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## Evaluation of Gallium-68 DOTA-TOC imaging of somatostatin receptor positive malignancies

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## Protocol Signature Page

Protocol No.:

Version Date: 7/28/2015

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

### UCSF Principal Investigator / Study Chair

**Thomas A. Hope**

\_\_\_\_\_  
Printed Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

**Abstract**

Title	Evaluation of Gallium-68 DOTA-TOC imaging of somatostatin receptor positive malignancies
Patient population	Patients with somatostatin receptor positive malignancies, which includes neuroendocrine tumors, paraganglioms/pheochromocytomas and neuroblastomas.
Rationale for Study	Gallium-68 DOTA-TOC has better image sensitivity for somatostatin receptor positive tumors compared to conventional imaging, and is more convenient in terms of timing of imaging.
Primary Objective	To determine if Gallium-68 labeled DOTA-TOC results in the delineation of more lesions than with conventional imaging.
Secondary Objectives	To determine if the incorporation of Gallium-68 DOTA-TOC imaging into the management decision making process results in a change in stage of the patient.
Study Design	This is a phase 1-2 single center open label study.
Number of patients	320 patients over three years.
Duration of Therapy	The study will involve a single PET/CT imaging study.
Duration of Follow up	The patients will be followed-up by phone 14 days after the study completion.
Duration of study	The study will reach completion two years from the time the study opens to accrual.
Study Drugs	Gallium-68 labeled DOTA-TOC
Safety Assessments	Patient vital signs will be taken immediately before and after the administration of the radiopharmaceutical. The patients will also be asked to report adverse events.

**List of Abbreviations**

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

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## 1 Introduction

### 1.1 Background on Indication

Gallium-68 DOTA-TOC is an investigational drug being evaluated for the imaging of somatostatin receptor positive malignancies.

One approach to imaging somatostatin receptor positive malignancies is to label a somatostatin analog with a radionuclide and image its distribution within the body. In the United States, the only clinically available agent is Indium-111 labeled pentetreotide (OctreoScan, Covidien), which was originally approved in 1994. Also known as octreotide, this agent is made of 8 amino acids that bind to the somatostatin receptor, primarily receptor subtype 2 (see Table 1). There are many issues with octreotide, in particular the long-half life of indium limits the administered dose. Additionally, indium is a gamma emitter and is imaged with using a SPECT scanner that inherently has worse spatial resolution than PET imaging. Lastly due to the required delay needed for imaging, there is often significant biliary excretion that interferes with interpretation sometimes requiring that the patient return for additional imaging time points. The first imaging time point is usually 24 hours after injection followed by repeat imaging at 48-72 hours.

Compound	SSR-1	SSR-2	SSR-3	SSR-4	SSR-5
DOTA-TATE	> 10,000	0.2	> 1,000	300	377
DOTA-NOC	> 10,000	1.9	40	260	7.2
DOTA-TOC	> 10,000	2.5	613	> 1,000	73
Octreotide	> 10,000	7.3	120	> 1,000	60

