UCSF Helen Diller Family Comprehensive Cancer Center

A First-in-Human, Phase 1 PET imaging Study of ^{11}C-YJH08, a Selective Glucocorticoid Receptor-Targeting Agent, in Patients with Advanced Solid Tumor Malignancies

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Principal Investigator
Rahul Aggarwal, MD
University of California, San Francisco
[redacted]

Co-Principal Investigators
Spencer Behr, MD

Statistician
Li Zhang, Ph.D.

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Protocol Signature Page

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-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.

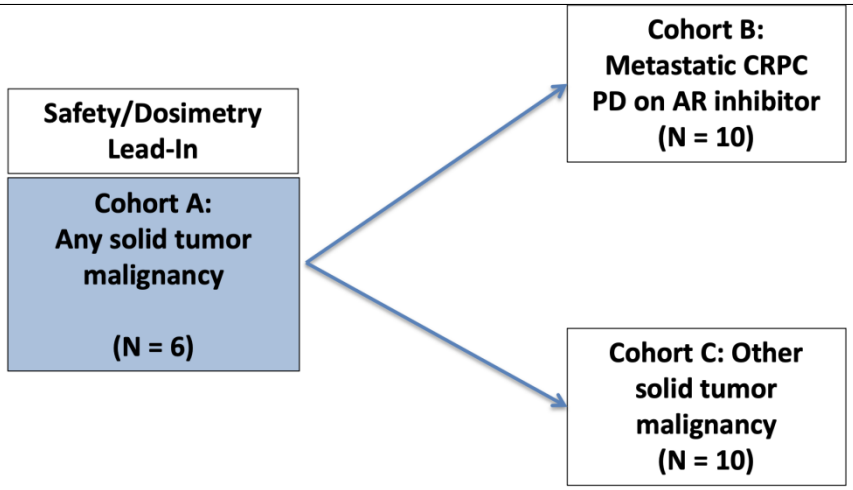
UCSF Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	A First-in-Human, Phase 1 PET imaging Study of ^{11}C-YJH08, a Selective Glucocorticoid Receptor-Targeting Agent, in Patients with Advanced Solid Tumor Malignancies
Study Description	This is a first-in-human phase 1 imaging study of ^{11}C-YJH08 PET in patients with advanced solid tumor malignancies, with a particular focus on enzalutamide/apalutamide-resistant mCRPC.
Phase of Study	Phase 1
Investigational Medicinal Product	^{11}C-YJH08 at a dose of up to 20 mCi will be administered. It will be injected intravenously. For cohort A (n = 6), dosimetry calculation will be performed by obtaining whole body (vertex to thighs) PET images up to five time points during 0-90 minutes post injections. For cohort B and C (n=10 each), one time point will be obtained based on the results of cohort A.
Study population	Approximately 26 patients total will be enrolled in one of two following cohorts: Cohort A (N = 6 patients): Patients with any solid tumor malignancy with evidence of one or metastases on conventional imaging. Cohort B (N = 10 patients): Patients with metastatic CRPC will undergo ^{11}C-YJH08 PET at the time of progression by PCWG3 criteria on systemic therapies (e.g. enzalutamide, apalutamide or darolutamide). Cohort C (N = 10 patients): Patients with any solid tumor malignancies other than prostate adenocarcinoma with one or more metastases on conventional imaging. Enrollment in Cohort B and C will be conducted after completion of enrollment in Cohort A.
Rationale for Study	The proposed patient studies represent the first-ever cancer patient imaging studies with 11C-YJH08 PET. The patient population for Cohort A is designed to determine the dosimetry of the imaging agent, and will enroll any solid tumor malignancy. The patient population for Cohort B is designed to enrich for GR-overexpressing tumors, by selecting mCRPC patients at the time of progression by PCWG criteria on systemic therapies. And Cohort C is designed to include patients with any solid tumor malignancies other than prostate adenocarcinoma with one or more metastases on conventional imaging. Successful completion of the dosimetry cohort (Cohort A) will provide the necessary preliminary data to support subsequent enrollment in Cohort B and C.
Primary Objectives	1. Cohort A: To determine the feasibility of metastatic lesion detection in using ^{11}C-YJH08 PET. 2. Cohort B and C: To determine the mean percent change from baseline at the time of progression on systemic therapy in $SUV_{max\text{-}ave}$ on paired ^{11}C-YJH08 PET on a per-patient and per-lesion basis.

Secondary Objectives	1. To determine the safety and determine average organ uptake of 11C-YJH08. 2. To descriptively report the patterns of intra-tumoral uptake of ^{11}C-YJH08 on whole-body PET, including by site of disease, uptake by tumor type, inter-tumoral and inter-patient heterogeneity, and tumor-to-background signal. 3. Cohort B and C: To determine whether baseline uptake on ^{11}C-YJH08 PET is associated with subsequent clinical outcomes including objective response rate, progression-free survival, and PSA50 response.
Exploratory Objective	To determine the association between uptake on ^{11}C-YJH08 PET with GR expression and transcriptional signature scores on paired metastatic tumor biopsies.
Sample size	Approximately 26 patients with various solid tumor malignancies will be enrolled in the two cohorts as outlined above.
Duration of study	Approximately 18-24 months from date of first patient enrolled.
Safety Assessments	Safety monitoring will include adverse event assessment during Screening, 60 minutes (+/- 15 min), and 2 hours (+/- 30 min) and 24 hours (+/- 4 hours) following ^{11}C-YJH08 injection.
Study Schema	

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG/EKG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FLC	free light chain
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBeAg	hepatitis B “e” antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IDS	Investigational Drug Services (UCSF)
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board

List of Abbreviations

IV	intravenous
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PD	disease progression
PK	pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase

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1 Introduction

1.1 Background and Rationale

With the widespread clinical implementation of potent and selective inhibitors of the androgen receptor for the treatment of CRPC, there is now an urgent unmet need to define and overcome mechanisms of resistance to these therapies. The landscape of resistance mechanisms to therapies like the AR antagonist Enz is highly complex, with several molecularly discrete mechanisms defined in preclinical models, and no clear understanding as to their relative incidence in patients. Moreover, biological screening to identify which mechanism(s) may have arisen in a given patient is not routine clinical practice, which complicates the development of well-organized clinical studies with experimental therapeutics to determine which resistance pathways are treatable.

