UCSF Helen Diller Family Comprehensive Cancer Center

NCT # 03463889

Gallium-68 Prostate Specific Membrane Antigen (68Ga-PSMA) PET for Imaging of Thyroid Cancer: A Feasibility Study

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Study Drug: Gallium 68 PSMA

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Protocol Signature Page

Protocol No.: 172016 **Version Date:** 04-10-2019

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	Gallium-68 Prostate Specific Membrane Antigen (68Ga-PSMA) PET for Imaging of Thyroid Cancer: A Feasibility Study
Patient population	The study population will consist of patients with thyroid cancer. Key Eligibility Criteria: • History of thyroid cancer. • Whole body 18F-FDG PET, I-123or I-131 scintigraphy within the past 360 days demonstrating uptake • Age 18 years or older at the time of study entry
Rationale for Study	Agents targeting prostate specific membrane antigen (PSMA) are under investigation for both imaging and therapy of prostate cancer. However, despite its name, PSMA expression is not specific to prostate, and is seen in a variety of normal tissues and cancers. In particular, recent case reports have demonstrated that ^{68}Ga-PSMA ligands demonstrate uptake in thyroid cancer. Intriguingly, a recent case report of a patient with thyroid cancer demonstrated a greater sensitivity for metastatic lesions using ^{68}Ga-PSMA as compared to ^{18}F-FDG. This suggests the potential use of PSMA PET as a diagnostic (and, in radioiodine-negative thyroid cancers, therapeutic) agent in patients with thyroid cancer.
Primary Objective	• To determine the feasibility and utility of ^{68}Ga-PSMA PET imaging in patients with thyroid cancer
Secondary Objectives	1. To assess the correlation between targeted molecular uptake of ^{68}Ga-PSMA-11 in thyroid cancer compared to areas identified as tumor by radioiodine uptake (in well-differentiated cancers) or ^{18}F-FDG uptake (in poorly differentiated and/or radioiodine-negative cancers). 2. To determine and compare the sensitivity and specificity of ^{68}Ga-PSMA-11 PET to ^{18}F-FDG PET and/or radioiodine scintigraphy
Exploratory Objectives	1. To determine if ^{68}Ga-PSMA PET uptake is related to tumor differentiation and PSMA staining in tissue pathology when available 2. To determine the correlation between SUV_{max} of target thyroid cancer lesions on ^{68}Ga-PSMA PET and serum thyroglobulin levels.
Study Design	This is a single center pilot study investigating the use of ^{68}Ga-PSMA PET in patients with thyroid cancer.
Number of patients	40 patients will be accrued over an approximate 24-month period. It is estimated that all patients will have routine diagnostic imaging, and all patients will have elevated serum thyroglobulin.
Duration of Therapy	The study will involve a whole-body ^{68}Ga-PSMA PET/MRI scan obtained at a single time point with optional repeat scan approximately 2-6 months after the first ^{68}Ga-PSMA PET/MRI scan.

Duration of Follow up	n/a
Duration of study	The study will reach completion approximately 24 months from the time the study opens to accrual.
Imaging Agent	^{68}Ga-PSMA-11 (also known as ^{68}Ga-PSMA-HBED-CC)

List of Abbreviations

AE	adverse event
CRC	Clinical Research Coordinator
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FCBP	female of childbearing potential
FDA	Food and Drug Administration
Ga	Gallium
GCP	Good Clinical Practice
HDFCCC	Helen Diller Family Comprehensive Cancer Center
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PRC	Protocol Review Committee (UCSF)
PSMA	prostate-specific membrane antigen
SD	stable disease
SD	standard deviation
SUV	Standardized Uptake Value

