presented with excellent contrast as early as 1 hour post-injection with high detection rates even at low PSA levels (31). In another study, a total of 78 lesions characteristic for prostate cancer were detected in 32 patients using \(^{68}\text{Ga}-\text{PSMA}\) PET/CT and 56 lesions were detected in 26 patients using choline PET/CT (30). The higher detection rate in \(^{68}\text{Ga}-\text{PSMA}\) PET/CT was statistically significant (\(P=0.04\)). All lesions detected by \(^{18}\text{F}\)-fluoromethylcholine PET/CT were also seen by \(^{68}\text{Ga}-\text{PSMA}\) PET/CT. In conclusion, \(^{68}\text{Ga}-\text{PSMA}\) PET/CT can detect prostate cancer lesions with improved contrast when compared to \(^{18}\text{F}\)-fluoromethylcholine PET/CT, especially at low PSA levels.
2. Clinical Protocol

2.1 CLINICAL PROTOCOL FOR RECURRENT PROSTATE CANCER DETECTION

2.1.1 STUDY DESIGN

2.1.1.1 This is a prospective, multi-center, open-label study in patients with prostate cancer. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive a one-time administration of $^{68}$Ga-PSMA-11 and undergo a PET/CT imaging study.

2.1.1.2 Number of subjects: Determined by each site.

2.1.1.3 Eligibility criteria: Patients must have baseline evaluations performed prior to the administration of the radiopharmaceutical and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study.

i. Inclusion criteria:
   1. Histopathological proven prostate adenocarcinoma.
   2. Rising PSA after definitive therapy with prostatectomy or radiation therapy.
      a. Post radical prostatectomy (RP)
         i. PSA equals to or greater than 0.2 ng/mL measured more than 6–13 weeks after RP
      b. Post-radiation therapy –ASTRO-Phoenix consensus definition
         i. Nadir + greater than or equal to 2 ng/mL rise in PSA
      4. Age > 18.
      5. Ability to understand a written informed consent document, and the willingness to sign it.

ii. Exclusion criteria:
   1. Investigational therapy for prostate cancer.
   2. Unable to lie flat, still or tolerate a PET scan.
   3. Prior history of any other malignancy within the last year, other than skin basal cell or cutaneous superficial squamous cell carcinoma that has not metastasized and superficial bladder cancer.
2.1.1.4 Study flow chart: see appendix B.

2.1.1.5 Patient screening:
- Laboratory values: all patients must have a recent PSA (within 30 days prior to the \(^{68}\text{Ga-PSMA-11 PET}\)) consistent with BCR
- Pathology: all patients must have histopathology/biopsy of the prostate with a documented Gleason score
- Performance status: all patients must have their Karnofsky performance status (or ECOG/WHO equivalent) evaluated (Appendix A).

2.1.2 BACKGROUND

i. Definition of biochemical recurrence (BCR):
   We will utilize the ASTRO-Phoenix definitions.
   - Post radical prostatectomy (RP)
     - PSA equals to or greater than 0.2 ng/mL measured 6–13 weeks after RP
   - Post-radiation therapy –ASTRO-Phoenix consensus definition (32)
     - nadir + greater than or equal to 2 ng/mL rise in PSA

ii. Current evidence regarding detection rate of BCR with \(^{68}\text{Ga-HBED-CC PSMA}\) \(^{68}\text{Ga-PSMA-11 PET}/CT\):
   High detection rates of BCR for low PSA values (≤1 ng/mL).
   - Detection rate was 50% when PSA was below 0.5 ng/mL, 69% for PSA 0.5–2.0 ng/mL, and 86% when PSA was above 2.0 (33).
   - Detection rate was 57.9% for PSA 0.2 to <0.5 ng/mL, 72.7% for PSA 0.5 to <1, 93.0% for 1 to <2.0, and 96.8% for ≥ 2.0 (34).

