**To:** Cancer Therapy Evaluation Program

**From:** Zin Myint, M.D.

**Date:** January 10, 2022

**Re:** Amendment for Protocol 10437: "A Single Arm Phase II Study of Bone-targeted Sn-117m-DTPA in Symptomatic Castration Resistant Prostate Cancer with Skeletal Metastases"

## SUMMARY OF CHANGES – Protocol

| # | Section | Amendments |
|---|---|---|
| 1. | Cover letter | Co-investigator name is added on page 1. |
| 2. | Cover letter | Local IRB number is added on page 1. |
| 3. | 3.1 | PSMA PET scan is added to be used as a baseline scan.<br>PSA value has modified from 5 ng/ml to 1 ng/ml.<br>Duration of EBRT for bone pain prior to starting study treatment has modified from 12 weeks to 4 weeks. |
| 4. | 5.1<br>5.5 | The total amount of whole blood in citrate CPT tubes requirement has changed from 20 mL to 24 mL. (as EET Biobank can only provide three 8mL CPT citrate tubes).<br>Changed three 8 mL of CPT citrate tubes. |
| 5. | 11 | PSMA PET scan is added as acceptable baseline scan.<br>Urinalysis collection time has changed to only two collection time-points (baseline and prior to C2)<br>Foot note (f) – urinalysis will be collected as indicated time-points or as clinically indicated.<br>Foot note (g) –PSMA PET CT scan is added as acceptable baseline scan. |

**NCI Protocol #:** 10437

**Local Protocol #:** 75028

**ClinicalTrials.gov Identifier:** NCT04616547

**TITLE:** A Single Arm Phase II Study of Bone-targeted Sn-117m-DTPA in Symptomatic Castration Resistant Prostate Cancer with Skeletal Metastases


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**NCI-Supplied Agent:** Sn-117m-DTPA (NSC 824376)

**IND #:** [redacted]
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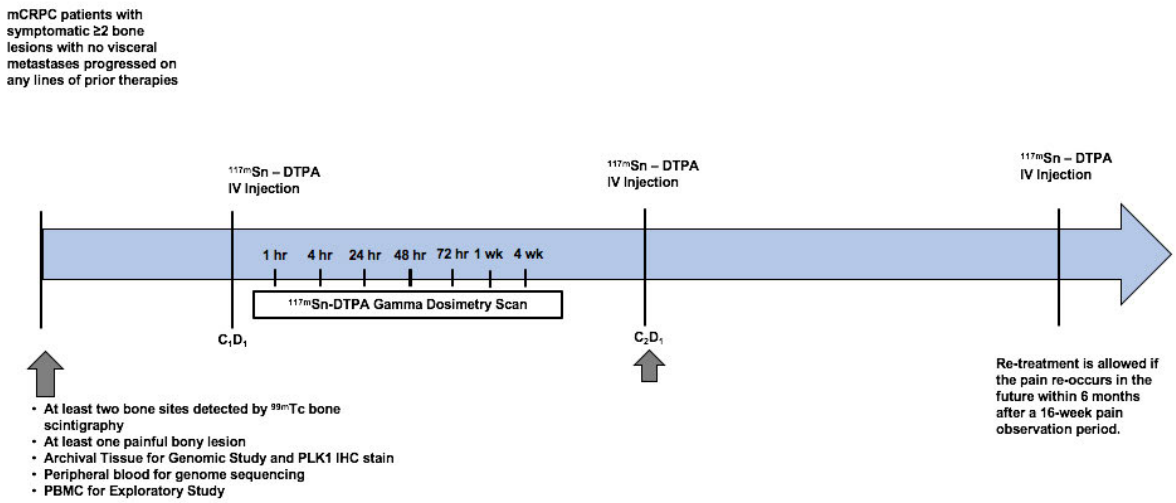
Revision 7/ January 10, 2022

## SCHEMA

**Study Schema**



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# 1. OBJECTIVES

## 1.1 Primary Objectives

1.1.1 To evaluate the efficacy of Sn-117m-DTPA on sustained pain response in patients with castration-resistant prostate cancer (CRPC) metastatic to at least two bone sites with at least one clinically meaningful pain at baseline (≥4 on an 11-point pain intensity scale). Sustained pain response is defined as: 1) achieving pain index ≤3 within a 12-week period and 2) maintaining pain index ≤3 over a 16-week period.

