

Gallium-68 PSMA-11 PET in patients with biochemical recurrence

Study Drug: Gallium-68 PSMA-11

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Abstract

Title	Gallium-68 PSMA-11 PET in patients with biochemical recurrence
Patient population	<ul style="list-style-type: none"> • Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy): <ul style="list-style-type: none"> ○ Post radical prostatectomy (RP) – AUA recommendation <ul style="list-style-type: none"> ▪ PSA greater than or equal to 0.2 ng/mL measured more than 6 weeks after RP. ○ Post-radiation therapy – ASTRO-Phoenix consensus definition <ul style="list-style-type: none"> ▪ Nadir + greater than or equal to 2 ng/mL rise in PSA
Rationale for Study	Gallium-68 PSMA-11 has been shown to have a higher sensitivity for the detection of metastatic prostate cancer compared to choline based imaging.
Primary Objective	<ul style="list-style-type: none"> • Sensitivity on a per-patient and per-region-basis of ⁶⁸Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy, clinical and conventional imaging follow-up.
Secondary Objectives	<ul style="list-style-type: none"> • PPV on a per-patient and per-region-basis of ⁶⁸Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy, clinical and conventional imaging follow-up. • Sensitivity and positive predictive value (PPV) on a per-patient and per-region basis of ⁶⁸Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy. • Detection rates on a per-patient basis of ⁶⁸Ga-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). Detection rate will be stratified by history of prostatectomy, radiation or both; as well as by whether the patient is on androgen deprivation therapy (ADT). • Impact of ⁶⁸Ga-PSMA-11 PET on clinical management in BCR patients. • Inter-reader reproducibility. • Safety of ⁶⁸Ga-PSMA-11 administration as categorized by CTCAE 4.03.
Study Design	This is a phase 3 multi-center open label study.
Number of patients	Total population of patients will be 1,500 patients across all institutions.

Duration of Therapy	The study will involve a single imaging study.
Duration of Follow up	The patients will be followed-up by phone one day after the study completion, and clinical and imaging follow-up will last for up to 12 months after the PSMA-11 PET study..
Duration of study	The study will reach completion three years from the time the study opens to accrual.
Study Drugs	Gallium-68 labeled PSMA-11 (PSMA-HBED-CC)
Safety Assessments	Patient vital signs will be taken immediately before and after the administration of the radiopharmaceutical. The patients will also be asked to report adverse events.

List of Abbreviations

AE	adverse event
CHR	Committee on Human Research (UCSF IRB)
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
Ga-68	Gallium 68
HDFCCC	Helen Diller Family Comprehensive Cancer Center
ICH	International Conference on Harmonization
IND	investigational new drug application
IRB	Institutional Review Board
IV	intravenous
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PET	Positron Emission Tomography
PK	pharmacokinetics
PRC	Protocol Review Committee (UCSF)
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
SD	standard deviation

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1 Introduction

1.1 Overview

Imaging and staging of prostate cancer is critical for surgical and treatment planning. We aim to image patients with suspected metastatic prostate cancer using Gallium-68 labeled HBED-CC PSMA (more commonly called ^{68}Ga -PSMA-11) in order to demonstrate its utility. We plan to utilize this data to obtain further approvals of the ^{68}Ga -PSMA-11 compound, so that this agent will become available for clinical imaging in prostate cancer patients.

This compound has been shown to be superior to choline based PET agents for the staging of prostate cancer, both Carbon-11 and Fluorine-18 compounds. But this compound was not patented and therefore no company or private entity will make the investment required to bring PSMA-11 to market. In the vacuum of availability, academic groups must take the lead in order to collect the necessary data for future FDA approval. This protocol was developed in collaboration with the Clinical Trials Network of the Society of Nuclear Medicine and Molecular Imaging. The inclusion criteria and study endpoints have been aligned so that inter-institutional sharing of data can be performed in order to pool data for final NDA submission.

