UCSF Helen Diller Family Comprehensive Cancer Center

A Phase 2 Study of ^{68}Ga-PSMA-11 PET in Patients with Metastatic Castration Resistant Prostate Cancer

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Protocol Signature Page

1. I agree to follow this protocol version as approved by the UCSF Protocol Review and Monitoring Committee (PRMC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

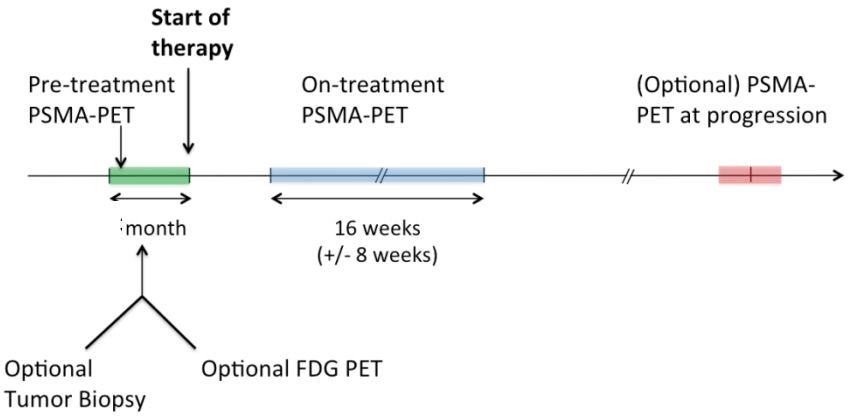
UCSF Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	**A Phase 2 Study of ^{68}Ga-PSMA-11 PET in Patients with Metastatic Castration Resistant Prostate Cancer**
Study Description	This is a phase 2 study investigating the utility of Ga-PSMA-11 PET in patients with metastatic castration resistant prostate cancer.
Phase of Study	Phase 2
Investigational Products	^{68}Ga-PSMA-11 at a dose of 3-7 mCi will be administered at up to three time points per patient, including baseline, after 16 weeks (+/- 8 weeks) of systemic treatment, and at the time of disease progression.
Study population	Approximately 100 patients with metastatic castration-resistant prostate cancer planning to receive, or currently receiving systemic therapy will be enrolled.
Primary Objective	To determine whether the percent change from baseline to 16 weeks (+/- 8 weeks) in SUV_{max} averaged across up to a maximum of 16 lesions per patient ($SUV_{max-ave}$) is associated with ≥ 50% decline from baseline in serum Prostate specific antigen (PSA50) response.
Secondary Objectives	• To determine whether the percent change from baseline in $SUV_{max-ave}$ on PSMA PET is associated with time-to-event endpoints including Prostate specific antigen (PSA) progression-free survival and overall survival. • To determine whether the percent change from baseline in SUV_{max} on PSMA PET is associated with objective response by RECIST 1.1 on a per-lesion basis among measurable soft tissue lesions present at baseline.

Exploratory Objectives	• To descriptively characterize the histologic, transcriptional, and genomic features of PSMA low/negative lesions among patients who undergo paired optional metastatic tumor biopsy. • To descriptively characterize the relationship between $SUV_{max-ave}$ on baseline Ga-PSMA PET with optional baseline FDG-PET. • To determine whether heterogeneity of PSMA expression on baseline Ga-PSMA PET is associated with overall survival. • To descriptively characterize the patterns of PSMA expression at the time of disease progression among patients who undergo optional PSMA PET. • To determine whether the percent change from baseline in PSMA PET is associated with PSA50 response among subgroups of patients defined by treatment modality received, including AR targeting treatment, PSMA-targeting radioligand therapy, cytotoxic chemotherapy, and immunotherapy.
Sample Size	Approximately 100 evaluable patients with metastatic castration-resistant prostate cancer will be enrolled.
Duration of Study Participation	Participants will receive Ga-PSMA-11 PET imaging at baseline, 16 weeks (+/- 8 weeks) after initiating therapy, and optional imaging at time of progression, as defined by Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria. After progression, survival follow-up will be performed every 3 months.
Study Schema	

List of Abbreviations

AE	adverse event
CBC	complete blood cell (count)
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IND	investigational new drug application
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PR	partial response
PRC	Protocol Review Committee (UCSF)
PSA	Prostate specific antigen
PSA50	≥ 50% decline from baseline in serum PSA

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1 Introduction

1.1 Background on mCRPC, Shortcomings of Conventional Imaging to Monitor Treatment Response in mCRPC

Prostate cancer is the most common cancer in men in the US, with over 170,000 estimated new cases and 31,000 deaths in 2019.[1] Androgen deprivation therapy is the cornerstone of treatment for all patients with metastatic disease, or for those who have failed definitive therapy. Although most patients respond to ADT at first, resistance invariably develops, and metastatic castration resistant prostate cancer remains an incurable disease. Accurate assessment of disease burden is often needed to select optimal therapy in patients with metastatic disease.[2–4] Early recognition of resistance can help to avoid unnecessary treatment and prevent cancer-related morbidity and mortality. Assessment of treatment response in mCRPC is currently performed through serial measurements of serum (Prostate specific antigen) PSA and cross-sectional imaging with computerized tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy. Yet these conventional imaging modalities have several limitations in the monitoring of treatment response in mCRPC.[5–7] Morphological imaging (such as CT scan and MRI) relies on size and anatomical changes to assess treatment response. It may fail to detect non-enlarged nodal metastases or early bone marrow involvement, and cannot measure skeletal metastases in the absence of a soft tissue component.[7] By visualizing secondary osteoblastic changes rather than underlying tumor, bone scintigraphy lacks specificity and may lag behind treatment changes.[6] Novel and more accurate markers of disease burden and treatment response are needed for patients with mCRPC.