   - Radical Prostatectomy Biochemical Failure (PROS-7)
   - Radiation Therapy Recurrence (PROS-8)
   - Principles of Imaging (PROS-B)
     - Imaging is performed for the detection and characterization of disease to select treatment or guide change in management
     - Imaging techniques can evaluate anatomic or functional parameters
       - Anatomic imaging techniques include plain film radiographs, ultrasound, CT, and MRI.
       - Functional imaging techniques include radionuclide bone scan, PET, and advanced MRI techniques such as spectroscopy and diffusion-weighted imaging (DWI).
2.1.3 PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

2.1.3.1 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Histopathological proven prostate adenocarcinoma.
2. Rising PSA after definitive therapy with prostatectomy or radiation therapy.
   a. Post radical prostatectomy (RP)
      i. PSA equals to or greater than 0.2 ng/mL measured more than 6–13 weeks after RP
   b. Post-radiation therapy –ASTRO-Phoenix consensus definition
      i. Nadir + greater than or equal to 2 ng/mL rise in PSA
4. Age > 18.
5. Ability to understand a written informed consent document, and the willingness to sign it.

Exclusion Criteria

1. Investigational therapy for prostate cancer.
2. Unable to lie flat, still or tolerate a PET scan.
3. Prior history of any other malignancy within the last 2 years, other than skin basal cell or cutaneous superficial squamous cell carcinoma that has not metastasized and superficial bladder cancer.

2.1.3.2 Informed Consent Process

All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

2.1.4 IMAGING AGENT INFORMATION

2.1.4.1 Study Agent

We will use $^{68}$Ga-PSMA-11 as the PET radiopharmaceutical. The administered dosage is 3-7 mCi i.v.

Measured human dosimetry data are available from the German Cancer Center.
To summarize the results of the published human studies, there were no observed adverse events to the radiopharmaceutical. The measured dosimetry showed that the critical organ with $^{68}$Ga-PSMA-11 is the spleen, followed by the stomach wall, pancreas and bladder wall. The effective dose of $^{68}$Ga-PSMA-11 reported (0.0129 mSv/MBq) is lower than those of $^{68}$Ga-DOTA-TOC (0.023 mSv/MBq), $^{68}$Ga-DOTA-NOC (0.025 mSv/MBq), $^{68}$Ga-DOTA-TATE (0.021 mSv/MBq) and $^{68}$Ga-NOTA-RGD (0.022 mSv/MBq) (35-38).

2.1.4.2 Source of the Study Agent
Determined by each site.

2.1.5 IMAGING SPECIFICS
2.1.5.1 Modality or Modalities to Be Used
PET/CT or PET/MRI

2.1.5.2 Details of Imaging
Whole-body (skull base to mid-thighs) PET/CT images will be acquired in 3D mode at 45-60 minutes after injection of 3-7 mCi of $^{68}$Ga-PSMA-11.

The PET emission scan is corrected using segmented attenuation data of the CT scan. PET images are reconstructed using ordered subset expectation maximization (OSEM) with 2 iterations and 8 subsets. Images will be reviewed and analyzed using imaging workstations.

Whole-body and pelvic PET/MRI will be obtained as per institutional protocol.

2.1.5.3 Details of Processing/analysis
i. $^{68}$Ga-PSMA-11 PET:
   PET images will be interpreted by a board certified nuclear medicine physician or a board certified radiologist experienced in reading PET and blinded to result of histopathology/biopsy and follow-up imaging. For the data sets included in the analysis for the Primary Endpoint, imaging data will be anonymized and collected at a central site. PET data will be interpreted by three different readers in a random order at separate reading sessions. $^{68}$Ga-PSMA PET/CT reading training set and guides will be provided and completion of this training will be required for all central review readers.

Visual interpretation:

Regions of suspected disease will be graded on a two-point scale by each reader (0=Negative or 1= Positive). A region will be judged as positive if at least one lesion in this region is visually positive.

1. Lymph nodes will be considered positive if the $^{68}$Ga-PSMA-11 uptake is focal and greater than blood pool (adjacent or mediastinal blood pool). Pelvic lymph
nodes will be subclassified according to their localization as follows: R/L obturator, R/L external iliac, R/L internal iliac and other (total of 7 subgroups).

2. Visceral lesions will be considered positive if the $^{68}$Ga-PSMA-11 uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

3. Bone lesions will be considered positive if the $^{68}$Ga-PSMA-11 uptake is focal and greater than physiologic bone marrow.