1.2 Background

Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer death in American men (1). Existing conventional imaging (CT, MRI and bone scans) has a low sensitivity in detecting local recurrence or metastatic disease (2). The one exception being NaF PET/CT for the detection of osseous metastasis. Due to this limitation, numerous approaches to stage patients have been evaluated.

Choline imaging has been frequently used, as prostate cancer exhibits increase choline uptake that has been associated with the presence of choline kinase (3). Choline uptake is increased in comparison to FDG in both androgen dependent and independent prostate cancer patients (4). Choline has also been shown to be sensitive for the detection of recurrent tumor in patients with PSA (prostate specific antigen) values of less than 1.0 ng/ml (5). There are two forms of choline that are used in imaging prostate cancer, C-11 and F-18 choline. C-11 choline has a short half-life of 20 minutes, which limits its detection for metastatic disease but results in improved local detection due to decreased urinary activity at the time of imaging. F-18 choline has significant urinary excretion that limits evaluation of the prostate but, but has been shown to have better detection rates for distant metastatic disease (6). C-11 choline has limited sensitivity for osseous metastasis, possibly due to the decreased uptake time (7). Additionally, the sensitivity of C-11 choline is limited in patients with PSA values < 1.0 ng/ml (8-10). Although choline PET may be limited in sensitivity, it clearly delineates more lesions than cross section imaging or bone scan in patients with known disease (11). In 2012, the Mayo Clinic obtained NDA (new drug application) approval from the FDA for the use of C-11 choline.

A separate approach is to image the prostate specific membrane antigen (PSMA). PSMA is expressed on the majority of prostate cancer cells, and so would be an ideal cell membrane protein to image. The initial imaging approach to PSMA imaging target the intracellular domain using Indium-111-capromab (Prostascint), a murine monoclonal antibody (12,13). Although there was early promise for the detection of nodal metastasis (14), the agent was never able to adequately visualize osseous metastasis (15). Although combination with SPECT/CT does improve lesion detection (16). One main limitation to In-111-capromab is that it takes a prolonged time to localize to the target tissue, which likely relates to both the size of the monoclonal antibody and the fact that agent targets the intracellular domain of the PSMA protein. Additionally, Prostascint also recognizes an intracellular epitope so the antibody must

cross the membrane to be effective. This likely only occurs in permeable dead or dying tumor cells.

Because of the limitations of In-111 capromab, there has been continued effort to develop agents that target the extracellular domain of the PSMA protein. The Ga-68 labeled PSMA-11 compound has become of particular interest because in the last year there have been two important articles. The first demonstrates that PSMA-11 has a higher sensitivity for the detection of disease than F-18 choline in a head-to-head intra-patient comparison that included 37 patients (17). The second paper looked at the sensitivity of PSMA-11 in the detection of metastatic lesions in patients with recurrent prostate cancer (18). Their results demonstrated a detection rate of 50% for patients with a PSA less than 1 ng/ml, and detection rate above 85% for patients with a PSA greater than 2 ng/ml. These detection rates are significantly higher than that reported by groups using choline (5).

Because of the improved resolution and image quality with PET, ability to quantitate uptake, increased sensitivity compared to choline, we intend to evaluate the utility of Ga-68 PSMA-11 for the imaging of prostate cancer. We expect that the data from this study will support applications for clinical approval of this imaging agent, leading to wider availability within the United States.

1.3 Patient Population

Patients with biochemical recurrence after prostatectomy or radiation therapy:

- (a) Post radical prostatectomy (RP) – AUA recommendation
 - PSA greater than or equal to 0.2 ng/mL measured more than 6 weeks after RP.
- (b) Post-radiation therapy –ASTRO-Phoenix consensus definition
 - Nadir + greater than or equal to 2 ng/mL rise in PSA

2 Objectives of the Study

Region	Description
1	Prostate Bed
2	Pelvis outside of prostate bed including lymph nodes
3	Extrapelvic soft tissue, lymph nodes and organ metastases (non-bone)
4	Bone metastases

2.1 Primary

- Sensitivity on a per-patient and per-region-basis (Table 1) of ⁶⁸Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy, clinical and conventional imaging follow-up.