1.2 Ga-PSMA PET in Newly Diagnosed and Biochemically Recurrent Prostate Cancer

Ga-PSMA PET is one of several novel molecular imaging modalities that have recently emerged in the field of prostate cancer.[6] Using radiolabeled small molecules targeted at PSMA on the surface of prostate cancer cells, Ga-PSMA PET demonstrates excellent tumor-to-background ratio with little physiological uptake in normal tissue. It is not limited by morphologic size criteria, and unlike bone scintigraphy can directly visualize bony metastasis.[6] Ga-PSMA PET imaging has had a significant impact on the management of early state prostate cancer. In a recently published multicenter randomized trial of 302 men with high-risk, clinically localized disease, Ga-PSMA PET was more accurate than conventional imaging with CT and bone scanning for identifying pelvic nodal or distant metastases.[8] Other studies have also shown increased sensitivity and specificity over conventional imaging for the localization of recurrent disease in patients with rising PSA after definitive therapy.[9,10] Although its impact on patient outcomes remains to be determined, Ga-PSMA PET is quickly emerging as an alternative to conventional imaging for the staging of men with early prostate cancer.

1.3 Preliminary Data with Ga-PSMA PET in Metastatic Castration Resistant Prostate Cancer

By comparison, the role of Ga-PSMA PET in patients with mCRPC is less established. Ga-PSMA PET imaging has been used to select patients for PSMA-targeted radioligand therapy, and pre-treatment PSMA uptake appears to predict PSA response to such therapies.[11–13] Prospective studies of serial Ga-PSMA PET imaging in men with mCRPC starting novel hormone therapies (e.g. abiraterone or enzalutamide) have reported heterogeneous initial increases in PSMA uptake despite PSA responses, suggestive of an early flare phenomenon.[14,15] Yet these studies are limited by their small sample sizes and short follow-up intervals; the clinical significance of these early changes in PSMA uptake is unclear. On the

other hand, several retrospectives studies using longer imaging intervals have shown an association between changes in Ga-PSMA PET parameters and treatment response.[16–18] In one such analysis of PSMA-targeted imaging in mCRPC, radiological response at 3 to 6 months was concordant with biochemical response in 56 of 68 patients started on abiraterone therapy.[19] Changes in PSMA uptake were also associated with progression free survival. These data suggest that Ga-PSMA PET imaging may have a role in monitoring treatment response in patients with mCRPC, with key theoretical advantages over conventional imaging for the assessment of bony metastases and early nodal metastases. Whether treatment mechanism of action,[20] or other baseline characteristics modulate PSMA response to therapy remains to be determined.

1.4 Rationale for Inclusion of Optional Paired Tumor Biopsy and FDG-PET

Whereas PSMA is uniformly expressed in the early prostate cancer, variable levels of PSMA expression have been reported in patients with castration-resistant disease.[21] PSMA expression is inversely related to neuroendocrine biomarker genes,[21] and treatment-emergent small-cell neuroendocrine prostate cancer (SCNC) may present as a low-uptake lesion on PSMA-based imaging.[22] Additionally, up to 25% of patients screened for enrollment in PSMA-targeted radioligand therapy fail to meet inclusion criteria due to low- or heterogeneous-PSMA expression.[11,12,23] “Discordant” metastases on serial Ga-PSMA- and FDG-PET imaging, with low PSMA and high Fluorodeoxyglucose (FDG) uptake, have also been described. Limited existing data on this subset of patients suggests a particularly aggressive cancer phenotype,[23] however the histologic and genomic features of this disease entity have yet to be defined. Furthermore, heterogeneous treatment effect and/or prior localized therapy may also contribute to intra-patient variations in PSMA expression. To address this and to better differentiate treatment-related PSMA suppression from discordant disease, we will offer an optional FDG-PET scan to patients with low- or heterogeneous PSMA uptake.[24] Additionally, we will offer optional paired tumor biopsies in selected patients with low PSMA expression, or heterogeneous PSMA uptake on Ga-PSMA PET imaging. As the use of Ga-PSMA PET imaging in mCRPC increases, there is an urgent need to better characterize these different patterns of PSMA expression. By quantifying variations in PSMA expression levels in patients with mCRPC, Ga-PSMA PET may offer non-invasive molecular insight into the underlying biology of advanced prostate cancer.

1.5 Overall Study Rationale

^{68}Ga-PSMA-PET has been shown to have significant utility and clinical impact in the detection of prostate cancer in newly diagnosed and biochemically recurrent patients. Preliminary retrospective evidence suggests that in patients with metastatic castration resistant prostate cancer, decline from baseline in PSMA PET upon application of systemic therapies in mCRPC may be associated with subsequent response, however this link has not been definitively established. A subset of patients with mCRPC may also present with low or heterogeneous PSMA expression, which may be associated with a poor prognosis. We aim to prospectively investigate the association between response on PSMA PET with subsequent treatment outcomes. We also hope to describe the clinical histologic, genomic features of patients with low or heterogeneous PSMA expression.