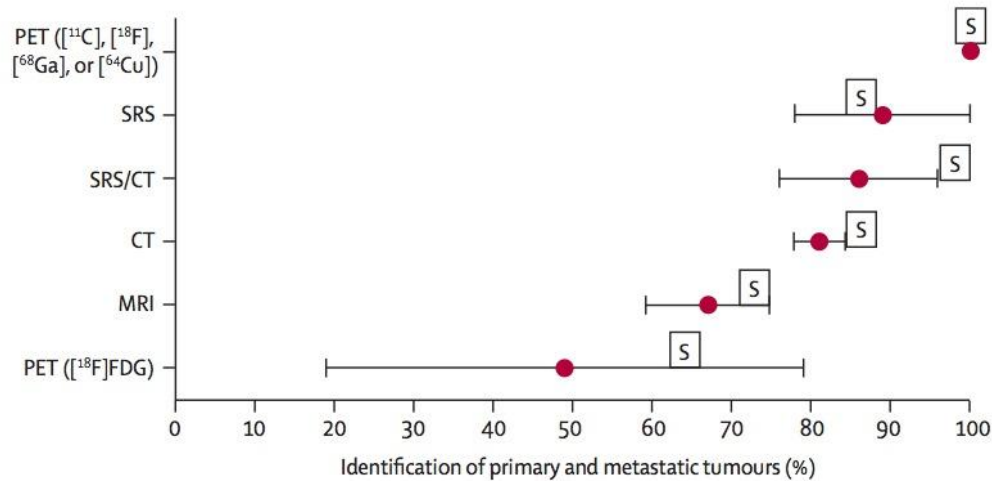
There are a large number of additional analogs that vary from octreotide by a few amino acids; each has a different affinity for the various somatostatin receptor subtypes (Figure 1). Of note, many have a stronger affinity for subtype 2 than octreotide. This increased affinity allows for an earlier imaging time point. In order to improve the image quality, these compounds are labeled with Gallium-68 rather than Indium-111. Gallium-68 is a PET emitter that has a 68-minute half-life. Gallium-68 due to its shorter half-life can be given in a higher dose without increasing the patient radiation exposure significantly increasing (Table 2).

**Table 2**

Selected organ and effective dose for Gallium-68 DOTA-TOC and various Gallium-68 labelled analogs, Indium-111 Octreotide and Flourine-18 FDG (2)

Organs	<sup>68</sup> Ga-DOTATATE	<sup>68</sup> Ga-DOTATOC	<sup>68</sup> Ga-DOTANOC	<sup>111</sup> In-DTPA-octreotide	<sup>18</sup> F-FDG
Kidneys (mSv/MBq)	9.21E-02	2.2E-01	8.97E-02	4.5E-01	1.7E-02
Liver	4.50E-02	7.4E-02	3.38E-02	7.0E-02	2.1E-02
Spleen	2.82E-01	2.4E-01	7.25E-02	3.2E-01	1.1E-02
Urinary bladder wall	1.25E-01	7.0E-02	8.36E-02	1.8E-01	1.3E-01
ED (mSv/MBq)	2.57E-02	2.3E-02	1.67E-02	8.0E-02	1.9E-02
Typical injected activity					
MBq	185	185	185	74	370
mCi	5	5	5	2	10
Estimated effective dose per exam (mSv)	4.8	4.3	3.1	5.9	7.0

Combined with the increased affinity and the better image characteristics, patients are able to undergo a diagnostic study all within two hours during one visit that is of higher quality than prior octreotide studies. There is extensive experience using these agents in Europe (3,4) where these compounds have replaced octreotide for clinical imaging. These compounds have shown a significant increase in sensitivity compared to In-111 Octreoscan (Figure 1) (5).



**Figure 1**

Estimated sensitivity of various imaging techniques (5). SRS refers to gamma emitting somatostatin receptor imaging techniques such as In-111 Octreotide which has a lower sensitivity compared to PET based somatostatin receptor imaging techniques.

In the United States, no company has taken on the investment required to bring an agent to market. In the vacuum of availability, multiple academic groups are currently joining together in order to develop a group FDA submission in the hopes of attaining approval. Through the help of the Society of Nuclear Medicine and Molecular Imaging, a joint IND process has been developed in order to increase the number of institutions involved.

A the same time, a phase III clinical trial has begun in the United States using Lutetium-177 labeled DOTA-TATE for the treatment of midgut neuroendocrine tumors with metastasis. This trial began patient enrollment in the summer of 2013. If this therapy becomes approved, it will be important to have an imaging study that will appropriately evaluate DOTA-TATE positive tumors prior to therapy.

There are a number of malignancies that express the somatostatin receptor. The neuroendocrine family of tumors is the most common, although pheochromocytomas/paragangliomas, medulloblastomas and neuroblastomas all express somatostatin receptors to varying degrees.