2.2 Secondary

- 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, clinical and conventional imaging follow-up.
- Sensitivity and 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.
- 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, \geq 5.0). Detection rate will also be stratified by history of prostatectomy, radiation or both; as well as by whether the patient is on androgen deprivation therapy (ADT).
- Impact of ^{68}Ga -PSMA-11 PET on clinical management in BCR patients.
- Inter-reader reproducibility.
- Safety, as characterized by CTCAE 4.03.

3 Study Design

3.1 Characteristics

This is a prospective, Phase 3, 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 Ga-68 PSMA-11 and undergo a PET/CT or PET/MRI imaging study.

3.2 Number of Subjects

It is anticipated that 1,500 patients will be enrolled in this study.

3.3 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:

3.3.1 Inclusion Criteria

1. Histopathologically proven prostate adenocarcinoma.
2. Rising PSA (at least two consecutive rising PSAs) after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy).
 - a. Post radical prostatectomy (RP) – AUA recommendation for biochemical recurrence after radical prostatectomy
 - i. PSA greater than or equal to 0.2 ng/mL measured more than 6 weeks after RP.

- b. Post-radiation therapy –ASTRO-Phoenix consensus definition of biochemical recurrence after radiation therapy
 - i. Nadir + greater than or equal to 2 ng/mL rise in PSA
3. Karnofsky performance status of ≥ 50 (or ECOG/WHO equivalent).
4. Age > 18.
5. Ability to understand a written informed consent document, and the willingness to sign it.

3.3.2 Exclusion Criteria

1. Unable to lie flat, still or tolerate a PET scan.
2. Concomitant investigational therapy.
3. Patient undergoing active treatment for non-prostate malignancy, other than skin basal cell or cutaneous superficial squamous cell carcinoma that has not metastasized and superficial bladder cancer.
4. Contraindication to furosemide administration including prior allergy or adverse reaction to furosemide or sulfa drugs. (Note: This exclusion criteria can be removed if Furosemide is omitted as part of the PET imaging protocol if a second-generation scatter correction is available for the used PET device).

3.4 Duration of Follow Up

Patients will be followed for one day after the administration of the radiopharmaceutical.

3.5 Study Timeline

3.5.1 Primary Completion

The study will reach primary completion 36 months from the time the study opens to accrual.

3.5.2 Study Completion

The study will reach study completion 48 months from the time the study opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Investigational Drug #1

Ga-68 labeled PSMA-11 (or PSMA-HBED-CC) is a radiopharmaceutical that will be produced under cGMP.

5 Treatment Plan

5.1 Dosage and Administration

The imaging agent (Ga-68 PSMA-11 or PSMA-HBED-CC) will be administered on an outpatient basis. It will be administered a single time intravenously prior to the PET imaging. The injected dose will be 3 to 7 mCi of ^{68}Ga -PSMA-11.

5.1.1 Other Modality(ies) or Procedures

5.1.1.1 Change in management surveys

Referring clinicians will be required to fill out a pre-imaging survey prior to imaging. Please see Appendix 3. Additionally within 30 days of the completion of imaging, the referring physician will be requested to fill out a post-imaging survey, and finally three to six months after imaging, a third survey will be filled out.

5.1.1.2 PET imaging

a) ^{68}Ga -PSMA-11 PET preparation and injection:

The intravenously injected dose will be 111-259 MBq (3-7 mCi) of ^{68}Ga -PSMA-11 PET. A dose of 20 mg of furosemide (Lasix) is recommended to be injected i.v. 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 is recommended on the day of the scan. 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.

b) Patient preparation: no fasting is required.

c) 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.

d) Patient monitoring: Vital signs will be assessed immediately 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. Additionally, patient's vitals (HR and supine BP) will be checked at the completion of the imaging study prior to leaving the imaging center.

e) Patient follow-up: Patients will be contacted 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 concerning study related adverse events requiring further evaluation. Patients will also be followed up clinically and using conventional imaging for up to 12 months after ^{68}Ga -PSMA-11 PET. Follow-up imaging will be performed as allowed under standard of care.