2 Study Objectives and Hypotheses

2.1 Hypothesis

We hypothesize that decline from baseline in uptake on Ga-PSMA-PET will be associated with PSA response.

2.2 Primary Objective and Endpoint(s)

Primary Objective	Endpoint(s)	Time Frame
1. To determine whether the percent change from baseline to 16 weeks (+/- 8 weeks) in SUV_{max} averaged across up to 16 lesions per patient ($SUV_{max\text{-}ave}$) is associated with PSA50 response	• Association between percent change from baseline to 16 weeks (+/- 8 weeks) in SUV_{max} averaged across up to 16 lesions per patient ($SUV_{max\text{-}ave}$) with PSA50 response, defined by ≥ 50% decline from baseline in serum PSA.	Baseline to 16 weeks (+/- 8 weeks) after initiation of therapy

2.3 Secondary Objective(s) and Endpoint(s)

Secondary Objective	Endpoint(s)	Time Frame
1. To determine whether the percent change from baseline in $SUV_{max\text{-}ave}$ on PSMA PET is associated with time-to-event endpoints including PSA progression-free survival by Prostate Cancer Clinical Trials Working Group 3 (PCWG3)[26] criteria and overall survival.	Association between percent change from baseline in $SUV_{max\text{-}ave}$ on PSMA PET with time-to-event endpoints including PSA progression-free survival by PCWG3 criteria and overall survival.	Baseline to time of progression Baseline to time of death
2. To determine whether the percent change from baseline in SUV_{max} on PSMA PET is associated with objective response by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[27] on a per-lesion basis among measurable soft tissue lesions present at baseline	Association between percent change from baseline in SUV_{max} on PSMA PET with objective response by RECIST 1.1 on a per-lesion basis among measurable soft tissue lesions present at baseline.	Baseline to time of objective response

2.4 Exploratory (Correlative) Objectives

Exploratory Objective
1. To descriptively characterize the histologic, transcriptional, and genomic features of PSMA low/negative lesions among patients who undergo paired optional metastatic tumor biopsy.
2. To descriptively characterize the relationship between $SUV_{max\text{-}ave}$ on baseline Ga-PSMA PET with optional baseline FDG-PET.
3. To determine whether heterogeneity of PSMA expression on baseline Ga-PSMA PET is associated with overall survival.
4. To descriptively characterize the patterns of PSMA expression at the time of disease progression among patients who undergo optional PSMA PET.
5. To determine whether the percent change from baseline in PSMA PET is associated with PSA50 response among subgroups of patients defined by treatment modality received, including AR targeting treatment, PSMA-targeting radioligand therapy, cytotoxic chemotherapy, and immunotherapy.

3 Study Design

3.1 Characteristics

This is a single site phase 2 prospective imaging study evaluating the utility of Ga-PSMA PET to detect treatment response in patients with metastatic castration resistant prostate cancer. There are two sub-cohorts:

- Sub-cohort A1: Patients with castration-resistant prostate cancer *planning* to start a new line of systemic therapy will be enrolled and undergo a baseline pre-treatment ^{68}Ga-PSMA-11 PET scan. Patients will then be monitored for treatment response and undergo a repeat ^{68}Ga-PSMA-11 PET scan 16 weeks (+/- 8 weeks) after the start of systemic therapy. *(Note: Patients in sub-cohort A1 who initiate systemic therapy during the screening period/prior to study enrollment may be re-consented to transition to sub-cohort A2.)*

- Sub-cohort A2: Patients with castration-resistant prostate cancer *currently* on systemic therapy will be enrolled if a baseline pre-treatment 68Ga-PSMA-11 PET scan was performed within 12 weeks prior to the start of systemic therapy, and the on-treatment PSMA PET can be performed within 16 weeks (+/- 8 weeks) after the start of systemic therapy. Patients will then be monitored for treatment response and undergo a repeat ^{68}Ga-PSMA-11 PET scan 16 weeks (+/- 8 weeks) after the start of systemic therapy.

3.2 Sample Size

Approximately 110 patients will be consented to achieve the target number of 100 evaluable participants (this includes both sub-cohorts A1 & A2).

Participants who did not complete paired PSMA PET imaging, those with negative baseline PSMA PET, or those who did not subsequently start a new systemic therapy for treatment of mCRPC following baseline PSMA PET will be considered unevaluable for the primary analysis and will be replaced.

3.3 Eligibility Criteria

Patients 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. Once it has been ascertained that subjects are eligible for the study, their authorization to use personal health information for this study and their informed consent will be obtained. Each subject will be assigned a unique study identification number at the time of study enrollment in order to ensure confidentiality of study data.

3.3.1 Inclusion Criteria

1. Sub-cohort A1: Patients must have baseline evaluations performed within 12 weeks prior to the start of systemic therapy. *(Note: Patients in sub-cohort A1 who initiate systemic therapy during the screening period/prior to study enrollment may be re-consented to transition to sub-cohort A2.)*
2. Sub-cohort A2: Patients must meet **all** the following requirements:

- Have had a baseline pre-treatment 68Ga-PSMA-11 PET scan and PSA measurement performed within 12 weeks prior to the start of current systemic therapy.
- Able to have an on-treatment 68Ga-PSMA-11 PET and a PSA measurement within 16 weeks (+/- 8 weeks) after the start of current systemic therapy.