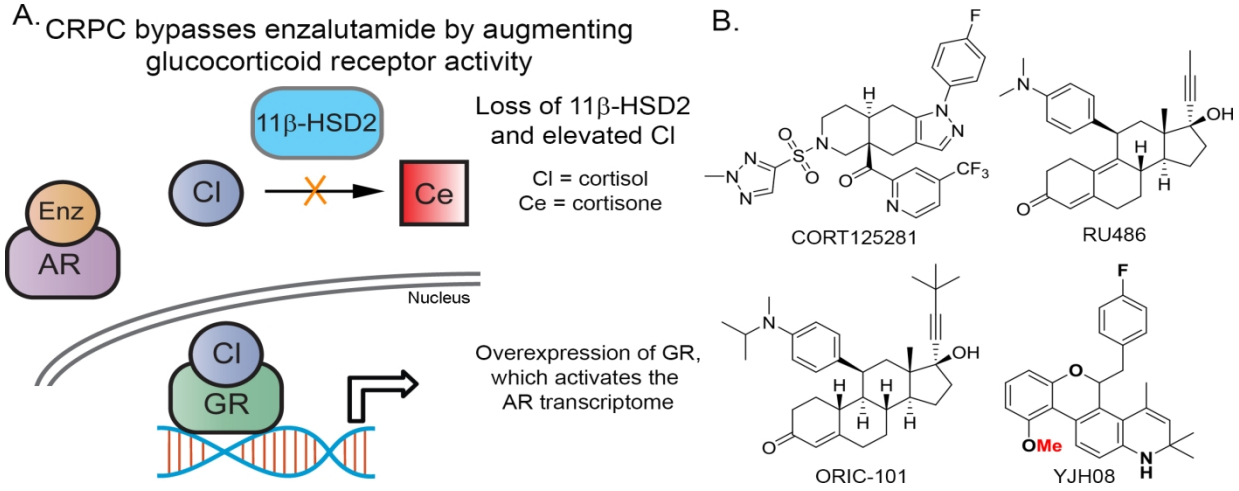


Figure 1. GR signaling as a mechanism of resistance to standard of care therapies for mCRPC that target AR. A. A schema showing how GR overexpression by CRPC cells can bypass the effects of Enz. For example, GR in complex with cortisol can bind to androgen response elements to induce transcription. Moreover, activation of E3 ligases like AMFR can lead to ubiquitin-mediated suppression of 11β-HSD2, which in turn increases cortisol within CRPC cells. **B.** Structures of three GR antagonists currently in clinical trials to test if GR suppression can extend overall survival in patients with mCRPC and other cancers. The structure of YJH08, the radiotracer we developed to measure GR expression in cells with PET, is also shown. The methyl group colored in red shows the site of radiolabeling with carbon-11.

Appreciating these concerns, several years ago we began developing small molecule radiotracers for PET to identify Enz resistant CRPC lesions that express GR. Our interest in this area stemmed from early preclinical reports showing that GR overexpression in human prostate cancer xenografts was a spontaneous response to chronic Enz treatment, and GR transcriptional activity overcame the antitumor effects of Enz therapy in vitro and in vivo (**Figure 1A**). Since this milestone, numerous manuscripts from other labs have disclosed biological findings supportive and consistent with these data. Moreover, preclinical studies have shown that dual AR/GR antagonists, or selective GR antagonists paired with Enz have antitumor activity (**Figure 1B**). Collectively, these data strongly support a role for GR expression and biology in resistance to anti-androgen therapy, and three ongoing clinical trials are testing the therapeutic potential of overcoming treatment resistant CRPC with GR antagonists more systematically (CORT125281: NCT03437941; ORIC-101: NCT03928314; RU486: NCT02012296).

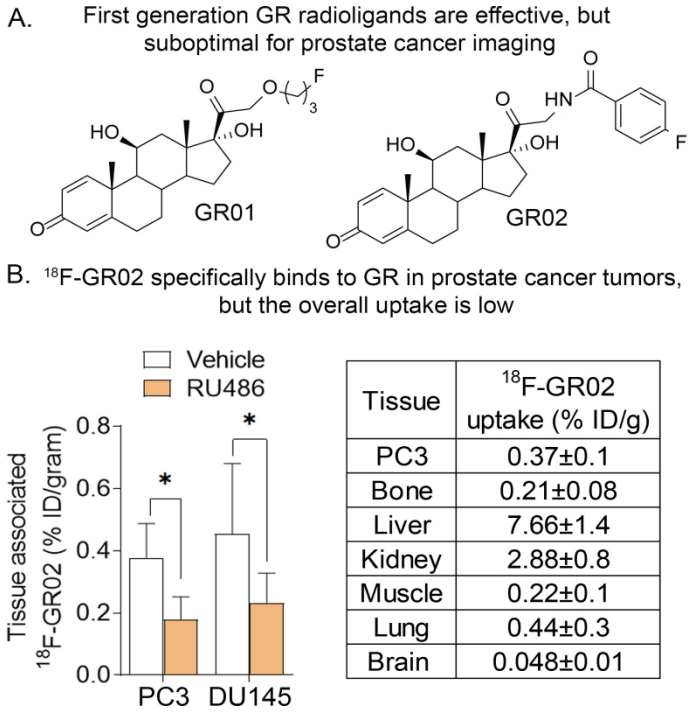
With the current enthusiasm for GR as a drug target, the timing is ideal to conduct human imaging studies to determine if GR expression in mCRPC can be visualized on PET. Achieving

this goal would empower the community with a crucial companion diagnostic for (1) prospectively identifying patients whose tumors express GR to evade Enz (and therefore may be likely to respond to a GR antagonist), and (2) studying the PD effects of GR antagonists holistically to identify dosing strategies that maximize antitumor effects while minimizing on-target, off tissue effects.