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1 Introduction

1.1 Background on Indication

Thyroid cancer is the most common endocrine malignancy, with approximately 62,000 new cases per year in the United States (1). The vast majority of thyroid cancers respond favorably to initial therapy with surgical resection and in some cases radioiodine ablation or external beam radiotherapy or a combination of these therapies. However, a subset of patients with aggressive and less differentiated thyroid cancer refractory to radioiodine therapy ultimately succumb to their illness, with approximately 2,000 deaths per year in the US (2). For patients with disease that is refractory to surgical management or radioiodine ablation, treatment options include external beam radiation and kinase inhibitors. Options for restaging of these patients with thyroglobulin elevation but negative iodine scintigraphy (TENIS syndrome) include 18F-FDG PET/CT and conventional anatomic imaging with ultrasound, CT, or MRI. Nevertheless, the prognosis for these patients remains poor. Therefore, there is an unmet clinical need for therapies to help slow the progression of disease in patients with aggressive forms of thyroid cancer.

1.2 Rationale for the Proposed Study

Agents targeting prostate specific membrane antigen (PSMA) are under investigation for both imaging and therapy of prostate cancer (3,4). However, despite its name, PSMA expression is not specific to prostate, and is seen in a variety of normal tissues and cancers (5,6). In particular, recent case reports have demonstrated that ^{68}Ga-PSMA ligands demonstrate uptake in thyroid cancer (7-10). Intriguingly, a recent case report of a patient with thyroid cancer demonstrated a greater sensitivity for metastatic lesions using ^{68}Ga-PSMA as compared to 18F-FDG (7). This suggests the potential use of ^{68}Ga-PSMA PET as a diagnostic (and, in radioiodine-negative thyroid cancers, therapeutic) agent in patients with aggressive forms of thyroid cancer.

2 Objectives of the Study

2.1 Primary

- To determine the feasibility and utility of ^{68}Ga-PSMA PET imaging in patients with thyroid cancer

2.2 Secondary

1. To assess the correlation between targeted molecular uptake of ^{68}Ga-PSMA PET in thyroid cancer compared to areas identified as tumor by radioiodine uptake (in well-differentiated cancers) or 18F-FDG uptake (in poorly differentiated and/or radioiodine-negative cancers).

2. To determine and compare the sensitivity and specificity of ^{68}Ga-PSMA PET to ^{18}F-FDG PET and/or radioiodine scintigraphy

2.3 Exploratory Objectives, Other Assessments

1. To determine if ^{68}Ga-PSMA PET uptake is related to tumor differentiation and PSMA staining in tissue pathology when available

2. To determine the correlation between SUV_{max} of target thyroid cancer lesions on ^{68}Ga-PSMA PET and serum thyroglobulin levels.

3 Study Design

3.1 Characteristics

This is a single center pilot study in patients with thyroid cancer. Eligible participants will receive a one-time administration of ^{68}Ga-PSMA-11 and undergo a whole-body PET/MRI imaging study. Patients may undergo an additional follow-up 68Ga-PSMA-11 PET/MRI 2-6 months after the initial imaging study, if they give consent.

3.2 Number of Subjects

The total sample size is 40 patients enrolled over approximately 24 months.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug 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 unless otherwise specified.

3.3.1 Inclusion Criteria

1. History of thyroid cancer
2. Whole body ^{18}F-FDG PET/CT, I-123or I-131 scintigraphy within the past 360 days of the scheduled ^{68}Ga-PSMA PET demonstrating uptake.
3. Age 18 years or older at the time of study entry
4. Creatinine </= 3.0 mg/dL
5. Ability to understand a written informed consent document, and the willingness to sign it

3.3.2 Exclusion Criteria

1. Patients who have had active infection within 15 days of study enrollment that may be considered to interfere with ^{68}Ga-PSMA PET imaging by the study investigators.
2. Patients who are unable to have placement of intravenous line access.
3. Pregnant or breastfeeding women.
4. Patients not capable of undergoing a PET/MRI study due to weight, claustrophobia, or inability to lie still for the duration of the exam.

3.4 Study Timeline

3.4.1 Primary Completion

The study is expected to reach primary completion 24 months from the time the study opens to accrual.

3.4.2 Study Completion

The study is expected to reach completion 24 months from the time the study opens to accrual.