Note: The screening period for sub-cohort A2 is within 24 weeks after the patient started their current systemic therapy.

3. Patients must have progressive castration resistant prostate cancer, according to PCWG3 criteria.
4. Patients must have planned initiation of systemic treatment (sub-cohort A1), or ongoing systemic treatment (sub-cohort A2) for castration resistant prostate cancer within 12 weeks of baseline Ga-PSMA PET.
5. Patients must have at least one metastatic lesion with PSMA uptake at or above the blood pool on their baseline PSMA PET scan.
6. The patient must be able and willing to comply with study procedures and provide signed and dated informed consent.
7. Patient must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
8. Patient must be Aged 18 years or older at the time of study entry
9. Patients who undergo optional metastatic tumor biopsy following completion of baseline Ga-PSMA PET (sub-cohort A1) must additionally meet **all** of the following criteria:
   - Presence of one or more metastases by standard radiographic scans that is safely accessible to tumor biopsy in the judgment of treating clinician and/or Interventional Radiology.
   - No history of radiation therapy to the target metastatic lesion selected for tumor biopsy
   - No contra-indication to biopsy including uncontrolled bleeding diathesis.
   - Platelets >75,000/μL and PT or INR and a PTT < 1.5 times the institutional ULN within 14 days prior to biopsy

3.3.2 Exclusion Criteria

1. Patients who because of age, general medical or psychiatric condition, or physiologic status cannot give valid informed consent.
2. Patients with any condition that, in the opinion of the Principal Investigator, would impair the patient's ability to comply with study procedures.
3. Patients with any contra-indication to MRI (e.g. pacemaker placement, severe claustrophobia)
   Note: The exclusion criteria above (3) is only applicable for patients scheduled for a PET/MRI.

3.4 Inclusion and Recruitment of Minorities

Participants must have a diagnosis of progressive castration resistant prostate cancer to be eligible for this study. Individuals of any race or ethnicity may participate. The inclusion of women is not appropriate for the trial design given this is a study of prostate cancer.

3.5 Duration of Study Participation

Participants will receive Ga-PSMA-11 PET imaging at baseline, 16 weeks (+/- 8 weeks) after initiating therapy, and optional imaging at time of disease progression, as defined by PCWG3 criteria. After progression, survival follow-up will be performed every 3 months.

3.6 Primary Completion

The expected primary completion date is 36 months from the date of first patient enrolled.

3.7 Study Completion

The expected study completion date is 48 months after the study opens to accrual.

3.8 Study Termination

The principal investigator reserves the right to terminate the study at any time.

Termination of the study will be considered in the event of any safety concerns arising at any time during the performance of the study.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigators and the Data and Safety Monitoring Committee (DSMC).

4 Investigational Product: ^{68}Ga-PSMA-11

^{68}Ga-PSMA-11 is a radiopharmaceutical that is produced under Current Good Manufacturing Practice in the Department of Radiology and Biomedical Imaging Radiopharmaceutical Facility. The radiopharmaceutical is prepared in the same facility in which the injection and imaging take place, the China Basin Imaging Center at UCSF.

4.1 Dosage and Administration

^{8}Ga-PSMA-11 imaging agent will be administered on an outpatient basis. The injected dose will be 3 to 7 mCi of ^{68}Ga-PSMA-11. It will be administered a single time intravenously prior to the PET imaging.

4.2 Description, Supply and Storage

Formulation and Appearance

PSMA-11 Ga 68 Injection is a positron emitting radiopharmaceutical containing radioactive 68Ga-labeled Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (PSMA-11), which is used for diagnostic purposes in conjunction with Positron Emission Tomography (PET). PSMA-11 Ga 68 Injection is a sterile, pyrogen free, clear, colorless aqueous solution presented in a multi-dose vial.

The final drug product volume is 12 mL and contains 10 mL Sodium Chloride 0.9% Injection, 1 mL of ethanol and 1 mL of Water for Injection. The solution has a pH between 4.0 and 7.0 and each mL of PSMA-11 Ga 68 Injection contains between 0.5 - 5 mCi (18.5 – 185 MBq) 68Ga-PSMA-11 at the end of synthesis (EOS).

Storage and handling

The investigational product is stored at 20-25°C, excursion permitted to 15-30°C. The stability of the investigational product is validated for 3 hours after EOS. Discard after expiration time.

4.3 Accountability Records for Investigational Product

68Ga-PSMA-11 will be provided by the Department of Radiology and Biomedical Imaging Radiopharmaceutical Facility. Upon receiving the investigational product, a certified Nuclear Medicine technologist will perform dose calibration and complete the radio pharmacy log. Any unused investigational products will be disposed of according to local radiation safety guidelines.

4.4 Ordering Investigational Product

68Ga-PSMA-11 will be obtained directly from the UCSF Department of Radiology and Biomedical Imaging Radiopharmaceutical Facility.

5 Study Procedures and Schedule of Events

The study-specific procedures and assessments are detailed in this section and outlined in the Study Calendar – Section 5.1.