Our studies identified a small molecule radiotracer, termed ^{11}C-YJH08 that specifically binds to GR in rodent models, and has excellent pharmacokinetic properties (**Figure 1B**).

1.2 Pre-Clinical Data

Our first-generation radiotracers targeting GR were derivatives of potent and GR-selective corticosteroids. We made two molecules, termed ^{18}F-GR01 and ^{18}F-GR02, which were both potent and selective for GR in vitro (**Figure 2A**). ^{18}F-GR01 was quickly abandoned due to metabolic instability in vivo. While ^{18}F-GR02 was highly stable in vivo, and specifically bound to GR in normal and prostate cancer tissue, the uptake of ^{18}F-GR02 was very low in prostate cancer tumors compared to virtually all normal tissues, including clinically relevant tissues like the bone (**Figure 2B**). After publishing our findings in *Oncotarget*, we began developing second-generation radiotracers that we expected would have better pharmacokinetics and tissue exposure.



Tissue	^{18}F-GR02 uptake (% ID/g)
PC3	0.37±0.1
Bone	0.21±0.08
Liver	7.66±1.4
Kidney	2.88±0.8
Muscle	0.22±0.1
Lung	0.44±0.3
Brain	0.048±0.01

Figure 2. First-generation radiotracers developed during the FY14 IDA were suboptimal for prostate cancer detection. A. Two steroid-based radiotracers, GR01 and GR02 were potent and selective for GR. However, GR01 was unstable in vivo. **B.** While ^{18}F-GR02 was stable, and the tracer bound GR in tumors, the uptake in prostate cancer was significantly lower than normal tissues and equivalent to bone.

After a focused medicinal chemistry screen, we discovered YJH08, a non-steroidal GR modulator with high affinity for GR (K_d ~ 0.4 nM) and at least 100-fold lower affinity for nuclear hormone receptors in the same family (**Table 1**).

To prepare ^{11}C-YJH08, the phenol **1** was alkylated with ^{11}C-methyl iodide (produced by the UCSF cyclotron and radiopharmacy) using chemistry that is applicable to GMP radiotracer synthesis[11]. The decay corrected yield was ~52% and the radiochemical purity was >99% (**Figure 3**). The specific activity was calculated to be 880 Ci/mmol. Parenthetically, we were also able to prepare ^{18}F-YJH08. While the yield was sufficiently high for animal and human studies (~12%), and fluorine-18 is more widely available than carbon-11, we opted to pursue ^{11}C-YJH08 for further studies given that the radiochemistry was more adaptable to clinical translation.

Ligand					
	GRα	AR	PR	MR	MRα
Reference	2.03 ×10	0.96 ×10	0.27 ×10	0.94 ×10	0.4
YJH08	4.01 ×10	0.20 ×10	0.55×10	0.90 ×10	7

Table 1. In vitro affinity data show that YJH08 is a potent and selective ligand for GR. These data were collected in cells overexpressing the indicated full-length nuclear hormone receptor using a ligand displacement assay. Reference ligands were dexamethasone, DHT, progesterone, estradiol, and eplerenone.

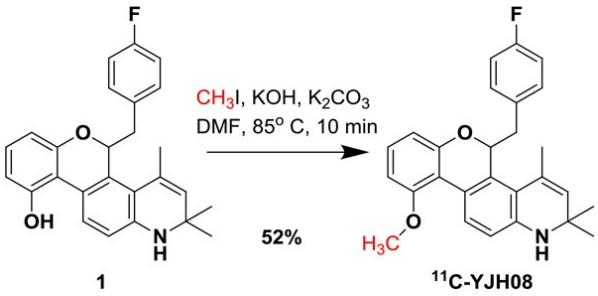


Figure 3. Radiosynthesis of ^{11}C-YJH08. A schema showing the conditions for the methylation reaction. This simple radiochemistry was consistently high yielding, and is readily adaptable for human dose preparation.

To characterize the biodistribution of ^{11}C-YJH08 in vivo, we first conducted a dynamic PET scan over 60 min in immunocompetent male C57Bl6/J mice. Region of interest analysis was applied to generate time activity curves, which showed that the radiotracer rapidly cleared from serum, as expected. We also observed radiotracer uptake in normal tissues known to harbor high GR expression. For instance, radiotracer uptake in the brain was very high (~2% ID/cc), and ~100 fold higher than what was observed for ^{18}F-GR02. Moreover, we observed high uptake in supraspinal brown adipose tissue (~4% ID/cc), a tissue in which GR expression is understood to control seminal processes like thermogenesis. Radiotracer uptake in the bone was low (<0.5% ID/cc), suggesting the radiotracer could be useful for detecting osseous mCRPC. Although radiotracer uptake in the liver was high, liver is not a common site of metastasis for mCRPC adenocarcinoma.