Unlike neuroendocrine tumors and octreotide, MIBG and DOTA-TOC are imaging different aspects of the tumor physiology. MIBG images norepinephrine reuptake of the cells while DOTA-TATE binds to somatostatin receptors. It has been demonstrated that octreotide does bind somatostatin receptors on neuroblastoma cells (6), and receptor subtypes 1 and 2 are upregulated in neuroblastoma (7). There has been no comparison between Gallium-68 DOTA-TATE and I-123 MIBG imaging for neuroblastoma imaging, although a comparison of Gallium-68 DOTA-TOC did show an increased sensitivity for lesions compared to I-123 MIBG (8).



Because of the dosimetry, convenience and image quality benefits, we intend to study the utility of Gallium-68 DOTA-TOC in the imaging of somatostatin receptor positive malignancies in order provide further clinical data to support a group FDA submission.

## **2 Objectives of the Study**

### **2.1 Primary**

- To determine if Gallium-68 labeled DOTA-TOC results in the delineation of more lesions than with conventional imaging.

### **2.2 Secondary**

- To determine if the incorporation of Ga-68 DOTA-TOC PET/CT into the management decision making process results in a change in stage of the patient.

### **2.3 Endpoints**

#### **2.3.1 Primary Endpoints**

- The 5 largest lesions in each of eight body regions (head and neck, mediastinum, lung, liver, pancreas, the remaining abdomen and pelvis, bone and lymph nodes) will be measured by size (short and long axis) as well as SUVmax on conventional imaging and the Ga-68 DOTA-TOC PET/CT.
- Additionally the confidence that each lesion represents a metastasis will be recorded.

#### **2.3.2 Secondary Endpoints**

- Clinical stage will be determined based upon conventional imaging, and then be re-determined incorporating the Ga-68 DOTA-TOC PET/CT.

## **3 Study Design**

### **3.1 Characteristics**

This is a prospective, Phase 1-2, single center, open-label study in patients with somatostatin receptor positive malignancies. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive a one-time administration of Ga-68 DOTA-TOC and undergo a PET/CT imaging study.

### **3.2 Number of Subjects**

It is anticipated that 320 patients over three years will be enrolled in this study, split between neuroendocrine tumors and paragangliomas.

### **3.3 Eligibility Criteria**

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

### 3.3.1 Inclusion Criteria

1. Known or suspected somatostatin receptor positive tumor such as carcinoid; neuroendocrine tumor; neuroblastoma; pheochromocytoma. Supporting evidence may include MRI, CT, biochemical markers, and or pathology report.
2. Age > 18.
3. Karnofsky performance status of > 50 (or ECOG/WHO equivalent).
4. Not pregnant. A negative serum pregnancy test is required for all female subjects with child-bearing potential.
5. Ability to understand a written informed consent document, and the willingness to sign it

### 3.3.2 Exclusion Criteria

1. Hepatic enzymes 5 times greater than the upper limits of normal, serum creatinine > 3.0 mg/dL (270 uM/L)
2. Patients exceeding the weight limitations of the scanner or are not able to enter the bore of the PET/CT scanner due to BMI
3. Inability to lie still for the entire imaging time (e.g. cough, severe arthritis, etc.)
4. Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia, radiation phobia, etc.)
5. Any additional medical condition, serious intercurrent illness, or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study compliance
6. Recognized concurrent active infection
7. Previous systemic or radiation treatment for another cancer of any type within the last 2 months
8. Use of any other investigational product or device within 30 days prior to dosing, or known requirement for any other investigational agent prior to completion of all scheduled study assessments.

### 3.4 Duration of Follow Up

Patients will be followed for 14 days after the administration of the radiopharmaceutical.

### 3.5 Study Timeline

#### 3.5.1 Primary Completion

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

#### 3.5.2 Study Completion

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

## **4 Study Drugs**

### **4.1 Description, Supply and Storage of Investigational Drugs**

#### **4.1.1 Investigational Drug #1**

Ga-68 DOTA-TOC is a radiopharmaceutical that will be produced under cGMP by a research pharmacist certified and highly experienced in the Department of Radiology and Biomedical Engineering, Jim Slater, PhD. The radiopharmaceutical will be made in the same facility in which the injection and imaging will take place, the China Basin Imaging Center.