5.2 Monitoring and Toxicity Management

Each patient receiving Ga-68 PSMA-11 will be evaluable for safety. The safety parameters include physical findings and spontaneous reports of adverse events reported to the investigator by patients.

6 Study Procedures and Observations (Appendix 2)

6.1 Schedule of Procedures and Observations

Screening assessments must be performed within 30 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

6.1.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 30 days of the day 1 Visit.

- Laboratory values: all patients must have a recent PSA (within 30 days prior to study enrollment) consistent with BCR
 - If only one PSA greater than or equal to 0.2 ng/dL post radical prostatectomy is available, then a second confirmatory PSA must be checked prior to the ⁶⁸Ga-PSMA-11 PET study.
- 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 1).
- Change in management: A pre-imaging survey of planned clinical management will be performed prior to ⁶⁸Ga PSMA-11 PET/CT imaging.

6.1.2 Treatment Period

6.1.2.1 Study Procedures, Imaging Day 1

- Vital signs
- Evaluation of adverse events

6.1.3 Post-treatment Follow Up Visits

Patients will be followed for 1-3 days after enrollment, by phone. The following procedure will be performed:

- Evaluation of adverse events

Additionally, the following post-treatment follow up will be performed:

- Change in management: A post-imaging survey of clinical management using PSMA-11 PET/CT information will be performed ≤ 30 days of PSMA-11 PET/CT imaging for assessment of change in clinical management.

- Change in management 6 months post imaging: A survey of clinical management will be performed approximately 6 months after the PSMA-11 PET/CT imaging for assessment of change in clinical management.
- Conventional imaging follow-up 3-12 months post imaging: Conventional imaging follow-up shall be performed as per institutional standard of care. DICOM images /or associated report should be collected for analysis.

6.2 Prohibited Medications

There are no prohibited medications.

7 Reporting and Documentation of Results

7.1 Evaluation of Side Effects

7.1.1.1 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of ⁶⁸Ga-PSMA-11.

7.2 Evaluation of Safety

Analyses will be performed for all patients receiving ⁶⁸Ga-PSMA-11. The study will use the [CTCAE v4.0](#) for reporting of adverse events.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as 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" indicates that 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 an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), 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,” as used in this definition, 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.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

7.3.2.3 Serious

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

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All grade 3 and above adverse events will be recorded using the NCI CTCAE v4.0. The Investigator will assign attribution of the possible association of the event with use of the investigational drug.

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE <i>is clearly NOT related</i> to the intervention
	Unlikely	The AE <i>is doubtfully related</i> to the intervention
Related to investigational drug/intervention	Possible	The AE <i>may be related</i> to the intervention
	Probable	The AE <i>is likely related</i> to the intervention
	Definite	The AE <i>is clearly related</i> to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none, mild, moderate* or *severe* according to the following grades and definitions:

- Grade 0 No AE (or within normal limits)
- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.6 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of “Unanticipated Problem” (UP) and the San Francisco VA Medical Center within 5 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 6.1.30)
- Unexpected (as defined in 0)
- Serious (as defined in 6.1.5)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

Per patient and per region ⁶⁸Ga-PSMA-11 sensitivity for the detection of prostate cancer recurrence .

8.1.1 Randomization

There will be no randomization performed.