## 1.2 Secondary Objectives

1.2.1 To assess the safety and tolerability of Sn-117m-DTPA per CTCAE v5.0.

1.2.2 To measure Sn-117m-DTPA activity by gamma-camera dosimetry scans (serial full body planar images) obtained at 1 hour, 4 hours (or within 4-6 hours), 24 hours (or within 16-24 hours), 48 hours (or within 36-48 hours), 72 hours (or within 60-72 hours), 1 week (±2 days), and 4 weeks (±2 days) after the first Sn-117m-DTPA administration.

1.2.3 To evaluate the therapeutic efficacy of Sn-117m-DTPA at 24 weeks as measured by Prostate Cancer Working Group 3 (PCWG3) criteria.

1.2.4 To evaluate time to the first symptomatic skeletal event defined as i) the first use of external-beam radiation therapy to relieve skeletal symptoms; ii) new symptomatic pathologic vertebral or nonvertebral bone fractures; iii) spinal cord compression; or iv) tumor-related orthopedic surgical intervention.

1.2.5 To evaluate the overall pain response rate at 24 weeks.

1.2.6 To evaluate the duration of pain response defined as from the time of improvement in pain response (pain index ≤3) until the pain recurs.

1.2.7 To measure changes and time to progression in serum prostate-specific antigen (PSA) and serum alkaline phosphatase (ALP) levels.

1.2.8 To measure patient-reported outcomes (PROs) and adverse events (AEs) (PRO-CTCAE) captured by digital instruments.

1.2.9 To evaluate progression-free survival (PFS) and overall survival (OS)

## 1.3 Exploratory Objectives

1.3.1 To examine any tumor genomic alterations that may be associated with response or resistance to Sn-117m-DTPA, a radiopharmaceutical agent.

1.3.2 To examine the changes in systemic inflammatory markers (such as interferon [IFN]-

gamma, tumor necrosis factor [TNF]-alpha, interleukins [IL]-8, IL-10, and IL-17) by flow cytometry, and changes in markers of immune function by measuring the percentage and absolute number of $CD4^+$ T helper cells, $CD8^+$ T cytotoxic cells, T regulatory cells, polymorphonuclear (PMN) myeloid-derived suppressor cells (MDSCs), and mononuclear MDSCs (M-MDSCs) prior to treatment *vs*. end of cycle 1, end of cycle 2, and at week 24 and correlate values and/or changes with treatment outcomes.

1.3.3 To evaluate the feasibility of measuring polo-like kinase 1 (Plk1) expression via immunohistochemistry (IHC) staining on archival tissues.

## 2. BACKGROUND

### 2.1 Study Disease

#### 2.1.1 Castration-Resistant Prostate Cancer (CRPC)

Metastatic CRPC (mCRPC) remains incurable with a poor prognosis despite improvements in treatment that include novel hormonal agents (Kirby *et al.*, 2011). This disease is the second leading cause of cancer deaths in the United States (Siegel *et al.*, 2018). mCRPC is largely driven by inactivation of the androgen receptor (AR) signaling pathway (Yamaoka *et al.*, 2010). The current therapeutic armamentarium for mCRPC is limited to chemotherapy and novel androgen blockers, such as enzalutamide or abiraterone, which provide only moderate survival benefit (Ryan *et al.*, 2013; Scher *et al*., 2012). To date, radium-223 is the first and only approved targeted alpha therapy for mCRPC, with a median OS benefit of approximately 3 months. Studies also showed that radium-223 significantly prolonged the time to the first symptomatic skeletal event with a median benefit of 5.8 months (Parker, *et al.*, 2013). mCRPC remains an area of significant unmet medical need for the development of new novel therapeutic agents.

#### 2.1.2 Bone Metastases in Prostate Cancer

Bone metastases are a major cause of morbidity from prostate cancer. Prostate cancer preferentially spreads to the bones. More than 80% of men who die from prostate cancer have bone metastases, the vertebral column, pelvis, ribs, and proximal long bones being the most common sites of bone metastases (Harada *et al.*, 1992). Metastases to vertebrae may cause spinal cord compression, nerve root compression, or cauda equina syndrome. Metastases to the base of the skull can impinge on cranial nerves. Clinical fractures are common, with most fractures involving the vertebral bodies. Most prostate bone metastases appear osteoblastic by radiographic imaging, characterized by excess bone formation and excess bone resorption (Chirgwin and Guise, 2007). This pathological acceleration of bone remodeling results in disorganized bone with impaired biomechanical properties.