4 Imaging Agent

^{68}Ga-PSMA is a radiopharmaceutical that will be produced in the Department of Radiology and Biomedical Imaging Radiopharmaceutical Facility. The radiopharmaceutical will be prepared in the same facility in which the administration will take place, the UCSF China Basin Imaging Center, using a germanium-68 generator.

5 Study Procedures and Observations

5.1 Dosage and Administration

^{68}Ga-PSMA will be administered on an outpatient basis. It will be administered at a single time point, intravenously, prior to PET imaging. The one-time nominal injected dose will be approved by the UCSF Radiation Safety Committee (RSC) and will be 3 to 7 mCi.. A simultaneous whole body PET/MRI will be used for attenuation correction and anatomic localization of ^{68}Ga-PSMA uptake and SUV calculation. ^{68}Ga-PSMA is currently in use at UCSF under an IND in prostate cancer with over 300 patients injected and no significant adverse events. Additionally, this radiotracer has been used safely in Europe with over a thousand studies performed without a significant adverse event. For this protocol, ^{68}Ga-PSMA will cross reference the currently active IND for prostate cancer that is being used at UCSF. A neck MRI with gadolinium (MR) will be performed at the time of the PET imaging. Gadolinium contrast will not be administered if the patient cannot receive contrast based on Radiology Department guidelines.

5.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 28 days of the Day 1 Visit, unless otherwise noted.

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.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

In addition to OnCore, REDCap will be used to collect data for this study. REDCap is a secure, HIPAA-compliant, web-based system.

- Complete medical history
- Baseline standard staging diagnostic exams may be done approximately 360 days before PSMA PET as clinically indicated. Patients may receive staging scans and ^{68}Ga-PSMA PET imaging on the same day if the patient meets eligibility criteria for the study as assessed by the Principal Investigator prior to the completion of the scan.
- Pregnancy testing in women of childbearing potential (WOCBP)
- Creatinine
- Thyroglobulin

5.1.2 Study Period

5.1.2.1 ^{68}Ga-PSMA PET/MRI

Subjects will be injected with ^{68}Ga-PSMA [redacted] and, if needed, transported to the imaging site. After the biodistribution period (50 to 80 minutes after radiotracer injection), coverage for the scan will extend from the patient's vertex through the thighs.

A standard neck MRI will be performed concurrently with the PET/MRI. This MRI will be performed without and with gadolinium contrast intravenously. Gadolinium contrast will not be administered if the patient cannot receive contrast based on Radiology Department guidelines. A whole body (vertex to toes) MRI (PET/MRI) will be performed for attenuation correction and anatomic localization. Patients may be given lorazepam as needed, to keep them from feeling anxious during the scan. The entire imaging study will take roughly 60 minutes. Imaging will be performed at [redacted] UCSF [redacted].

No formal report of the findings from imaging studies will be created. Each study will be reviewed by a board-certified nuclear medicine physician and a board-certified radiologist within two working days of the completion of the study. ^{68}Ga-PSMA PET results will not be used for clinical care. If any unexpected findings are visualized, these will be reported to the treating health care provider, who will then contact the patient if additional work-up needs to be performed.

5.1.3 Pathology

In those patients with adequate archival Formalin-Fixed Paraffin-Embedded (FFPE) tissue, analysis will be performed retrospectively when available after successful completion of ^{68}Ga-PSMA PET.

5.1.4 Optional repeat scan

An optional follow up ^{68}Ga-PSMA PET study may be obtained between 2 and 6 months after completion of the first PET. Optional PET will be performed to determine any interval changes in PSMA uptake and compare them to clinical changes including thyroglobulin. The potential for follow-up examination will be discussed and consented for during the original consent process. The study team will contact the patient after completion of the PET about repeat imaging. Sections 5.1.2 and 5.1.3 will be followed during the follow-up imaging.

A maximum number of **two** ^{68}Ga-PSMA studies (initial and optional follow up) will be performed under this protocol.