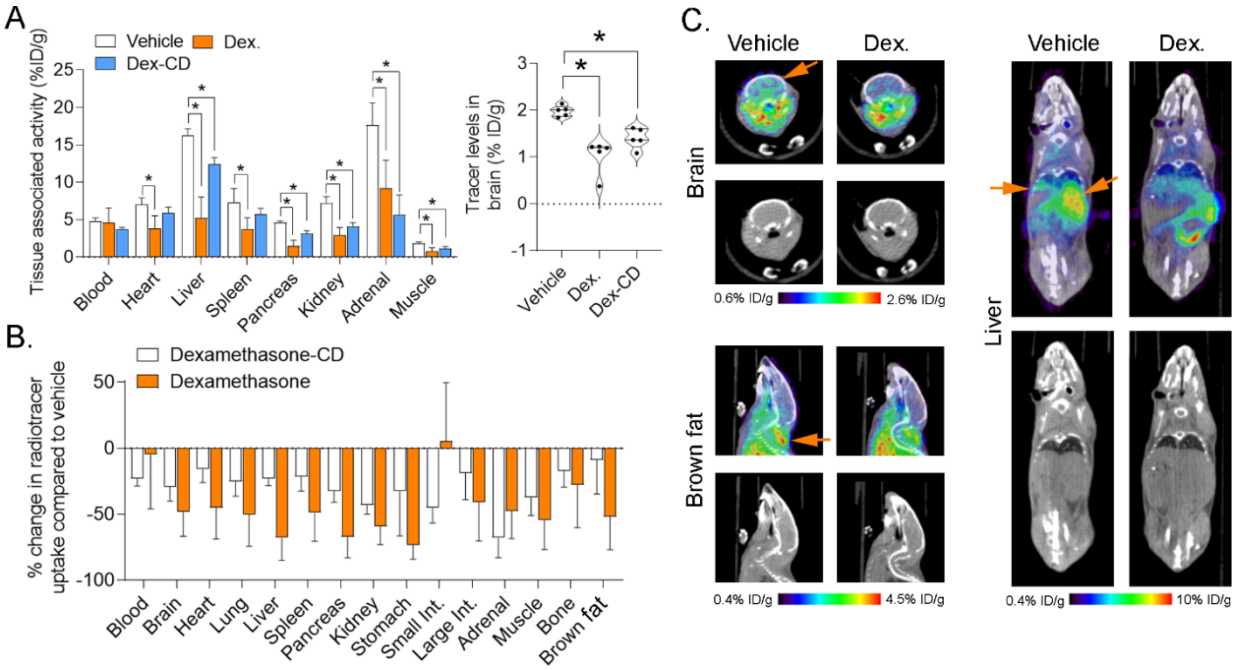


Figure 4. In vivo blocking studies reveal that ^{11}C-YJH08 specifically binds GR in vivo. A. Biodistribution data collected 20 min post-injection showing the suppression of ^{11}C-YJH08 uptake in several mouse tissues by dexamethasone (Dex, n = 5/arm). Dex was administered via two routes involving oral gavage of 50 mg/kg for three days prior to radiotracer injection or administration of a water-soluble dexamethasone-cyclodextrin (CD) complex via intraperitoneal injection at 10 mg/kg one hour prior to radiotracer injection. *P<0.05. At right is shown the blocking data observed in the brain. *P<0.01 **B.** The percent changes in radiotracer uptake per tissue among mice exposed to dexamethasone or Dex-CD versus vehicle. **C.** Representative CT and PET/CT images showing the suppression of ^{11}C-YJH08 binding in selected organs in vivo by Dex treatment.

We next performed treatment studies to demonstrate that ^{11}C-YJH08 accumulation in tissues is due to specific GR binding. Wild type C57Bl6/J mice were treated with the synthetic agonist dexamethasone via oral gavage for three days to occupy the ligand binding domain on GR, which in turn suppressed ^{11}C-YJH08 uptake in nearly every normal tissue (**Figure 4A**). Moreover, ^{11}C-YJH08 uptake in tissues was significantly higher in adrenalectomized mice compared to intact mice, consistent with a GR dependent mechanism of action (**Figure 4B**). Collectively, these data underscore that ^{11}C-YJH08 binds GR in vivo, and show that ^{11}C-YJH08 can measure GR occupancy by endogenous or synthetic ligands.

We next conducted a pilot study to test if ^{11}C-YJH08 can detect a PC3 tumor in vivo. PC3 tumors embedded in the renal capsule took up very high levels of ^{11}C-YJH08 (Figure 5A). Radiotracer uptake (~3% ID/g) was significantly higher in the tumor compared to GR rich tissues like the brain and lungs. Moreover, the radiotracer uptake was significantly higher than what was observed in bone, further underscoring the clinical utility of the radioligand. Lastly, digital autoradiography of the affected kidney was applied to define relative uptake of the radiotracer in the tumor and normal kidney parenchyma (**Figure 5B** and **5C**). The radiotracer uptake in the tumor was qualitatively much higher than the level observed in the kidney. These early data suggest that ^{11}C-YJH08 could be a useful tool for measuring GR expression in mCRPC.

The rodent dosimetry was recently performed at UCSF, and the estimated effective dose to an adult human male (73 kg) is 0.0067 mSv/MBq (**Table 2**). This value shows that the radiotracer is very safe, and a dose of up to 20 mCi per scan is justifiable. Using this funding mechanism, we are also performing single species rodent toxicity studies with Charles River Laboratories.

The radiotracer will be synthesized to GMP standards in the UCSF radiopharmacy, a FDA certified PET drug manufacturer. Anticipated timeline for IND submission is first quarter of 2021.

1.3 Overall Study Rationale

The proposed patient studies represent the first-ever cancer patient imaging studies with ^{11}C-YJH08 PET. The patient population for Cohort A is designed to determine the dosimetry of the imaging agent, and will enroll any solid tumor malignancy. The patient population for Cohort B is designed to enrich for GR-overexpressing tumors, by selecting mCRPC patients at the time of progression by PCWG criteria on systemic therapies. And Cohort C is designed to include patients with any solid tumor malignancies other than prostate adenocarcinoma with one or more metastases on conventional imaging. Successful completion of the feasibility portion of the study (Cohort A) will provide the necessary preliminary data to support subsequent enrollment in Cohort B or C.