4. Prostate bed and prostate lesions will be considered positive if the $^{68}$Ga-PSMA-11 uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

ii. Follow-up Imaging:
All patients will be followed up 3-12 months with conventional imaging (dedicated CT, MRI and/or bone scan). Interpretation of follow-up imaging will be performed by local read. The follow-up conventional imaging should be the same modality/modalities as the initial staging work-up to allow for reproducible and accurate comparisons.

$^{68}$Ga-PSMA-11 PET positive findings will be validated as true or false positive as outlined in more detail below. False negative $^{68}$Ga-PSMA-11 PET findings cannot be determined as this would require biopsies of $^{68}$Ga-PSMA-11 negative lesions that are present on conventional imaging.

$^{68}$Ga-PSMA-11 PET validation based on follow-up imaging:

1. Lymph nodes will be assessed by change in size. $^{68}$Ga-PSMA-11 positive lymph nodes will be considered:
   a. True positive:
      - If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size).
      - If patients with solitary lymph node regions show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and the lymph nodes do not change in size (less than 30% decrease or less than 20% increase in short axis diameter).
   b. False positive:
      - If on follow-up imaging within 3-12 months, sites of initial $^{68}$Ga-PSMA-11 positive lymph node lesions seen on CT or MRI decrease by more than 30% without systemic therapy or focal therapy at this site.
      - If $^{68}$Ga-PSMA-11 positive lymph node lesions do not meet the criteria for above false positive or true positive findings.
2. Visceral lesions (non-lymph node soft tissue or organ) will be assessed by change in size. $^{68}$Ga-PSMA-11 positive visceral lesions will be considered:
   a. True positive:
      - If on follow-up imaging within 3-12 months, visceral lesions seen on CT or MRI decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by 20% in largest diameter.
      - If patients with solitary visceral metastasis show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and lesions do not change in size (less than 30% decrease or 20% increase in largest diameter).
   b. False positive:
      - If on follow-up imaging within 3-12 months, sites of initial $^{68}$Ga-PSMA-11 positive lesions seen on CT or MRI decrease by more than 30% without systemic therapy or focal therapy at this site.
      - If $^{68}$Ga-PSMA-11 positive lesions do not meet the criteria for above false positive or true positive findings.

3. $^{68}$Ga-PSMA-11 positive bone lesions will be considered:
   a. True positive:
      - If there was a corresponding positive sclerotic lesion on the CT portion of the $^{68}$Ga-PSMA-11 PET in the same location as the PSMA uptake.
      - If there is focal uptake seen on the baseline bone scan performed within one month of $^{68}$Ga-PSMA-11 PET.
      - If there is a lesion noted on the initial MRI performed within one month of $^{68}$Ga-PSMA-11 PET.
      - If within 12 months follow-up CT demonstrates development of sclerosis.
      - If within 12 months follow-up MRI demonstrates a new bone lesion.
      - If within 12 months follow-up bone scan demonstrates new focal uptake.
   b. False positive:
      - If $^{68}$Ga-PSMA-11 positive bone lesions do not meet the criteria for true positive findings.

4. $^{68}$Ga-PSMA-11 positive prostate bed and prostate lesions will be considered:
   a. True positive:
      - If on follow-up imaging within 12 months, lesions seen on CT or MRI decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by 20% in largest diameter.
      - If patients with prostate bed lesions show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and lesions do not change in size (less than 30% decrease or 20% increase in largest diameter).
b. False positive:
- If on follow-up imaging within 3-12 months, sites of initial $^{68}$Ga-PSMA-11 positive lesions seen on CT or MRI decrease by more than 30% without systemic therapy or focal therapy at this site.
- If $^{68}$Ga-PSMA-11 positive lesions do not meet the criteria for above false positive or true positive findings.

i. Histopathology/Biopsy:

1. Localization of lesions for histopathology/biopsy will be a classified according to the regions in table 1.

2. $^{68}$Ga-PSMA-11 positive findings are aimed to be confirmed by histopathology/biopsy if clinically feasible.

3. Histopathological procedures, biopsies and follow-up imaging will be performed as clinically indicated and as per institutional protocol. The following elective procedures may guide the investigator:

   (1) **Positive HP/Biopsy:** Confirmed sites of metastatic or tumor involvement by histopathology/biopsy will be discussed with the responsible physician/surgeon.