Period/ Procedure	Screening	Imaging	Optional Imaging
Study Day/Visit Day	**-28 to 1**	**D1**	**2-6 months after 1st ^{68}Ga-PSMA PET**
Informed consent	X		
AE assessment			X[2]
Concomitant medications	X	X	X[2]
Clinical procedures			
Medical history including prior/concomitant systemic therapies for thyroid cancer	X		
Laboratory procedures			
Creatinine	X		
Thyroglobulin	X		
Pregnancy test (HCG) (WOCBP only)	X		
Imaging procedures			
Standard diagnostic scans as clinically indicated[1]	X[1]		
^{68}Ga-PSMA-11 administration		X	X[2]
Whole body PET/MRI		X	X[2]

1. Standard of care PET scan may be done up to 360 days before PSMA PET. Patients may receive staging scans and 68Ga-PSMA PET imaging on the same day if the patient meets eligibility criteria for the study as assessed by the Principal Investigator prior to the completion of the scan.

2. Only required if patient agrees to optional follow-up 68Ga-PSMA PET.

6 Reporting and Documentation of Results

6.1 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of ^{68}Ga-PSMA administration.

6.2 Evaluation of Safety

Analyses will be performed for all patients having received ^{68}Ga-PSMA. The study will use the CTCAE v4.0 for reporting of adverse events.

6.3 Definitions of Adverse Events

6.3.1 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.

6.3.2 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.

6.3.2.1 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.

6.3.2.2 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.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

6.3.2.3 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.

6.3.2.4 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.

6.4 Recording of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity 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, and this information will be entered into OnCore® using the classification system listed below:

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

6.5 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.

6.6 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 IRB definition of “Unanticipated Problem” (UP) within 10 business days of his/her awareness of the event.

6.7 Image Processing and Analysis

A trained nuclear medicine physician blinded to results of tissue analysis will evaluate the reconstructed PET, MRI, and fused PET/MR images using a PET volume computer-assisted reading software package. A positive lesion on gallium PSMA-11 PET will be defined as a focus of activity with at least 1.5 times higher SUV compared with mediastinal blood pool that is not attributable to other etiologies of tracer distribution (e.g. excretion) or above liver background. A volume of interest (VOI) will be semiautomatically placed around each lesion, and the calculated maximum standard uptake value (SUV_{max}) will be recorded for each lesion. Adjusted SUV_{max} data will then be averaged across all lesions within a given patient ($SUV_{max\text{-}avg}$) if needed. In order to avoid clustering effects, analysis will be limited to the five largest lesions per study.

6.8 Determination of Sample Size and Accrual Rate

Although this is a feasibility study, we will provide a sample size estimate based on the difference in sensitivities between ^{68}Ga-PSMA PET and either ^{131}I and ^{18}F-FDG. To provide an estimate of the needed sample size we assumed that half of the patients will be imaged with ^{131}I and half the patients will be imaged using ^{18}F-FDG PET within 360 days of the ^{68}Ga-PSMA-11 imaging study. We will compare the sensitivity of both ^{131}I and ^{18}F-FDG to ^{68}Ga-PSMA PET. Assuming that both ^{131}I and ^{18}F-FDG have a sensitivity of 0.65 and ^{68}Ga-PSMA PET has a sensitivity of 0.90. Our null hypothesis is that there is no difference between either ^{131}I and ^{18}F-FDG and ^{68}Ga-PSMA PET misclassification rates (H_null: ^{131}I/^{18}F-FDG_misclass = PSMA PET misclass = 65%). The alternative hypothesis is that the FET PET misclassification rate is lower (H_alt: PSMA PET misclass < ^{131}I/^{18}F-FDG_misclass = 65%). Given a power of 0.87, a significance level of 0.05, and a one-sided test, we will require 20 patients for comparison to ^{18}F-FDG and 20 patients for comparison to ^{131}I. This will result in a total sample size of 40. The anticipated accrual rate is approximately 1 to 2 patients per month, leading to an estimated total accrual period of up to 18 to 24 months.