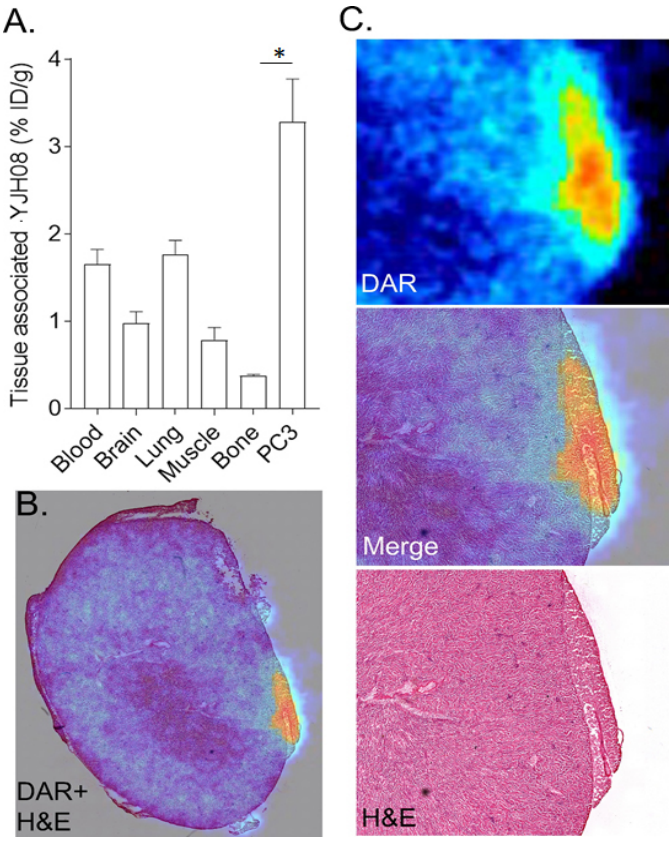


Figure 5. ^{11}C-YJH08 detects a GR-rich PC3 tumor in the renal capsule. A. Ex vivo biodistribution data showing that radiotracer accumulation in the PC3 tumor is higher than the level observed in GR-rich tissues like the brain and lungs. Radiotracer uptake is also higher than the level observed in bone, suggesting the signal to noise in the PET assay may be substantial enough to detect mCRPC.**B.** Digital auto-radiography overlaid with H&E show the high uptake of the radiotracer in the PC3 tumor compared to the normal kidney. **C.** A higher magnification field of view shows the colocalization of high radiotracer uptake with the tumor.

Table 2. A summary of the mouse dosimetry data for (±)-^{11}C-YJH08. The values were calculated from a 90 min dynamic PET acquisition in intact male or female C57Bl6/J mice.

Organ	Absorbed Dose (mGy/MBq) or Equivalent Dose (mSv/MBq)	
	Adult male (73 kg)	Adult female (60 kg)

Adrenals	0.00533 ± 0.000748	0.00578 ± 0.000156
Brain	0.00140 ± 0.000022	0.00229 ± 0.000078
Breasts		0.00286 ± 0.000129
Esophagus	0.00831 ± 0.004249	0.00544 ± 0.000439
Eyes	0.00194 ± 0.000092	0.00223 ± 0.000061
Gallbladder Wall	0.00602 ± 0.000876	0.00459 ± 0.000041
Left colon	0.00374 ± 0.000769	0.00437 ± 0.000314
Small Intestine	0.00325 ± 0.000446	0.00325 ± 0.000114
Stomach Wall	0.01628 ± 0.005962	0.01925 ± 0.002944
Right colon	0.00367 ± 0.000548	0.00339 ± 0.000070
Rectum	0.00249 ± 0.000093	0.00280 ± 0.000087
Heart Wall	0.06753 ± 0.050725	0.02570 ± 0.005677
Kidneys	0.00714 ± 0.000174	0.00785 ± 0.001344
Liver	0.01568 ± 0.001377	0.01863 ± 0.001258
Lungs	0.01350 ± 0.011132	0.00909 ± 0.000339
Pancreas	0.00665 ± 0.002374	0.00545 ± 0.000182
Ovaries		0.00288 ± 0.000090
Prostate	0.00250 ± 0.000105	
Salivary Glands	0.00226 ± 0.000156	0.00241 ± 0.000068
Red Marrow	0.00310 ± 0.000771	0.00289 ± 0.000101
Osteogenic Cells	0.00223 ± 0.000391	0.00217 ± 0.000069
Spleen	0.00378 ± 0.000828	0.00432 ± 0.000300
Testes	0.00204 ± 0.000046	
Thymus	0.01004 ± 0.005999	0.00498 ± 0.000454
Thyroid	0.00355 ± 0.001070	0.00297 ± 0.000118
Urinary Bladder Wall	0.00247 ± 0.000136	0.00288 ± 0.000114
Uterus		0.00284 ± 0.000085
Total Body	0.00355 ± 0.000856	0.00366 ± 0.000121
Effective Dose (mSv/MBq)	**0.00673 ± 0.002757**	**0.00649 ± 0.000433**

2 Study Objectives and Hypotheses

2.1 Study Hypotheses

1. **Cohort A:** ^{11}C-YJH08 PET will demonstrate feasibility of uptake within one or more metastatic lesions.
2. **Cohort B and C:** ^{11}C-YJH08 PET will detect metastatic lesions with high sensitivity using conventional imaging as a reference standard.

2.2 Primary Objectives

Primary Objective	Endpoint(s)	Time Frame
1. Cohort A: To determine the feasibility of metastatic lesion detection in using 11C-YJH08 PET.	Cohort A: Sensitivity of metastatic lesion detection in using ^{11}C-YJH08 PET.	2 days
2. Cohort B and C: To determine the mean percent change from baseline at the time of progression on systemic therapy in $SUV_{max\text{-}ave}$ on paired ^{11}C-YJH08 PET on a per-patient and per-lesion basis.	Cohort B and C: Mean percent change from baseline at the time of progression on systemic therapy in $SUV_{max\text{-}ave}$ on paired ^{11}C-YJH08 PET on a per-patient and per-lesion basis.	Baseline to time of progression

2.3 Secondary Objectives

Secondary Objective	Endpoint(s)	Time Frame
1. To determine the safety and determine average organ uptake of ^{11}C-YJH08.	Safety as recorded by CTCAE v 5.0 criteria and organ dosimetry of ^{11}C-YJH08 PET.	2 days
2. To descriptively report the patterns of intra-tumoral uptake of ^{11}C-YJH08 on whole body PET, including by site of disease, uptake by tumor type, inter-tumoral and inter-patient heterogeneity, and tumor-to-background signal.	Descriptive patterns of intra-tumoral uptake of ^{11}C-YJH08 on whole body PET, including by site of disease, uptake by tumor type, inter-tumoral and inter-patient heterogeneity, and tumor-to-background signal will be assessed.	2 days
3. Cohort B and C: To determine whether baseline uptake on ^{11}C-YJH08 PET is associated with subsequent clinical outcomes including objective response rate, progression-free survival, and PSA50 response.	Association between baseline uptake on ^{11}C-YJH08 PET with subsequent clinical outcomes including objective response rate, progression-free survival, and PSA50 response	Baseline to time of progression.