   (2) **Negative Biopsy:** Patients with suspected tumor recurrence on $^{68}$Ga-PSMA-11 PET with negative histopathology/biopsy will be handled as outlined below:

   (a) Lymph nodes:

   - For patients undergoing nodal dissection: Patients will be rescanned with dedicated CT or MRI if clinically feasible to determine if the suspicious $^{68}$Ga-PSMA-11 positive node was removed.

     1. If $^{68}$Ga-PSMA-11 positive lymph node is still present, a repeat biopsy can be pursued if clinically feasible and applicable, or follow-up using imaging as described above will be performed.

     2. If the corresponding node was removed, then this will be considered a False Positive.

   - For patients undergoing needle biopsy: Images of the procedure will be reviewed to determine if the correct node was biopsied.

     1. If the correct node was biopsied, then a negative biopsy will be considered a False Positive.

     2. If the incorrect node was biopsied, then follow-up imaging as described above will be performed if clinically feasible.

   (b) Bone lesions: Given the high rate of false negative biopsies for osseous metastases in patients with prostate cancer, patients with negative bone biopsies of PSMA PET positive lesions will be further evaluated:

   - If pathology demonstrates alternative diagnoses that is known to be PSMA positive (e.g. Renal Cell Carcinoma metastases, Paget’s disease), then this will be considered a False Positive.
– If pathology is indeterminate, then follow-up imaging as described above will be performed to determine if the lesion is a True Positive or False Positive.

(c) Additionally a repeat $^{68}$Ga-PSMA-11 can also be obtained, as allowable, in addition to repeat conventional imaging (CT and/or MRI) in cases of negative biopsy to determine if the biopsy was true negative or false negative.

(3) Although not routinely performed during standard practice, immunohistochemical staining for PSMA of tumor specimens (primary and lymph node metastases) may be performed, although not required.

2.1.6 STUDY PROCEDURES

2.1.6.1 Imaging Protocol

1. $^{68}$Ga-PSMA-11 PET preparation and injection:

   The injected dose will be 3-7 mCi of $^{68}$Ga-PSMA-11 PET. A dose of 20 mg of Furosemide (Lasix) is recommended to be injected together with, shortly before or after administration of the radiotracer in order to minimize PET scatter artifacts from excreted radiotracer accumulation in the kidney and urinary bladder that can occur with the gallium-68 radionuclide. Oral hydration and voiding is recommended immediately before start of the scan. Furosemide should not be administered in patients with medical contraindications to Furosemide administration including allergies and adverse reactions including sulfa allergies. (Note: Application of Furosemide can be omitted as part of the PET imaging protocol if a second-generation scatter correction algorithm is available for the PET scanner used in this protocol). PET imaging will begin 50-100 minutes after injection. Scan time per bed position will be determined based on each sites PET scanner capabilities.

2. Patient preparation: no fasting is required.

3. PET protocol: Scan coverage will extend from mid thigh to the base of the skull, starting from the mid-thighs to prevent urinary bladder radiotracer accumulation at the start of PET imaging. Bed position scan time will be dependent on each sites scanner capabilities. At a minimum, 3 minutes per bed position will be used. In certain circumstances, coverage may be extended to the toes. Contrast may be administered if requested by the referring clinician and is decided site dependent.

4. Patient monitoring: Vital signs will be assessed before and after injection of $^{68}$Ga-PSMA-11 (HR and supine BP). Patients will be monitored for adverse events during injection and for two hours after radiotracer administration.

5. Patient follow-up: Patients will be contacted by phone one to three days after $^{68}$Ga-PSMA-11 PET to assess for the development of delayed adverse events. Patients will be seen in the clinic if there are any concerns regarding adverse events requiring further evaluation.
2.1.6.2 Criteria for Removal from Study

The Principal Investigator may withdraw subjects from the study for one or more of the following reasons: failure to follow the instructions of the Principal Investigator and/or study staff; determination that continuing the participation could be harmful to the subject; the study is cancelled or other administrative reasons.

2.1.6.3 Alternatives

The alternative is to not participate in the study.