Most patients with mCRPC develop bone metastases with debilitating pain that is itself associated with shorter survival (Armstrong *et al.*, 2007). For many, pain symptoms are rarely fully eliminated despite optimal management with narcotic analgesics, which confer numerous other side effects. Given the rising rate of prostate cancer secondary to the U.S. aging demographic imperative, novel treatments are needed that effectively control pain and enable

reduction of narcotics. Thus, non-pharmacological modalities of treatment are being revisited, such as palliative targeted radiation therapy.

### 2.1.3 Bone-seeking Radionuclide Therapy

Several bone-seeking radionuclides have been developed for palliation of metastatic bone pain (Joshi *et al.*, 1965; Lawrence and Tobias, 1956; Firusian *et al.*, 1976). Among these, phosphorus-32 (Joshi *et al.*, 1965), strontium-89 (Blake *et al.*, 1986; Porter *et al.*, 1993), samarium-153 (Collins *et al.*, 1993; Resche *et al.*, 1997), and rhenium-186 (De Klerk *et al.*, 1997; Maxon *et al.*, 1991) are all beta-emitters, and radium-223 dichloride is an alpha particle-emitter (Parker, *et al.*, 2013); the major dose limitation is bone marrow toxicity. Unlike conventional external beam radiotherapy (EBRT), targeted bone-seeking radionuclide therapy allows targeted drug delivery with reduction of collateral damage to normal tissues (Sfakianakis and DeLand, 1982). To date, these agents have demonstrated modest pain palliation. However, trials have not consistently evaluated pain and other associated PROs (such as physical function, fatigue, *etc.*) in concordance with Food and Drug Administration (FDA) guidance and contemporary methodology (Basch *et al.*, 2012; Basch *et al.*, 2014; Farrar *et al.*, 2010).

## 2.2 CTEP IND Agent

Sn-117m-diethylenetriaminepentaacetic acid (DPTA; stannic pentetate injection) is a radiopharmaceutical being developed for treatment of malignant bone metastases, starting in the 1980s by Srivastava and colleagues at Brookhaven National Laboratory (Srivastava *et al.*, 1985; Sn-117m-DPTA Investigator's Brochure, 2020). It has undergone both nonclinical and clinical study; as of February 24, 2020, 107 patients have been enrolled in Sn-117m-DPTA interventional clinical trials, including patients with bone-metastatic cancers of the prostate, breast, kidney, lung, and pancreas (Sn-117m-DPTA Investigator's Brochure, 2020).

### 2.2.1 Mechanism of Action

Sn-117m is a radioactive isotope of tin that is a low-energy conversion electron emitter (127 keV, 129 keV, 152 keV, and 140 keV) and also yields a gamma emission of 159 keV (Ponsard *et al.*, 2009). These low-energy conversion electron and gamma emissions can be used for therapy and imaging, respectively. The penetration depth of the conversion electrons produced by Sn-117m is 300 mcm, resulting in irradiation of tissues only to that distance, sparing bone marrow and other tissues adjacent to the bone-tumor interface (Srivastava *et al.*, 1985). The gamma radiation also produced by the isotope enables imaging similar to Tc-99m (Oster *et al.*, 1985). Tin binds to bone and especially to hypermetabolic areas in bone, such as bone adjacent to tumor metastases, similarly to calcium (Sn-117m-DPTA Investigator's Brochure, 2020).

### 2.2.2 Nonclinical Studies

Systematic study of the distribution and excretion of inorganic tin in its various chemical forms began in the mid-1980s. Radioactive isotopes of tin were used to assess the biological behavior of the metal in each of its oxidation states in salts and coordination complexes upon intravenous (IV) injection in mice (Srivastava *et al.,* 1985). Sn-117m-DTPA demonstrated the best

characteristics in terms of specificity toward bone. Its uptake in bone equaled that of stannous chloride (20% injected dose [ID]/g at 30 minutes after injection), but with much less nontarget organ uptake. Bone retained about 50% ID at one day, while blood pool, liver, and kidney retained much less than 1% ID each at that time. Nonosseous tin appeared to have undergone rapid excretion via the urinary system after Sn-117m-DTPA administration: nearly half of the ID disappeared from the animal in the span of 30 minutes after injection. Concentration of tin in bone declined only slightly throughout the 168-hour post-injection observation period (to 17% ID/g), while concentration in other tissues declined rapidly in concert with the tracer's appearance in urine.