2.4 Exploratory Objective

Exploratory Objective	Endpoint(s)
1. To determine the association between uptake on ^{11}C-YJH08 PET with GR expression and transcriptional signature scores on paired metastatic tumor biopsies	Association between uptake on ^{11}C-YJH08 PET with GR expression by IHC and transcriptional signature scores on paired metastatic tumor biopsies

3 Study Design

3.1 Characteristics

This is a first-in-human phase 1 imaging study of ^{11}C-YJH08 PET in patients with advanced solid tumor malignancies.

3.2 Number of Subjects

Approximately 26 patients will be enrolled in one of the following cohorts:

Cohort A (N = 6 patients): Patients with any solid tumor malignancy with evidence of one or more metastases on conventional imaging.

Cohort B (N = 10 patients): Patients with metastatic CRPC will undergo ^{11}C-YJH08 PET at the time of progression by PCWG3 criteria on systemic therapies.

Cohort C (N = 10 patients): Patients with any solid tumor malignancies other than prostate adenocarcinoma with one or more metastases on conventional imaging will undergo 11C-YJH08 PET at the time of progression.

Enrollment in Cohort B and C will be conducted after completion of enrollment in Cohort A.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed within 28 days prior to the baseline ^{11}C-YJH08 PET, except for baseline conventional imaging which must be completed 12 weeks prior to and including baseline visit. 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

Subjects may be included in the study if they meet all of the following criteria:

1. Disease characteristics by cohort, as defined by:

   Cohort A) Histologically-confirmed metastatic solid tumor malignancy.

   Cohort B) Metastatic castration-resistant prostate cancer with progression on systemic therapies by PCWG3 criteria.

   Cohort C) Metastatic advanced solid tumor malignancy other than prostate adenocarcinoma with at least one metastasis on conventional imaging.

2. The subject is able and willing to comply with study procedures and provide signed and dated informed consent.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
4. Age 18 years or older at the time of study entry
5. Adequate organ function, as defined by:
   - Serum creatinine ≤ 1.5 x ULN OR estimated creatinine clearance > 50 ml/min
   - Total bilirubin ≤ 1.5 x ULN
   - Hemoglobin ≥ 8.0 g/dL
   - Platelet count ≥ 50,000/microliter
   - Absolute neutrophil count ≥ 1000/microliter

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. Concurrent treatment with any dose of systemic glucocorticoids within 7 days prior to C1D1.
3. History of adrenal insufficiency requiring use of systemic glucocorticoid replacement.
4. History of Cushing's disease or Cushing's syndrome.
5. Any condition that, in the opinion of the Principal Investigator, would impair the patient's ability to comply with study procedures.
6. Contra-indication to MRI (e.g. pacemaker placement, severe claustrophobia) (applicable only for patients scheduled for PET/MRI).

3.4 Study Timeline

3.4.1 Primary Completion

The estimated study period is approximately 36 months from the date of first patient enrolled.

3.4.2 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 DSMC.

4 Investigational Medicinal Product

^{11}C-YJH08 is a radiopharmaceutical that will be produced under cGMP in the Department of Radiology and Biomedical Imaging Radiopharmaceutical Facility. The radiopharmaceutical will be prepared in the same facility in which the injection and imaging will take place, the China Basin Imaging Center.

^{11}C-YJH08 will be administered on an outpatient basis. It will be administered intravenously prior to PET imaging. The injected dose will be approximately 20 mCi. Between 10-60 minutes following ^{11}C-YJH08 injection, one or more whole body CT (PET/CT) or MRI (PET/MR) scans will be used for attenuation correction and anatomic localization of ^{11}C-YJH08 and SUV calculation.

^{11}C-YJH08 Injection is the IMP in this study.

5 Study Procedures and Schedules of Events

5.1 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.

5.2 Schedule of Procedures and Assessments

5.2.1 Screening Assessments

The screening procedures and assessments must be completed within 28 days of baseline PET (PET/CT or PET/MR) scan except for staging scans which need to be completed 12 weeks prior to baseline PET. All screening procedures may be performed on the same day as baseline PET, provided screening and eligibility confirmation is completed and verified by Principal Investigator prior to initiation of PET.

- Baseline conditions
- Vital signs including heart rate and blood pressure

- Concomitant medication review
- AE assessment
- Demographic information (e.g. age, race, height, weight, and body mass index)
- Staging scans - cross-sectional imaging of the chest/abdomen/pelvis (CT or MRI; with IV contrast if medically permissible) within 12 weeks of baseline ^{11}C-YJH08 PET.
- ECOG or Karnofsky Performance status
- Laboratory procedures
    - Serum creatinine
    - Total bilirubin
    - Aspartate aminotransferase (AST)
    - Alanine aminotransferase (ALT)
    - Complete blood count + differential
    - Prostate-specific antigen (PSA)
    - Serum testosterone. Result may be pending at the time of completion of baseline PET provided documentation of ongoing LHRH analog treatment is available (see eligibility criteria above)

5.2.2 Day 1, Baseline ^{11}C-YJH08 PET

For cohort A (dosimetry calculation), multiple time points (up to 5 time points) will be obtained. Imaging will begin immediately after injection of radiotracer and continue up to ~90 minutes after injection of the radiopharmaceutical. From the 90 minutes of data collected, up to 5 time points will be selected, and reconstructions will be performed. For Cohorts B and C, one to two time point whole body PET/CT or PET/MR scans will be performed extending from the patient's vertex through the thighs. Uptake time will be based on the initial results of Cohort A, though may be adjusted based on the data obtain during the study.