2.1.6.4 Study calendar

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<th>Pre-Study</th>
<th>Week 1</th>
<th>12 Months</th>
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2.1.7 ADVERSE EVENTS AND REPORTING PROCEDURES

2.1.7.1 Potential Adverse Events

The administration of the radioactive substance will feel like a slight pinprick if given by intravenous injection. Patients who are claustrophobic may feel some anxiety while positioned in the scanner. Also, some patients find it uncomfortable to hold one position for more than a few minutes. The subjects will not feel anything related to the radioactivity of the substance in their body. Because the radioactivity is very short-lived, the radiation exposure is low. The substance amount is so small that it does not affect the normal processes of the body.

This research study involves exposure to radiation from one $^{68}$Ga-PSMA-11 PET/CT. The effective dose from one typical 140 MBq administration of $^{68}$Ga-PSMA-11 is 3.54 mSv. The effective dose from one CT attenuation scan is 4 mSv. Therefore, the effective dose from one $^{68}$Ga-PSMA-11 PET/CT is 7.54 mSv, approximately equal to 15% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year.

2.1.7.2 Adverse Event Reporting

We do not anticipate hazardous situations for the subjects as a result of this protocol. However, procedures will be in place for verification of correct radiopharmaceutical dose and route of administration (i.e., each dose will be double checked for dosimetry and quality by a researcher and technologist). The study Principal Investigator (PI) or his designee will report unanticipated
AEs to the IRB within 10 working days of becoming aware of the event (5 days if the event is life-threatening or resulted in death). If the principal investigator determines the unanticipated adverse device effect presents an unreasonable risk to subjects, the study will be terminated as soon as possible. Adverse events will be reported to the FDA.

2.1.8 REGULATORY CONSIDERATIONS

2.1.8.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the IRB. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Principal Investigator will disseminate the protocol amendment information to all participating investigators.

2.1.8.2 Data Management Plan

The CRFs will be stored in a locked office in the Nuclear Medicine Clinic.

During the clinical investigation, the Principal Investigator will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome.

The Clinic’s Data and Safety Monitoring Committee (DSMC) may audit study related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of regulatory binders, case report forms, eligibility checklists, and source documents.

2.1.9 STUDY ENDPOINTS

1. Primary endpoint:
   i. Positive predictive value (PPV) on a per-patient and per-region-basis (Table 1) of $^{68}$Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy.

2. Secondary endpoints:
   i. PPV on a per-patient and per-region-basis (Table 1) of $^{68}$Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up.
   ii. Sensitivity, specificity, and negative predictive value (NPV) on a per-patient basis of $^{68}$Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up.
   iii. Detection rates on a per-patient basis of $^{68}$Ga-PSMA-11 PET stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, ≥5.0).
   iv. Impact of $^{68}$Ga-PSMA-11 PET on clinical management in BCR patients.
   v. Inter-reader reproducibility
vii. Detection rates on a per-patient basis of $^{68}$Ga-PSMA-11 PET stratified by PSA velocity and PSA doubling-time

### Table 1: Region Definition

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<thead>
<tr>
<th>Region</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prostate Bed</td>
</tr>
<tr>
<td>2</td>
<td>Pelvis outside of prostate bed including lymph nodes</td>
</tr>
<tr>
<td>3</td>
<td>Extrapelvic soft tissue, lymph nodes and organ metastases (non-bone)</td>
</tr>
<tr>
<td>4</td>
<td>Bone metastases</td>
</tr>
</tbody>
</table>

#### 2.1.9.1 Statistical considerations

**Sample Size and Statistical Analysis Plan:**

The primary endpoint is to evaluate the positive predictive value (PPV) on a (1) per-patient and (2) per-region-basis (prostate bed, pelvis, extrapelvic soft tissue, and bone metastases) of $^{68}$Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy. Based on the results of previous studies, the following distribution of disease across the four regions are anticipated (34, 39, 40):

- a) Prostate bed: 30%
- b) Pelvis: 15%
- c) Extrapelvic soft tissue: 20%
- d) Bone metastases: 35%