On-study procedure or visit delays for public holidays, public emergencies, or weather conditions do not constitute a protocol violation.

5.1 Study Calendar

5.1.1 Study Calendar for Sub-Cohort A1

Period / Procedure	Screening (Within 12 weeks prior to C1D1)	Cycle 1 Day 1 (Start of systemic therapy) [10]	Follow up Response Monitoring 8 weeks (+/-4 weeks)	Follow up PET 16 weeks (+/- 8 weeks) Following Treatment Initiation[9]	Disease Progression by PCWG3
Informed consent	X				
Baseline conditions	X				
Concomitant medications	X				
Demographics	X				
Serum PSA[1]	X		X	X	X
Performance status	X				
LDH, CBC + diff, Liver function tests	X				
Disease assessment by cross sectional imaging	X[2]		X[3]	X[4]	X[4]
^{68}Ga-PSMA-11 PET/CT or PET/MRI	X[8]			X	X (Optional)
Tumor biopsy[5] (optional)	X				
Circulating tumor nucleic acid collection[6] (optional)	X			X	X
FDG PET/CT[7] (optional)	X				

[1] Response monitoring with respect to serum PSA will occur per standard of care and provider discretion. A minimum of three serum PSA values are required including: at baseline prior to initiation of systemic treatment (+/- 12 weeks), at 8 weeks (+/- 4 weeks), and at 16 weeks (+/- 8) weeks).

[2] Cross-sectional imaging of the chest/abdomen/pelvis (CT or MRI; with IV contrast if medically permissible), including paired CT or MRI obtained with baseline PET scan.

[3] Response monitoring with respect to conventional imaging will occur per standard of care and provider discretion.

[4] Cross-sectional imaging of the chest/abdomen/pelvis (CT or MRI; with IV contrast if medically permissible), including paired CT or MRI obtained with PET scan. Patients who underwent PET/CT at baseline should have same imaging modality performed during follow-up, and likewise patients who underwent PET/MR at baseline should have same imaging modality performed for follow up PSMA PET imaging.

[5] Metastatic tumor biopsy is optional for eligible participants. Tumor biopsy should be performed within 12 weeks following baseline PET. Soft tissue, PET-avid lesions should be prioritized for biopsy whenever feasible. Biopsy will be performed under companion protocol CC# 155518.

[6] Circulating tumor nucleic acid collection via peripheral blood collection is optional. Collection will be performed under companion protocol CC # 155518.

[7] FDG PET/CT is optional. FDG PET will be performed at baseline (+/ 12 weeks from date of baseline Ga-PSMA PET).

[8] At least one metastatic lesion with PSMA uptake at or above that of the blood pool will be required for study entry. A ^{68}Ga-PSMA-11 PET/CT or PET/MRI obtained prior to study entry may serve as the patient's baseline PSMA PET scan if within 12 weeks of C1D1 (start of systemic therapy).

[9] Specific timing of follow up PET to be determined based on modality of therapy (see Section 5.3.6).

[10] Patients started on systemic therapy during the screening period/prior to study enrollment will be transitioned to sub-cohort A2.

5.1.2 Study Calendar for Sub-Cohort A2

Period / Procedure	Screening (Within 24 weeks after the start of current systemic therapy)	Follow up Response Monitoring 8 weeks (+/-4 weeks)	Follow up PET 16 weeks (+/- 8 weeks) Following Treatment Initiation[7]	Disease Progression by PCWG3
Informed consent	**X**			
Baseline conditions	**X**			
Concomitant medications	**X**			
Demographics	**X**			
Serum PSA[1]	**X**	**X**	**X**	**X**
Performance status	**X**			
LDH, CBC + diff, Liver function tests	**X**			
Disease assessment by cross sectional imaging	**(X)**[2]	**X**[3]	**X**[4]	**X**[3]
^{68}Ga-PSMA-11 PET/CT or PET/MRI	**(X)**[5,6]		**X**	**X (Optional)**

[1] Response monitoring with respect to serum PSA will occur per standard of care and provider discretion. A minimum of two serum PSA values are required including: at baseline prior to initiation of systemic treatment (+/- 12 weeks), and at 16 weeks (+/- 8) weeks).

[2] Prior cross-sectional imaging of the chest/abdomen/pelvis (CT or MRI) performed within 12 weeks of the baseline 68Ga-PSMA-11 PET scan (including paired CT or MRI obtained with baseline PET scan) may serve as a baseline and does not need to be repeated.

[3] Response monitoring with respect to conventional imaging will occur per standard of care and provider discretion.

[4] Cross-sectional imaging of the chest/abdomen/pelvis (CT or MRI; with IV contrast if medically permissible), including paired CT or MRI obtained with PET scan. Patients who underwent PET/CT at baseline should have same imaging modality performed during follow-up, and likewise patients who underwent PET/MR at baseline should have same imaging modality performed for follow up PSMA PET imaging.

[5] A ^{68}Ga-PSMA-11 PET scan performed prior to study enrollment may serve as a baseline PSMA PET if performed within 12 weeks prior to the start of current systemic therapy. This scan is required within window as part of eligibility requirements (See Section 3.3.1). Patients must also have an on-treatment PSMA PET within 16 weeks (+/-8 weeks) after starting treatment.

[6] At least one metastatic lesion with PSMA uptake at or above that of the blood pool will be required for study entry.