The following procedures and assessments will be performed:

- Imaging will begin immediately after injection of ^{11}C-YJH08.
    - Cohort A imaging will be performed up to 5 time points
    - Cohorts B and C whole body PET/CT (or PET/MR) will be performed one or two times.
- Vital signs including heart rate and blood pressure will be collected at screening, before and after administration of ^{11}C-YJH08 injection, then at 60 minutes (+/- 15 min), and 2 hours (+/- 30 min), following ^{11}C-YJH08 injection.
- Safety monitoring will include adverse event assessment during screening, 60 minutes (+/- 15 min), 2 hours (+/- 30 min) and 24 hours (+/- 4 hours) following ^{11}C-YJH08 injection. No iodinated contrast or gadolinium will be administered.
- Serum creatinine, total bilirubin, AST, ALT, and CBC + diff will be performed at screening and at 24 hours (+/- 4 hours) following ^{11}C-YJH08 injection.
- EKG/ECG will be performed prior to ^{11}C-YJH08 injection (up to 4 hours prior) and at 2 hours (+/- 30 min) following ^{11}C-YJH08 injection.

No formal report of the findings from imaging studies will be created. Each scan will be reviewed by a board-certified nuclear medicine physician and radiologist within two working days of the

completion of the study. 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. The reviewing nuclear medicine physician will be required to sign a written form indicating that they have reviewed the scan results and communicated any clinically pertinent findings to the treating physician within two business days of scan completion.

Baseline Tumor Biopsy (Optional)

Patients will undergo optional metastatic tumor biopsy within 14 days following completion of baseline PET scan. The biopsy sample will be analyzed for protein expression of GR by IHC and RNA-seq for application of GR transcriptional signature when sufficient tumor content is present. Soft tissue, PET-avid lesions will be prioritized for biopsy.

5.2.3 OPTIONAL ^{11}C-YJH08 PET at Progression (Cohorts B and C)

Patients will undergo optional repeat ^{11}C-YJH08 PET at the time of progression by PCWG3 criteria for Cohort B and RECIST 1.1 criteria for Cohort C. 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.

- Vital Signs
- Concomitant medication review

Period/ Procedure	Screening (Day -28 thru C1D1)	Cycle 1, Day 1 (Baseline PET)	Disease Progression (Cohort B and C)
Study / Investigational Product Administration			
^{11}C-YJH08 PET		X	X
Administrative Procedures			
Informed consent	X		
Clinical Assessments			
Baseline conditions	X		
Vital signs[1]	X	X	X
Concomitant medications	X		X
AE assessment[2]	X	X	
Demographics	X		
Performance status	X		
Laboratory Assessments			
Serum creatinine, total bilirubin, AST, ALT, CBC + diff[3]	X	X	
PSA, Serum Testosterone	X		
Imaging Procedures			
Staging scans (CT or MRI)	X		
ECG/EKG		X[4]	
Tissue Collection/ Biopsy			
Tumor biopsy (optional)[5]		X	

1 Vital signs (blood pressure, heart rate) will be collected at screening, before and after administration of ^{11}C-YJH08 injection, then at 60 minutes (+/- 15 min), and 2 hours (+/- 30 min) following ^{11}C-YJH08 injection.

2 Safety monitoring will include adverse event assessment at screening, 60 minutes (+/- 15 min), 2 hours (+/- 30 min) and 24 hours (+/- 4 hours) following ^{11}C-YJH08 injection.

3 Serum creatinine, total bilirubin, AST, ALT, and CBC + diff will be performed at screening and at 24 hours (+/- 4 hours) following ^{11}C-YJH08 injection.

4 EKG will be performed prior to ^{11}C-YJH08 injection and at 2 hours (+/- 30 min) following ^{11}C-YJH08 injection.

5 Metastatic tumor biopsy is optional. Tumor biopsy should be performed within 14 days following baseline PET. Soft tissue, PET-avid lesions should be prioritized for biopsy whenever feasible.

Supportive Care

Subjects will receive full supportive care as medically indicated.

The Principal Investigator or designee will be present during the administration and monitoring period. Any events occurring during or subsequent to the administration of IMP will be addressed as required by the monitoring nurse and/or physician as deemed appropriate.

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 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 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.

6.2.4 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.

6.2.5 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
- Cancer

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.

6.2.6 Serious

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.

6.3 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 IMP. Data about these events and their severity will be recorded using the NCI CTCAE v5.0.

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

6.4 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.

6.5 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the IMP, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board; and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will

review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the IMP(s).

In addition, all adverse events and suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis, discussed at DSMC meetings which take place every six (6) weeks. For a detailed description of the Data and Safety Monitoring Plan.

6.6 Expedited Reporting

6.6.1 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 IMP(s) and it is determined to be related either to the IMP(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.

6.6.2 Reporting to UCSF 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.

6.6.3 Expedited Reporting to the Food and Drug Administration

The Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

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

- Suspected adverse reaction
- 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 Analysis

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 at least 1.5 times 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 semiautomatically 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 across all lesions within a given patient ($SUV_{max\text{-}avg}$). In order to avoid clustering effects, analysis will be limited to the five largest osseous metastases and all visceral/soft tissue metastases.

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7.2 Determination of Sample Size

A convenience sample size of approximately 6 patients for Cohort A is selected to collect sufficient scan data to ensure adequate organ dosimetry and determination of the optimal uptake time following administration of ^{11}C-YJH08. Additional patients may be accrued as necessary to optimize imaging acquisition parameters prior to proceeding to Cohort B and C enrollment.