It is anticipated that the PPV for the four regions and for all regions combined using conventional imaging ranges from 30-60%. An overall PPV for $^{68}$Ga-PSMA-11 PET of at most 50% will be considered as unacceptably low. Hence, the null hypothesis that the PPV is at most 50% will be tested against the alternative hypothesis that the PPV is greater than 50%. It is hypothesized that $^{68}$Ga-PSMA-11 PET imaging on the per-region and per-patient basis will substantially increase the PPV for the four regions to at least 70%. A sample size of 75 true positives is required for rejecting the null hypothesis that the PPV is at most 50% with 90% power at the one-sided 0.01 ($=0.05/5$ – a Bonferroni adjustment for evaluating the PPV for the four regions and for all regions combined) significance level, assuming an average regions specific prevalence of 20%. It is
expected that approximately 25% of the accrued patients will undergo a biopsy. Hence, the
proposed total number of patients requiring a biopsy is 375 in order to power the analysis at a per
region level. Assuming a prevalence rate of 20% for disease in each individual region, a total
sample size of 1,500 patients is required (across all institutions). The following table shows the
attainable power levels for detecting an increase in the PPV from 50% to 70% at the one-sided
0.01 significance level for the four disease regions and for all regions combined with the proposed
sample size of 1500 patients: (across all institutions)

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence</th>
<th>Number of Biopsies with True Positives</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate bed</td>
<td>30%</td>
<td>113</td>
<td>98%</td>
</tr>
<tr>
<td>Pelvis</td>
<td>15%</td>
<td>56</td>
<td>78%</td>
</tr>
<tr>
<td>Extrapelvic soft tissue</td>
<td>20%</td>
<td>75</td>
<td>90%</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>35%</td>
<td>131</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>All regions combined</td>
<td>100%</td>
<td>375</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

In summary, the proposed target accrual of 1,500 patients (across all institutions) (375 with
biopsies) will provide adequate power for detecting the anticipated improvement in the PPV for
both the per-patient and per-region based \(^{68}\)Ga-PSMA-11 PET imaging when compared to
conventional imaging.

However, a sample size of 107 patients with biopsies in total is sufficient for detecting the
anticipated improvement in PPV when evaluating per-patient based positive predictive value.

**Statistical Analysis Plan:**

**Primary Endpoint:** PPVs on a per-patient and per-region-basis of \(^{68}\)Ga-PSMA-11 PET for
detection of tumor location confirmed by histopathology/biopsy will be calculated and reported
along with the corresponding two-sided 95% confidence intervals. The confidence intervals will
be constructed using the Wilson score method.

**Secondary Endpoints:** PPVs on a per-patient and per-region-basis of \(^{68}\)Ga-PSMA-11 PET for
detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-
up will be calculated and reported along with the corresponding two-sided 95% confidence intervals. The paired McNemar’s test will be used to compare the PPVs of $^{68}$Ga-PSMA-11 PET imaging to the PPVs of conventional imaging.

Sensitivity, specificity, and NPVs on a per-patient basis of $^{68}$Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy will be summarized in tabular format. Ninety-five confidence intervals of sensitivity, specificity, and NPV will be calculated using the Wilson score method.

Detection rates on a per-patient basis of $^{68}$Ga-PSMA-11 PET stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, ≥5.0) and PSA velocity/doubling-time will be summarized in tabular format and compared between PSA strata using chi-square analysis. The impact of $^{68}$Ga-PSMA-11 PET on clinical management in BCR patients will be evaluated using descriptive statistics.

Inter-reader reproducibility for positivity at the patient level and region level will be reported using the Fleiss’ Kappa test for multiple readers.

Safety will be reported descriptively as rates of patient reported adverse events. Additionally, adverse events will be characterized and quantified by CTCAE 4.03.
### Appendix A: Performance Status Criteria

<table>
<thead>
<tr>
<th>ECOG Performance Status Scale</th>
<th>Karnofsky Performance Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
<td><strong>Descriptions</strong></td>
</tr>
<tr>
<td>0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;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.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>
Appendix B: Study Flow Chart for Recurrent Prostate Cancer Detection

PCa BCR Study Entry Criteria:
- Post-Prostatectomy – PSA ≥0.2 ng/mL measured more than 6–13 weeks after RP
- Post-Radiation Therapy - (ASTRO-Phoenix criteria) Nadir + ≥ 2 ng/mL
- Contraindications to furosemide administration including allergies and adverse reactions (including sulfa drugs); Note: furosemide can be omitted if second-generation scatter correction PET imaging is utilized.