8.1.2 Blinding

- For primary endpoint analysis of ⁶⁸Ga-PSMA-11 PET imaging studies central readers will be fully blinded to clinical information and any conventional imaging results. Central readers will have access to the concomitant CT or MRI used for attenuation purposes.
- For local interpretation of ⁶⁸Ga-PSMA-11 PET imaging studies, local readers will be unblinded to both clinical information and other conventional imaging data.
- For local interpretation of conventional imaging follow-up images 3-12 months post ⁶⁸Ga-PSMA-11 PET scan, local readers will be unblinded to all results and will be specifically informed of the location of ⁶⁸Ga-PSMA-11 PET positive lesions so that follow-up measurements may be performed on these lesions.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

The primary endpoint is to evaluate the sensitivity 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 our first protocol in biochemical recurrent patients, we have updated the distribution of disease that we expect to find:

- a) Prostate bed: 15%
- b) Pelvis: 27%
- c) Extrapelvic soft tissue: 24%
- d) Bone metastases: 11%
- e) No evidence of disease on PSMA PET: 24%

Of our first cohort of patients, 19% of patients underwent biopsy after a positive PSMA PET imaging. Based on biopsy results there was 100% sensitivity and 87% specificity. There were no True Negatives or False Negatives on biopsy. Imaging follow-up is not complete for our first study so we cannot estimate the percent of patients that will have imaging follow-up, but it appears that roughly 15 to 20% of patients will have imaging follow-up. Consistent with our second protocol, we anticipated that the sensitivity for the four regions and for all regions combined using conventional imaging ranges from 30-60%. An overall sensitivity for ^{68}Ga -PSMA-11 PET of at most 50% will be considered as unacceptably low. Hence, the null hypothesis that the sensitivity is at most 50% will be tested against the alternative hypothesis that the sensitivity 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 sensitivity for the four regions to at least 70%. A sample size of 75 true positives is required for rejecting the null hypothesis that the sensitivity is at most 50% with 90% power at the one-sided 0.01 ($=0.05/5$ – a Bonferroni adjustment for evaluating the sensitivity for the four regions and for all regions combined) significance level, assuming an average regions specific prevalence of 20%. Although 19% of patients underwent biopsy and 15% of patients have imaging follow-up, we anticipate that the biopsy rate will fall in this study as referring clinicians become more comfortable with the imaging results. Therefore, we will combine imaging and biopsy follow-up in the primary aim, and will require 375 with both imaging and/or biopsy follow-up 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. In summary, the proposed target accrual of 1,500 patients (375 with biopsies or imaging follow-up) will provide adequate power for detecting the anticipated improvement in the sensitivity for both the per-patient and per-region based ^{68}Ga -PSMA-11 PET imaging. However, a sample size of 107 patients with biopsies/follow-up in total is sufficient for detecting the anticipated improvement in sensitivity when evaluating per-patient based sensitivity.

Our current biochemical recurrence protocol has not completed analysis or enrollment. Therefore we will perform an analysis of our first protocol and based on those results we may adjust the sample size of this protocol using updated assumptions based on the interim analysis of our existing protocol.

8.2.2 Accrual estimates

We estimate that roughly 250 patients with prostate cancer will be enrolled in this trial per year. Over a two-year period this will result in up to 500 patients being enrolled in the study.

8.3 Analyses Plans

8.3.1 Analysis Population

Patients with histopathology correlates will be analyzed for the Primary Aim. All remaining patients will be analyzed for the secondary endpoints.

8.3.2 Analysis of Primary Endpoints

Sensitivity on a per-patient and per-region-basis of ^{68}Ga -PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy, clinical and conventional imaging follow-up 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. For successful completion of the primary endpoint, two of the three readers will need to have an 70% sensitivity for the detection of disease on a per patient level for the cases that have a) imaging follow-up, b) pathology correlation or c) combination of pathology and imaging follow-up and/or pathology correlation.

^{68}Ga -PSMA-11 PET Results Definition

a) Imaging interpretation ^{68}Ga -PSMA-11 PET:

Local Interpretations: PET images will initially be interpreted by a board certified nuclear medicine physician or a board-certified radiologist experienced in reading PET at the time of the imaging study at the institution that the study is being performed. These interpretations will not be used for final evaluation, and will not be reported as part of the primary or secondary endpoints.