Success for Cohort A will be defined as technically successful injection of radiotracer with expected biodistribution and visualization of radiotracer uptake in the expected location of a metastasis based on conventional imaging in at least one patient. If no metastases are visualized despite varying uptake time and injected dose after 6 or more patients are enrolled in Cohort A, then accrual will not proceed to Cohorts B and C.

For patients enrolled in Cohorts B and C, a convenience sample size of 10 evaluable patients per cohort is chosen to provide preliminary estimates of sensitivity of lesion detection on PET compared to conventional imaging. We expect 20% inevaluable rate over the course of the study; we will recruit 12 patients in each cohort to achieve the target sample size.

7.3 Subject Characteristics

Demographic information (e.g., age, race, height, weight, and body mass index) will be summarized using descriptive statistics.

Concurrent medications will be recorded and coded using a standard classification system.

Disease factors for subjects accrued to the study will be characterized using descriptive statistics.

7.4 Replacement Policy

Patients may be replaced for the following reasons:

- Inability to tolerate/complete baseline PET
- Sub-optimal timing of post-injection PET scan compromising ability to detect metastatic lesions

7.5 Accrual estimates

The estimated accrual period is approximately 36 months.

7.6 Interim Analysis

An interim analysis for safety will be performed after 6 patients have enrolled to Cohort A. If more than 33% of patients experience a Grade ≥ 2 related adverse event, study accrual will be halted and alternative dose levels may be explored.

An informal analysis to confirm feasibility will be performed after approximately 6 patients are enrolled on Cohort A. Images will be qualitatively reviewed and preliminary data with respect to signal-to-noise ratio within metastatic lesions will be assessed by body site. If it is determined that insufficient signal- to-noise ratio is present, additional patients may be accrued in Cohort A with proper technological adjustments (e.g. timing of post-injection scan acquisition, injected dose of radiotracer) to ensure optimal intra-tumoral uptake of tracer before proceeding to Cohort B and C enrollment.

7.7 Analytic Plan

7.7.1 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.

7.7.2 Primary Analysis

For Cohort A, Using as a cut-off to define a positive lesion on PET as a lesion with SUV at least 1.5 times higher than mediastinal blood pool, the sensitivity of 11C-YJH08 PET will be descriptively reported on a lesion-per-lesion basis, using as reference standard staging scans including CT or MRI of the chest/abdomen/pelvis.

For Cohorts B and C, the median percent change from baseline, and range of SUV_{max} (across all metastatic lesions per patient) and $SUV_{max\text{-}ave}$ (in each study cohort) will be descriptively reported using mediastinal blood pool and normal organ as background uptake values. Wilcoxon signed rank test will be used to compare the follow up to baseline PET scan values at lesion level and patient level.

7.7.3 Analysis of Secondary and Exploratory Endpoints

The frequency and severity of adverse events following 11C-YJH08 injection will be descriptively reported, using CTCAE v 5.0. Organ dosimetry on PET will be calculated using standard technique.

The median and range for intra-tumoral SUV_{max} within metastatic lesions will be descriptively reported to asses for intra-tumoral heterogeneity and differences in uptake by site of disease.

For the purposes of analyzing the association between baseline and percent change from baseline in $SUV_{max\text{-}ave}$ with subsequent clinical outcomes, the cohort will be dichotomized above and below the median for the study cohort. The PSA response rate (PCWG3 criteria; Cohort B only), clinical benefit rate, and objective response rate (in subset of measurable tumors by RECIST 1.1) will be compared between dichotomized groups using the chi-squared test. The

log rank test will be used to compare progression-free survival between dichotomized subgroups.

For patients who undergo optional tumor biopsy with evaluable tumor content, the correlation between SUV_{max} of the target lesion on PET with GR expression by IHC (using H-score method) will computed using Pearson correlation method. Likewise, the correlation between SUV_{max} on PET with GR transcriptional signature activity by RNA-seq will be determined using Pearson correlation method when sufficient tumor content permits transcriptional analysis.

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 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 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.

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

8.2 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. 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 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 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. The date, quantity and batch or code number of the drug, and the identification of patients to whom IMP has been dispensed by patient number and initials will be included. The sponsor- investigator will maintain written records of any disposition of the IMP.

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

8.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her 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. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the 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 patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

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 NCI-approved 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. 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 patient 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 for a Non-therapeutic Institutional Trial

1. 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 participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Annual auditing
- Review of serious adverse events
- Minimum of biennial regulatory auditing

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all HDFCCC institutional clinical trials. Greater than minimal risk nontherapeutic studies are characterized as low risk studies due to the trial design, as there isn't administration of drugs or complementary therapy that puts the participants at significant risk.

2. Monitoring and Reporting Guidelines

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the status of each participant is discussed and documented in the site committee minutes.

For "greater than minimal risk" nontherapeutic trials, the assigned DSMC Senior Monitor/Auditor will audit three of the enrolled participants once per year, with a maximum of ten participant charts audited during the entire course of auditing this trial until IRB closure.

After completion of each auditing visit, the 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. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 10 enrolled participants have been audited. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered expected or unexpected and whether or not considered associated with the study intervention or 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 study intervention or procedure. Attribution categories are:

- Definite – The adverse event is clearly related to the study intervention or procedure.
- Probable – The adverse event is likely related to study intervention or procedure.
- Possible – The adverse event may be related to study intervention or procedure.
- Unrelated – the adverse event is clearly not related to the study intervention or procedure.

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

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 adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of a study.

*A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

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. 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 was sent to all required reporting agencies will be documented in OnCore.

If a death occurs during the treatment phase of the study and is determined to be possibly, probably, or definitely related either to the study intervention or procedure, the Investigator or his/her designee must notify the DSMC Chair or Vice Chair and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

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 requirements.

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

John McAdams (DSMC Director)
[redacted]
UCSF HDFCCC
San Francisco, CA 94143

Research Study Monitor Contact:

Melody Gawliu, (Sr. Data Safety Monitor)
[redacted]
UCSF HDFCCC

San Francisco, CA 94143