[7] Specific timing of follow up PET to be determined based on modality of therapy (see Section 5.3.6).

5.2 Participant Registration

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 participants consented to the study 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.

A list of study subjects will be completed, and will include each subject's study number and initials. The investigator must also maintain a separate log of all the subjects screened for participation in the study but who will not participate, the reasons for their exclusion or non-participation, their initials, and the date on which the subject was excluded.

5.3 Schedule of Procedures and Assessments

5.3.1 Screening Assessments

The screening procedures and assessments must be completed within 12 weeks prior to the start of planned systemic therapy (sub-cohort A1) or within 24 weeks after the start of current systemic therapy (sub-cohort A2). *(Note: Patients in sub-cohort A1 who initiate systemic therapy during the screening period/prior to study enrollment may be re-consented to transition to sub-cohort A2.)*

- Baseline conditions
- Concomitant medications
- Demographic information (e.g. age, race, height, weight, and body mass index)
- ECOG or Karnofsky Performance status
- Laboratory procedures
    - Prostate-specific antigen
    - Complete blood count + differential
    - Lactate dehydrogenase
    - Liver function tests including AST, ALT, total bilirubin, and alkaline phosphatase

Additional screening assessments for sub-cohort A1:

- Baseline ^{68}Ga-PSMA-11 PET scan will performed and reviewed to confirm the presence of at least one metastatic lesion with PSMA uptake at or above that of the blood pool. A ^{68}Ga-PSMA-11 PET scan performed prior to study entry may serve as the baseline PSMA PET scan if within 12 weeks of the start of systemic therapy.
- Cross-sectional imaging of the chest/abdomen/pelvis (CT or MRI; with IV contrast if medically permissible) within 12 weeks of baseline ^{68}Ga-PSMA-11 PET scan (including the same day as baseline PET). Cross-sectional imaging performed prior to study entry may serve as baseline imaging if within 12 weeks of the start of systemic therapy.

Additional screening assessments for sub-cohort A2:

- Baseline ^{68}Ga-PSMA-11 PET scan performed within 12 weeks prior to start of current systemic therapy will be reviewed to confirm the presence of at least one metastatic lesion with PSMA uptake at or above that of the blood pool
- Cross-sectional imaging of the chest/abdomen/pelvis (CT or MRI; with IV contrast if medically permissible) performed within 12 weeks of baseline ^{68}Ga-PSMA-11 PET scan (including the same day as baseline PET) will be reviewed

5.3.2 Baseline ^{68}Ga-PSMA-11 PET/MRI or PET/CT

- ^{68}Ga-PSMA-11 PET/CT or PET/MRI
    - Participants will begin PET imaging between 55 and 70 minutes after the injection of Ga-PSMA-11 at a dose of at a dose of 3-7 mCi.
    - A dose of 20 mg of furosemide (Lasix) is recommended to be injected intravenously 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. Furosemide should not be administered in patients with medical contraindications to Furosemide.
    - Contrast agent for MRI or CT will be administered as clinically indicated.
    - Participants will be monitored for adverse events for two hours after Ga-PSMA-11 administration.
    - A formal radiology report from the imaging scan will be generated by the Nuclear Medicine department. 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.
    - If the patient has received a 68Ga-PSMA-11 PET scan prior to study enrollment and within 12 weeks prior to the start of current systemic therapy (sub-cohort A2), the PET scan may serve as the baseline PET scan and does not need to be repeated at screening.

5.3.3 Baseline Tumor Biopsy and Circulating Tumor Nucleic Acid Collection (Optional – Within 12 weeks of Baseline PSMA PET)

Patients in sub-cohort A1 will undergo optional metastatic tumor biopsy and circulating tumor nucleic acid collection within 12 weeks of baseline PSMA PET scan. Biopsy and/or circulating nucleic acid collection will be performed under protocol CC # 155518. Soft tissue lesions with low/negative PSMA uptake will be prioritized for tissue acquisition. However, either bone or soft tissue lesions that are deemed safely accessible per Interventional Radiology assessment will be potentially considered for imaging.

Optional circulating tumor nucleic acid collection under companion protocol CC# 155518 will also be performed at the following times:

- Initiation of systemic treatment
- Disease progression

5.3.4 Baseline FDG PET (Optional for sub-cohort A1 only – within 12 weeks of Baseline PSMA PET)

Patients in sub-cohort A1 may undergo optional FDG PET/CT scan (within 12 weeks after date of baseline Ga-PSMA PET) per standard imaging procedures.

5.3.5 Initiation of Systemic Therapy

- Sub-cohort A1: Patients will subsequently initiate systemic treatment for castration resistant prostate cancer. Choice of therapy will be per discretion of the treating physician. Response monitoring with respect to serum PSA and conventional imaging will occur per standard of care and provider discretion. A minimum of three serum PSA values are required including at baseline within 12 weeks prior to initiation of systemic treatment, at 8 weeks (+/- 4 weeks), and at 16 weeks (+/- 8) weeks) from start of systemic therapy.
- Sub-cohort A2: Patients must be currently receiving systemic treatment for castration resistant prostate cancer, initiated within 12 weeks after their baseline 68Ga-PSMA -11 PET scan. Choice of therapy will be per discretion of the treating physician. Response monitoring with respect to serum PSA and conventional imaging will occur per standard of care and provider discretion. A minimum of two serum PSA values are required including at baseline within 12 weeks prior to initiation of systemic treatment and at 16 weeks (+/- 8) weeks)) from start of systemic therapy.