Central Read Logistics: 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. Cross sectional imaging (CT or MRI) from the ^{68}Ga -PSMA-11 PET will be available for anatomic correlate. The Central readers will be blinded to all other imaging results and all other clinical data.

Reader Positivity and Negativity Definition: Regions defined in Table 1 will be graded for the presence of suspected disease 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.

Reader Training: ^{68}Ga -PSMA-11 PET/CT reading training set and guides will be provided and completion of this training will be required for all central review readers. Common pitfalls will be reviewed as part of the reader training.

Criteria for visual interpretation:

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

- i) 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).
 - (1) Lymph nodes will be classified further by region: pelvic, retroperitoneal, thoracic, other. Additionally, 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). These regions will not be used for evaluation of the primary or secondary endpoints, but for exploratory analysis.
- ii) 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.
 - (1) Visceral lesions will be classified further by major organ: lung, liver, other tissue. These regions will not be used for evaluation of the primary or secondary endpoints, but for exploratory analysis.
- iii) Bone lesions will be considered positive if the ^{68}Ga -PSMA-11 uptake is focal and greater than physiologic bone marrow.
 - (1) Bone lesions will be classified by further by region: spine, ribs, pelvis, extremities, skull, sternum, clavicle. These regions will not be used for evaluation of the primary or secondary endpoints, but for exploratory analysis.
- iv) 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.

Reference Standard Definition

b) 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. For lesions that are reported in the blinded reads but not reported in the local evaluation of follow-up imaging, the local readers will be informed of the location of the lesions and follow-up will be performed for these additional lesions. Preferably, 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 validation based on follow-up imaging:

- i) Lymph nodes will be assessed by change in size. ^{68}Ga -PSMA-11 positive lymph nodes will be considered:
 - (1) True positive:
 - For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter and PSA declines by more than 50%.

- If PSA increases by more than 50% on systemic therapy, then a increase in the size of lesion by more than 20% will be considered a true positive lesion.
- In subjects with localized suspected lymph node(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet true positive disease:
- If the subject shows a decrease of PSA by greater than 50% after targeted treatment and the lymph node does not enlarge (change in size less than 20% or less than 3 mm increase in short axis diameter) [OR]
 - If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter (with a minimum of 3 mm in change in size)
- For untreated patients: If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size).
- (2) False positive:
- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter and PSA decreases by more than 50%.
- In subjects with localized suspected lymph node(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet false positive disease:
- If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment [OR]
 - If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size)
- For untreated patients: If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter (with a minimum of 3 mm in change in size).
- (3) If all regions in a patient/region do not meet criteria for either True positive or False positive disease, then the patient/region will be considered inevaluable for primary endpoint.
- ii) Visceral lesions (non-lymph node soft tissue or organ) will be assessed by change in size. ⁶⁸Ga-PSMA-11 positive visceral lesions will be considered:
- (1) True positive:
- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12

months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter and PSA declines by more than 50%.

- If PSA increases by more than 50% on systemic therapy, then a increase in the size of lesion by more than 20% will be considered a true positive lesion.

- In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet true positive disease:

- If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment [OR]
- If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size).

(2) False positive:

- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter and PSA decreases by more than 50%.

- In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet false positive disease:

- If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment [OR]
- If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size).