## **5 Treatment Plan**

### **5.1 Dosage and Administration**

The imaging agent (Ga-68 DOTA-TOC) will be administered on an outpatient basis. It will be administered a single time intravenously prior to the PET/CT imaging. The one-time nominal injected dose will be 5 to 7 mCi in a volume of 3 - 5 ml containing 10 - 25 µg Ga-68 DOTA-TOC.

#### **5.1.1 Other Modality(ies) or Procedures**

##### **5.1.1.1 PET/CT imaging**

Study participants will undergo the Ga-68 DOTA-TOC PET/CT after all screening and baseline assessments have been completed. Prior to imaging, participants will be asked to drink water as a “negative” oral contrast since many NETs involve the GI tract. Patient shall begin imaging between 55 and 70 minutes after the injection of the radiopharmaceutical. Intravenous iodinated contrast will be administered depending on the clinical need. For example if the patient’s referring oncologist requests a contrast enhanced CT, this will be performed concurrently with the study in place of the convention low dose CT acquired for attenuation correction purposes only. Coverage for the scan will extend from the patients vertex through the mid thighs.

The Ga-68 DOTA-TOC PET/CT will be read by a board certified nuclear medicine physician within two working days of the completion of the study in line with the Department of Radiology policy. This initial read will be performed by a single nuclear medicine physician.

### **5.2 Monitoring and Toxicity Management**

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

## **6 Study Procedures and Observations**

### **6.1 Schedule of Procedures and Observations**

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

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

### **6.1.1.1 Screening Assessments**

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

- Vital signs
- Physical examination, medical history
- Serum or urine pregnancy test
- Performance status

### **6.1.2 Treatment Period**

#### **6.1.2.1 Study Procedures, Imaging Day 1**

- Vital signs
- Evaluation of adverse events

### **6.1.3 Post-treatment Follow Up Visits**

Patients will be followed for two weeks after enrollment, by phone. The following procedure will be performed at two weeks:

- Evaluation of adverse events

**Table 3.1 Schedule of Study Procedures and Assessments**

Period/ Procedure	Screening	Imaging day 1	Two weeks post imaging
Study Day/Visit Day	-30 to 1	1	14
Informed consent	X		
Medical History	X		
Physical examination	X		
Performance status	X		
Blood Pressure, HR	X	X	
Pulse Oximetry	X	X	
Pregnancy Test		X	
<b>Imaging procedure</b>			
Ga-68 DOTA-TATE administration		X	
PET/CT imaging		X	
<b>Follow-up</b>			
Adverse event reporting		X	X

## 6.2 Prohibited Medications

There are no prohibited medications.

## 7 Reporting and Documentation of Results

### 7.1 Evaluation of Efficacy (or Activity)

#### 7.1.1.1 Definitions

##### Evaluable for toxicity

All patients will be evaluable for toxicity from the time of Ga-68 DOTA-TOC.

### 7.2 Evaluation of Safety

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

### 7.3 Definitions of Adverse Events

#### 7.3.1 Adverse Event

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

#### 7.3.2 Adverse reaction

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

##### 7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

##### 7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or

as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

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

### 7.3.2.3 Serious

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

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

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### 7.3.2.4 Life-threatening

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

## 7.4 Recording of an Adverse Event

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

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

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

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

## 7.5 Follow-up of Adverse Events

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

## 7.6 Expedited Reporting

### **Reporting to the Data and Safety Monitoring Committee**

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

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

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

### **Expedited Reporting to the Food and Drug Administration**

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

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

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



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

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

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

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

## **8 Statistical Considerations and Evaluation of Results**

### **8.1 Study Endpoints**

Primary endpoint: The 5 largest lesions in each of eight body regions (head and neck, mediastinum, lung, liver, pancreas, the remaining abdomen and pelvis, bone and lymph nodes), will be measured by size (short and long axis) as well as SUVmax on conventional imaging and the Ga-68 DOTA-TOC PET/CT. Additionally the confidence that each lesion represents a metastasis will be recorded.