6.9 Interim Analyses and Stopping Rules

After each patient is imaged, the acquired data will be reviewed to determine the optimal image acquisition. If ^{68}Ga-PSMA uptake is not appreciated in any of the first five patients imaged, study accrual will be halted and the imaging protocol will be re-evaluated. A sample size of five patients for interim analysis will allow for a preliminary analysis of image quality and ability of ^{68}Ga-PSMA PET to detect thyroid cancer metastases.

6.10 Analyses Plans

The number of ^{68}Ga PSMA-11 PET-positive lesions and number of overall thyroid cancer lesions detected by standard staging scans will be descriptively reported for each patient and correlated with the lesions observed in standard MRI imaging. In addition, the mean, range, and standard deviation of SUV_{max} (across all visualized lesions per patient) and $SUV_{max\text{-}avg}$ (across all patients in the study cohort) will be descriptively reported.

For each lesion detected on ^{18}F-FDG PET or radioiodine scintigraphy (^{131}I), the presence or absence of ^{68}Ga-PSMA-11 uptake will be reviewed and tabulated. Presence on either ^{131}I and ^{18}F-FDG will be considered true positive disease. If additional lesions are detected on ^{68}Ga-PSMA-11 as compared to ^{18}F-FDG or ^{131}I, the lesions will be characterized as either true or false positives in comparison to the appearance of the lesion on conventional imaging (thyroid ultrasound, CT and MRI). The gold standard for an individual lesion will be FDG or ^{131}I, if the individual lesion is positive on either imaging study. If the lesions are not seen on either FDG or ^{131}I, then consensus reading of conventional imaging will be performed to determine true and

false positive lesions. The total number of lesions detected using each technique will be compared, and this data will be used to determine the sensitivity and specificity of ^{68}Ga-PSMA-11 for the detection of disease. If a larger number of lesions are detected using of ^{68}Ga-PSMA-11 compared to ^{18}F-FDG PET and ^{131}I, this provides promising preliminary data, which can be used to justify study in a larger clinical trial.

The patient cohort will be dichotomized by thyroglobulin level. The mean $SUV_{max\text{-}avg}$ between dichotomized subgroups will be compared using the non-parametric Mann-Whitney U test. The correlation between SUV_{max} on ^{68}Ga-PSMA PET and thyroglobulin level as a continuous variable will also be determined using Pearson correlation method.

In those patients with adequate archival FFPE the correlation between SUV_{max} on ^{68}Ga-PSMA PET and tumor PSMA expression will be explored using Pearson correlation method.

7 Study Management

7.1 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 UCSF RSC and IRB approval is received.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

7.2 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 IRB (UCSF Institutional Review Board). Prior to obtaining IRB 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.

7.3 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 IRB-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.

7.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, 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 IRB 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 IRB approval. In this circumstance, however, the Investigator must then notify the IRB 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.

8 Protection of Human Subjects

8.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

8.2 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.

8.3 Data Safety Monitoring Plan

Data and Safety Monitoring Plan for a Non-therapeutic Institutional Study

Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Auditing on a yearly basis.
- Minimum of a yearly regulatory audit.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for subject safety for all HDFCCC institutional clinical studies. Nontherapeutic studies are characterized as low risk studies due to the study design, as there isn't administration of drugs or complementary therapy that put the patient at significant risk. Twenty percent of all enrolled subjects will be audited once per year.

Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and patient safety at monthly Site Committee meetings. The risk assessment for this type of trial is low; hence, the study would be audited only once per year, with 20 percent of the enrolled subject being selected for audit.

Review and Oversight Requirements

Adverse Event Monitoring

All clinically significant adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All clinically significant adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings

Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.

- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

FDA website for guidance in reporting serious adverse events:

www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All Serious Adverse Events are entered into OnCore®, as well as submitted to the IRB via iRIS®. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six (6) weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

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 is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Investigator or his/her designee must notify the DSMC Chair or Vice Chair within 1 business day. The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day and the IRB must be notified within 10 business days.

Data and Safety Monitoring Committee Contacts:

DSMC Chair:
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

DSMC Monitors:
[redacted]
UCSF HDFCCC
San Francisco, CA 94143

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