(3) If all regions in a patient/region do not meet criteria for either True positive or False positive disease, then the patient/region will be considered inevaluable for primary endpoint.

iii) ⁶⁸Ga-PSMA-11 positive bone lesions will be considered:

(1) True positive:

- If there was a corresponding positive sclerotic lesion on the CT portion of the ^{68}Ga -PSMA-11 PET or on a separate CT obtained ≤ 30 days before or after the PET/CT in the same location as the PSMA uptake.
- If there is focal uptake seen in the same location as the PSMA uptake on the baseline bone scan performed within one month of ^{68}Ga -PSMA-11 PET.
- If there is a lesion noted in the same location as the PSMA uptake 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 in the same location as the PSMA uptake.
- If within 12 months follow-up MRI demonstrates a new bone lesion in the same location as the PSMA uptake.
- If within 12 months follow-up bone scan demonstrates new focal uptake in the same location as the PSMA uptake.
- In subjects with localized suspected bone lesion(s) receiving targeted treatment without concomitant systemic treatment:
 - o If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment.

(2) False positive:

- In subjects with localized suspected bone lesion(s) receiving targeted treatment without concomitant systemic treatment:
 - o If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment with curative intent (ie non-palliative radiation).
- If ^{68}Ga -PSMA-11 positive bone lesions do not meet the criteria for true positive findings, and appropriate correlative and follow-up imaging was acquired.

(3) If bone lesions do not meet criteria for either true positive or false positive disease listed above, then the patient/region will be considered inevaluable for primary endpoint.

iv) ^{68}Ga -PSMA-11 positive prostate bed and prostate lesions will be considered:

(1) True positive:

- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter
- In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet true positive disease:

- If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment [OR]
- If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size).

(2) False positive:

- For patients undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter and PSA decreases by more than 50%.

- In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet false positive disease:

- If the subject does not demonstrate a decrease of PSA by greater than 50% after targeted treatment [OR]
- If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20% in long axis diameter (with a minimum of 3 mm in change in size)

- For untreated patients: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size).

(3) If the lesion does not meet criteria for either True positive or False positive disease, then the lesion will be considered inevaluable for primary endpoint.

c) Histopathology/Biopsy:

- i) ⁶⁸Ga-PSMA-11 positive findings are aimed to be confirmed by histopathology/biopsy if clinically feasible. Pathology performed 60 days before the PSMA PET will be available for correlation.
- ii) Histopathological procedures and biopsies will be performed as clinically indicated and as per institutional protocol.

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

- (a) True Positive: lesion is positive on targeted biopsy/surgical sampling and is read as positive on PSMA PET.
- (b) False Negative: lesion is positive on targeted biopsy/surgical sampling and is read as negative on PSMA PET.

- (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, MRI or a repeat ^{68}Ga -PSMA-11 PET 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.
- (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 an alternative diagnoses that is known to be PSMA positive (eg 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.
- (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.
- d) Definitions of True Positive, False Positive, True Negative, and False Negative patients and regions: Pathology will be considered superior to imaging and clinical follow-up when available as described below. Patient and region level classification will be performed for each blinded reader, and be reported separately. The following criteria serve as a guide for interpretation. However not all findings on a lesions, region and patient level can be detailed here and investigators may deviate from these criteria in individual patients. These will be recorded for each interpretation that is not described in this protocol for the definition of a region or patient.
- i) Patient level evaluation:
- (1) True positive patient: A single region in a patient contains a true positive node either by pathology or imaging/clinical follow-up.