5.3.6 Follow up ^{68}Ga-PSMA-11 PET (16 weeks +/- 8 weeks from date of systemic treatment initiation)

Patients will undergo repeat ^{68}Ga-PSMA-11 PET after 16 weeks (+/- 8 weeks) from date of initiation of systemic treatment.

The specific time frame for imaging will depend on the treatment modality administered, and will be standardized as follows:

- Androgen Receptor (AR) targeted therapy (20 weeks +/- 4 weeks)
- PSMA-targeting radioligand therapy (12 weeks +/- 4 weeks)
- Cytotoxic chemotherapy (12 weeks +/- 4 weeks)
- Immunotherapy (12 weeks +/- 4 weeks)

Patients with a negative baseline PSMA PET scan (i.e. no metastatic lesion with PSMA uptake at or above that of the blood pool) will not be eligible for the follow up PSMA PET.

Patients who underwent PET/CT at baseline should have same imaging modality performed during follow-up, and likewise patients who underwent PET/MR at baseline should have same imaging modality performed for follow up PSMA PET imaging.

5.3.7 Time of Disease Progression by PCWG3 Criteria (Optional)

Patients will undergo an optional third ^{68}Ga-PSMA-11 PET at the time of progression by PCWG3 criteria. Patients who underwent PET/CT at baseline should have same imaging modality performed during follow-up, and likewise patients who underwent PET/MR at baseline should have same imaging modality performed during follow up.

5.3.8 Long Term Survival Follow Up

Participants will be followed by telephone call and/or chart review every 3 months to record survival status until death, study withdrawal, or study closure, whichever occurs first.

5.4 Dietary Restrictions

None. No fasting is required for PSMA PET imaging.

5.5 Prohibited Medications

None. There are no prohibited medications.

6 Reporting and Documentation of Results

6.1 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of IMP. The study will use the Common Terminology Criteria for Adverse Events (CTCAE v5.0) criteria for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events.

6.2 Definitions of Adverse Events

6.2.1 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.

Laboratory test value abnormalities will not be recorded as AEs unless they are designated as clinically significant, defined as any one of the following: symptomatic, requiring treatment, resulting in dose modification or delay or premature study withdrawal, or placing the subject at risk for other toxicity in the judgment of the treating investigator.

6.2.2 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.

6.2.3 Suspected Adverse Reaction

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 investigational new drug (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.

6.2.3.1 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 participants exposed to drugs in the angiotensin-converting enzyme 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.

6.2.3.2 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 participant 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.

6.2.3.3 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 participant 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.

6.2.4 Recording of Adverse Events

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

6.2.5 Follow-up of Adverse Events

All participants who experience adverse events will be followed with appropriate medical management until resolved or stabilized, as determined by the investigator. For selected adverse events for which administration of the investigational product was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the investigator.

6.2.6 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 2.

6.2.7 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 Institutional Review Board

The UCSF PI must report events to the UCSF IRB according to institutional guidelines.

UCSF IRB website for guidance in reporting adverse events: https://irb.ucsf.edu/adverse-event

Expedited Reporting to the Food and Drug Administration (FDA)

If the study is being conducted under an IND, the Sponsor (or 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 needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

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)).

7 Statistical Considerations and Evaluation of Results

7.1 Imaging Analysis

A trained nuclear medicine physician will evaluate the reconstructed PET, CT or MRI, and fused PET/CT or PET/MR images using a PET volume computer-assisted reading software package. A positive lesion on PET will be defined as a focus of activity with higher SUV compared with mediastinal blood pool that is not attributable to other etiologies of tracer distribution (e.g. inflammation, excretion). A volume of interest (VOI) will be semi-automatically placed around each lesion, and the calculated maximum standard uptake value (SUV_{max}) will be recorded for each lesion, including lesions that are detected on standard scans but are not positive on PET. Adjusted SUV_{max} data will then be averaged the primary tumor and 5 largest lesions in each of three metastatic site (nodal, visceral, and osseous) within a given patient, up to a maximum of 16 lesions per patient ($SUV_{max\text{-}avg)}$. Irradiated lesions will be excluded from this analysis.

7.2 Sample Size Considerations

7.2.1 Sample Size and Power Estimate

The sample size of 100 evaluable patients is based on the primary study endpoint. Based on the available standard of care and investigational therapies available in mCRPC, it is estimated that 40% of patients will experience a PSA50 response on the systemic treatment chosen by investigator. Based on prior data from retrospective studies evaluating PSMA PET as an indicator of clinical response, patients with clinical response have an approximate 50% reduction from baseline in $SUV_{max\text{-}ave}$ on serial PSMA PET. A sample size of 100 patients (estimated 40 PSA50 responders, 60 non-responders) provides 89% power to detect an effect size of 0.67 with respect to the percent change from baseline in $SUV_{max\text{-}ave}$ on PSMA PET in PSA50 responders vs. non-responders, using the Mann-Whitney test and bi-directional alpha = 0.05. This translates into an absolute mean difference in the percent change from baseline on PSMA PET between responders vs. non-responders of 20% (within group SD 30%).