Secondary Endpoint: Clinical stage will be determined based upon conventional imaging, and then be re-determined incorporating the Ga-68 DOTA-TOC PET/CT.

#### **8.1.1 Randomization**

There will be no randomization performed. There for there will be no blinding performed.

### **8.2 Determination of Sample Size and Accrual Rate**

The sample size will be determined by the number of patients enrolled in the trial. As the goal of this trial is to pool data with multiple centers to submit for FDA approval of the imaging agent, our goal is to enroll as many patients as possible, rather than power the study for a particular endpoint.

#### **8.2.1 Sample Size and Power Estimate**

If you were to look at a comparison of number of lesions identified using conventional imaging compared to the Ga-68 DOTA-TOC PET/CT. Using 60 pairs of observations with a difference of one lesion between the pairs and a standard distribution of 2, we would be able to reject the null hypothesis that the difference is zero with a probability of (ie power) 0.967 given a type I error probability of 0.05.

#### **8.2.2 Accrual estimates**

We anticipate enrolling 320 patients over three years through this protocol.

## 8.3 Analyses Plans

### 8.3.1 Analysis Population

There will only be one population. The total cohort of imaged patients.

### 8.3.2 Analysis of Primary Endpoints

Interpreting physicians will be board-certified in nuclear medicine and experienced in interpretation of PET/CT scans. At least 2 nuclear medicine physicians will independently interpret the examinations blinded to each other's interpretation but otherwise fully cognizant of other clinical, imaging and laboratory data. Discrepancies will be resolved by consensus between the two imaging physicians, or, if not resolved, by a third similarly qualified physician. Discrepancies and concurrences will be recorded.

Eight body regions are defined: head and neck, mediastinum, lung, liver, pancreas, the remaining abdomen and pelvis, bone and lymph nodes. The five largest lesions will be measured in each region in long and short axis as well as the SUVmax values for each lesion, in accordance with RECIST 1.1 and PERCIST criteria (10). Additionally the confidence that each lesion represents a primary or metastatic lesion will be recorded (1 = benign, 2 = likely benign, 3 = indeterminate, 4 = likely malignant, 5 = malignant).

Comment will be made as to whether or not areas of tumor involvement are visible on the investigational Ga-68 DOTA-TOC PET/CT scan that are not otherwise visible prospectively on conventional imaging (conventional imaging, CI, is defined as any US FDA approved imaging means for diagnosis, staging, restaging or assessing treatment response for malignancy). CI used for comparison include contrast enhanced CT and MRI scans, Indium-111 octreotide scans, ultrasounds and x-ray plain films.

The number of positive body regions using conventional imaging and Ga-68 DOTA-TOC PET/CT will be compared using a paired t-test (or Wilcoxon signed-rank test if the data appear to be non-normally distributed). The Wilcoxon signed-rank test will also be used to compare reader confidence of paired lesions between conventional imaging and Ga-68 DOTA-TOC PET/CT. Inter-reader variability for the number of positive regions will be compared using Kappa statistics. In all cases we will provide point estimates and 95% confidence intervals for effects along with p-values.

### 8.3.3 Analysis of Secondary Endpoints

In discussion with clinical staff, impact on care will be assessed for value added by the investigational Ga-68 DOTA-TOC PET/CT scan similar to assessment for impact on care as in the National Oncology PET registry, such as:

1. Change in stage

A percentage will then be calculated for both "Change in stage" with a 95% confidence interval determined.

## **9 Study Management**

### **9.1 Pre-study Documentation**

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

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

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

### **9.2 Institutional Review Board Approval**

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

### **9.3 Informed Consent**

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

### **9.4 Changes in the Protocol**

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

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

## **10 Protection of Human Subjects**

### **10.1 Protection of Privacy**

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will

become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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**Appendices**

**Appendix 1 Performance Status Criteria**

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