68Ga-PSMA-11 PET Imaging: Positive imaging findings are aimed to be confirmed by histopathology (HP) biopsy, if clinically feasible, or imaging follow-up.

HP/Biopsy of accessible site(s)

Target Lesion(s) – HP/Biopsy Positive

- 3-12 month f/u conventional imaging similar to initial staging modality (CT, bone scan and/or MRI)

Bone: Further imaging of suspected bone metastasis by MRI (and/or repeat 68Ga-PSMA-11 as allowable).

Target Lesion(s) – HP/Biopsy Negative

- 3-12 month f/u conventional imaging similar to initial staging modality (CT, bone scan and/or MRI)

UN: If LN was resected, repeat dedicated CT or MRI (and/or repeat 68Ga-PSMA-11 PET as allowable) to determine if the PSMA PET positive node was removed. If LN is still present on imaging then biopsy is considered false negative.

- 3-12 month f/u conventional imaging similar to initial staging modality (CT, bone scan and/or MRI)

- Document change in clinical management

68Ga-PSMA-11 PET Negative Regions 2-4

68Ga-PSMA-11 PET Positive in Region 1 s/p - Prostatectomy?

No

- In case of Salvage Radiation Therapy of the prostate bed: monitor PSA level
- In case of no salvage radiation therapy: HP/Biopsy or 3-12 month f/u conventional imaging similar to initial staging modality (CT, bone scan and/or MRI)

Yes
References


24. Vees H, Buchegger F, Albrecht S, et al. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy.


26. Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases.

27. Eder M, Eisenhut M, Babich J, Haberkorn U. PSMA as a target for radiolabelled small molecules.


The $^{68}$Ga-PSMA-11 radiopharmaceutical drug product is expected to be formulated in isotonic solution, typically 0.9% NaCl for Injection, containing ≤10% ethanol.

Product release criteria, and process validation standards, are outlined below.

**Batch Release Criteria for 68Ga-PSMA**

<table>
<thead>
<tr>
<th>Test</th>
<th>Suggested Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance Visual Inspection</td>
<td>Clear, colorless solution; no visible foreign matter</td>
</tr>
<tr>
<td>pH</td>
<td>4 – 8</td>
</tr>
<tr>
<td>Endotoxins</td>
<td>&lt;175 EU per dose or &lt; 17.5 EU/mL whichever is lower</td>
</tr>
<tr>
<td>Radiochemical Identity and Purity</td>
<td>≥90% Ga-68 PSMA-11</td>
</tr>
<tr>
<td>Radioisotope Identity and purity</td>
<td>Target half-life of 68 min (accepted range: 64-72 minutes)</td>
</tr>
<tr>
<td>Mass Dose</td>
<td>≤ 10 micrograms</td>
</tr>
<tr>
<td>Filter Integrity Test</td>
<td>Meets or exceeds filter manufacturer’s defined testing specifications</td>
</tr>
<tr>
<td>Retrospective USP Sterility Test</td>
<td>Pass</td>
</tr>
</tbody>
</table>

Testing performed during Process Qualification and Periodic Verification (3 consecutive lots) + annual or for each new batch of PSMA or Ge/Ga-Generator

<table>
<thead>
<tr>
<th>Test</th>
<th>Suggested Qualification and Validation Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiochemical Identity</td>
<td>HPLC: Retention matches reference standard (i.e., cold Ga-PSMA-11) and ITLC: &gt;90% radiochemical purity based on ITLC analysis for initial qualification. Perform one test annually.</td>
</tr>
<tr>
<td>Residual solvents - Acetonitrile</td>
<td>Meets USP specifications for any class 2 solvents used (GC)</td>
</tr>
<tr>
<td>(if used in process)</td>
<td></td>
</tr>
<tr>
<td>Residual solvents - Acetone</td>
<td>≤ 5 mg/mL for any Class 3 solvents used (GC)</td>
</tr>
<tr>
<td>(if used in labeling process)</td>
<td></td>
</tr>
<tr>
<td>Upper limit for contamination by Ge-68 Breakthrough*</td>
<td>&lt;0.01% of the total radioactivity is 68-Ge at the time of product expiration.</td>
</tr>
</tbody>
</table>

*It is recommended that sites check for Ge-68 breakthrough on a weekly basis.*