7.2.2 Accrual Estimates

The estimated accrual period is 18-24 months.

7.3 Interim Analyses

An interim analysis for feasibility will be performed after 30 patients are enrolled. Baseline and on-treatment PSMA PET images will be qualitatively reviewed and preliminary data with respect to the mean percent change from baseline in $SUV_{max\text{-}ave}$ will be determined. If it is determined that insufficient change is detected, adjustment of on-treatment PSMA PET scan time point may be instituted along with specification of the type of systemic therapy allowed post –baseline PSMA PET.

7.4 Analyses Plans

7.4.1 Analysis Population

All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate. Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation.

7.4.2 Primary Analysis (or Analysis of Primary Endpoints)

The mean ($SUV_{max,ave}$), median, and range of SUV_{max} across the primary tumor and the 5 largest lesions in each of three metastatic sites (nodal, visceral and osseous; for a maximum of 16 lesions per patient) will be descriptively reported. The study cohort will be divided into subgroups based on whether or not patient experienced a ≥ 50% decline from baseline in serum PSA (PSA50 responder) or not (PSA50 non-responder). The mean percent change from baseline in $SUV_{max-ave}$ on PSMA PET between PSA50 responders vs. non-responders will be compared using the Mann-Whitney test.

7.4.3 Secondary Analysis (or Analysis of Secondary Endpoints)

The study cohort will be dichotomized by the median with respect to percent change from baseline in $SUV_{max-ave}$ on PSMA PET. The time-to-event variables including PSA progression-free defined by PCWG3, and overall survival will be compared between dichotomized subgroups using the log-rank test. Kaplan-Meier product limit method will be used to estimate median survival in each subgroup.

Amongst the subset of measurable soft tissue lesions by RECIST 1.1 criteria, on a per-lesion basis, the mean percent change from baseline in SUV_{max} on PSMA PET will be compared between responding lesions by RECIST 1.1 criteria vs. those without response, using Mann-Whitney test.

PSMA negative lesions will be defined as those with SUV values below the mediastinal blood pool. Low positive lesions will be defined as those with SUV_{max} values above the blood pool, but below background liver uptake. Intermediate positive lesions are those defined by SUV_{max} values above background liver, but below parotid gland uptake. High positive lesions are those with SUV_{max} values above that of parotid gland. The histologic, genomic and transcriptional features of each subgroup of PSMA lesion category that has matching tumor tissue will be descriptively reported with particular emphasis on the low and negative PSMA lesions that have paired tumor tissue available.

The median and range for inter-tumoral SUV_{max} across metastatic lesions within individual patients will be descriptively reported, to assess for heterogeneity of PSMA uptake. The cohort will be dichotomized above and below median range of SUV_{max} values to define low and high heterogeneity subgroups. Overall survival from date of onset of mCRPC will be compared between high vs. low heterogeneity subgroups.

Analysis of the correlation between SUV_{max} PSMA and FDG PET will be performed on a per-lesion basis amongst the subset of patients who have paired evaluable imaging using Pearson r correlation coefficient.

Patterns of PSMA expression at the time of progression by PCWG3 criteria will be descriptively characterized.

Comparison of mean percent change from baseline in $SUV_{max-ave}$ in PSA50 responders vs. non-responders will be performed in pre-specified subgroups based on modality of systemic

treatment, including AR targeted therapy, PSMA-directed radioligand therapy, cytotoxic chemotherapy, and immunotherapy.

No adjustment will be made for multiple comparisons for the analysis of the secondary and exploratory endpoints.

8 Study Management

8.1 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 Good Clinical Practice (GCP) and all applicable regulatory requirements.

Before initiating this trial, the PI 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 participants before any protocol related procedures are performed on any participants.

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

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 FDA has determined that the study is exempt from IND requirements.

8.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant-facing materials related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB. 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.

8.3 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.

8.4 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 PI and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements.

8.5 Handling and Documentation of Clinical Supplies

The Principal Investigator will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity and batch or code number of the drug, and the identification of participants to whom the investigational product has been dispensed by participant number and initials will be included.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study participants. Furthermore, the Principal Investigator will not allow the investigational product to be used in any manner other than that specified in this protocol.

8.6 Case Report Forms (CRFs)

The Principal Investigator and/or designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel will complete the CRFs; the Principal Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the participant's medical records maintained by study personnel. All source documentation should be kept in separate research files for each participant.

In accordance with federal regulations, the Principal Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

8.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the National Cancer Institute-approved (NCI) Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 - Data and Safety Monitoring Plan.

8.8 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed participant consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the Principal Investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

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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 Data and Safety Monitoring Plan

Data and Safety Monitoring Plan for a Phase II or III Institutional Study

1. Oversight and Monitoring Plan

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

- Semiannual auditing (depending on study accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III studies are designated with a moderate risk assessment. The data is audited semiannually with a random selection of twenty percent of the participants audited (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for the review, or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. Additionally, a regulatory audit will occur on a biennial basis to review all regulatory documents for the trial.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 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 investigational agent(s) or study procedure, 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 investigational agent or study procedure. Attribution categories are:

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

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 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 all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

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 (per IRB guidelines). 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 weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

1.3 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 via report 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 voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

Data and Safety Monitoring Committee Contacts:

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