- (a) For a patient to be considered a True Positive, only one region is required to have a true positive lesion as described above, unless one region is categorized as a false positive based on pathology. This means that a single pathology false positive region outweighs regions with imaging/clinical follow-up true positive disease.
 - (b) A patient will be considered a True Positive if one region contains a lesion that is True Positive, even if other regions are categorized as inevaluable or false positive based on imaging or clinical follow-up.
- (2) True negative patient: in the absence of True Positive or False Positive lesions, a patient will be considered a True Negative if there is pathology that is negative for disease and corresponding lesion is negative by PSMA PET.
 - (3) False positive patient:
 - (a) Pathology confirms a false positive lesion that is read as positive on PSMA PET.
 - (b) In the absence of pathology: there are no true positive regions, and there is a region that is categorized as false positive based on imaging or clinical follow-up.
 - (4) False negative patient: in the absence of True Positive or False Positive lesions, a patient will be considered a False Negative if there is pathology that is positive for disease and corresponding lesion is negative by PSMA PET. Additionally, patients without evidence of disease on PSMA PET but with biochemical evidence of disease will be considered a False Negative.
- ii) Region level evaluation: Each patient will have four evaluable regions (Table 1: prostate bed, pelvis, extrapelvic soft tissue, and bone metastases). Each region will be categorized as true positive or false positive as described above. Regions without evidence of PSMA positive disease or deemed inevaluable will not be included in the analysis.
 - (1) True positive region:
 - (a) Pathology confirms a PSMA avid lesion as a true positive in the region.
 - (b) In the absence of pathology, clinical or imaging follow-up demonstrates a true positive lesion within the region independent of the presence of an inevaluable lesion or a false positive lesion
 - ie true positive disease will supersede a false positive lesion in the region based analysis if based on imaging/clinical follow-up
 - (2) True negative region: in the absence of True Positive or False Positive lesions within a region, the region will be considered a True Negative if there is pathology that is negative for disease in the region and corresponding lesion is negative by PSMA PET.
 - (3) False positive region:
 - (a) Pathology confirms a PSMA avid lesion as a false positive in the region

- (b) In the absence of pathology, there are no true positive lesions in the region, and there is a false positive lesion by clinical or imaging follow-up.
- (4) False negative region: in the absence of True Positive or False Positive lesions in a region, the region will be considered a False Negative if there is pathology that is positive for disease in the region and corresponding lesion is negative by PSMA PET.

8.3.3 Analysis of Secondary Endpoints

1. PPVs on a per-patient and per-region-basis of ^{68}Ga -PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy, clinical and conventional imaging follow-up 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. PPV will be reported for each of the three blinded readers independently.
2. Sensitivity and 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 summarized in tabular format. Ninety-five percent confidence intervals of sensitivity, specificity, NPV and PPV will be calculated using the Wilson score method. These will be reported for each of the three blinded readers.
3. 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) will be summarized in tabular format and compared between PSA strata using chi-square analysis. Detection rate will also be stratified by history of prostatectomy, radiation or both; as well as by whether the patient is on androgen deprivation therapy (ADT). We will use local interpretations for this analysis.
 - a. Detection rate is defined as number of patients with PSMA positive disease, independent of pathology, imaging or clinical follow-up. A detection rate will be reported for each reader independently stratified by PSA.
4. The impact of ^{68}Ga -PSMA-11 PET on clinical management in BCR patients will be evaluated using descriptive statistics.
5. Inter-reader reproducibility for positivity at the patient level and region level will be reported using the Fleiss' Kappa test for multiple readers. We will use the three blinded reads for this analysis.
6. Safety will be reported descriptively as rates of patient reported adverse events. Additionally, adverse events will be characterized and quantified by CTCAE 4.03.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment

materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form 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.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10 Protection of Human Subjects

10.1 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendices

Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Schedule of Study Procedures and Assessments

Schedule of Study Procedures and Assessments						
Period/ Procedure	Screening	Imaging day 1	1-3 day post imaging	Follow-up survey 1	Follow-up survey 2	Clinical/imaging follow-up
Study day / Visit day	-30 to 1	1	2-4	2 – 30 days	Six months	3-12 months
Informed consent	X					
Laboratory values, history from medical record	X					
Pre-survey	X					
Performance status	X					
Blood pressure, HR	X					
Imaging Procedure						
⁶⁸ Ga-PSMA-11		X				
PET/CT or PET/MRI		X				
Follow-up						
Adverse event reporting			X			
Post-survey				X	X	
Clinical follow-up						X
Follow-up imaging						X*

* in patients who do not have biopsy proof or other criteria to qualify disease, repeat imaging 3-12 months after initiation of treatment or imaging will be performed

Appendix 3 (pre- and post-surveys)