Biodistribution of Sn-117m-DTPA in various animal models of human bone diseases showed preferential skeletal uptake with rapid disappearance from soft tissue after IV injection (Oster *et al.*, 1985). In mice, most of the radioactivity was found by whole-body autoradiography to reside in cortical bone three hours after IV injection of Sn-117m-DTPA. Autoradiographs did not show any radioactivity in the adjacent bone marrow cavity. Sn-117m-DTPA behaved like technetium diphosphonate and technetium pyrophosphate bone-scanning radiopharmaceuticals in other ways, as well. For example, Sn-117m-DTPA localized in areas of ischemic muscle damage in rabbits, a phenomenon observed with the technetium-based bone-seeking tracers and attributed to calcification in the infarcted muscle. Also in rabbits, it demonstrated uptake in areas of osteomyelitis and in areas of induced osteogenesis (healing after surgical bone lesion). In rats, experimentally induced hypervitaminosis A reduced bone:soft tissue values of Sn-117m-DTPA, in correspondence to the vitamin's actions on bone metabolism. Sn-117m-DTPA also displayed uptake autoradiographically in human osteosarcoma xenografts in nude (athymic) mice. Bone levels of radioactivity after IV injection of Sn-117m-DTPA were as high as or higher than those measured after other bone-seeking radiopharmaceuticals, including the diagnostic tracer technetium (Tc-99m-etidronate), as well as the other investigational therapeutic radiopharmaceuticals, rhenium (Re-186-etidronate) and samarium (Sm-153-EDTMP) (Srivastava *et al.*, 1994).

Lam *et al.* reported that bisphosphonate does not influence samarium bone uptake when combined bisphosphonate and samarium ($^{153}$Sm-EDTMP) is used to treat hormone-refractory prostate cancer patients (Lam *et al*., 2008). The *post hoc* analyses from the ASLYMPCA (radium-223) study indicated that bisphosphonates have a beneficial additive effect on bone health when given in combination with radium-223 (Sartor *et al*., 2014). As these combinations have been shown to be safe and feasible, we propose the combination of bisphosphonate and Sn-117m-DTPA will be safe and effective as well.

Acute IV toxicity of Sn-117m-DTPA was evaluated in groups of three mice at each of three dose levels: 5.1, 25.5, and 51 mg/kg, expressed in terms of tin (Sn-117m-DTPA Investigator's Brochure, 2020). Mice given the lowest dose displayed no observable toxic response, one of the three mice at the middle dose level died, and all animals at the highest dose level succumbed. The median lethal dose, estimated from these data at about 30 mg tin/kg, agrees reasonably well with values in rodents for the soluble tin salt, stannous tartrate (about 20 mg tin/kg, IV in rats). In another group of mice, an intraperitoneal injection of Sn-117m-DTPA at a dose of 51 mg tin/kg (uniformly lethal when given IV), resulted in only one of three mice dying. Thus, it appears that the rate at which the animal becomes exposed to the drug affects toxic response,

implying that a slower rate of administration will benefit tolerability. In later studies of Sn-117m-DTPA at doses of 4.7 to 5.1 mg tin/kg IV, some mice displayed mild reactions upon injection, and displayed occasional dyspnea and hemorrhagic areas of the lungs a day later.

A single-dose acute IV toxicology study of 2, 4, or 18 mcmol Sn-117m-DTPA/kg in mice found no clinical observations indicative of toxicity during the in-life phase of the study (Sn-117m-DTPA Investigator's Brochure, 2020). No animals died, nor were any animals sacrificed moribund, during the in-life phase of the study. There were no significant body weight changes between control and test group animals at both the 2-day and 14-day time points post-dosing. Gross necropsy did not reveal any signs of toxicity. No differences in spleen or liver weights at gross necropsy were reported. Hematologic findings were limited to a minor yet statistically significant elevation in neutrophils and a depression of lymphocyte levels in the males relative to the control (low and high-dose groups) at 48 hours post-dose. Red blood cells were decreased at 48 hours in the mid-dose group males. These changes were not considered biologically meaningful. There was a decrease in blood urea nitrogen at 48 hours in the low-dose male mice relative to the control group that was not considered biologically meaningful. Histopathologic examination revealed an increase in hepatocyte mitotic figures in only the high-dose males at 48 hours post-dose. This finding was resolved at 14 days post-dose. Other lesions were considered incidental and/or unrelated to treatment.

### 2.2.3 Clinical Pharmacology

#### 2.2.3.1 Phase 1 Biodistribution and Dosimetry Study

Sn-117m-DTPA was administered at doses ranging from 0.1 to 1.7 mCi IV to 10 cancer patients with bone metastases (Atkins *et al.*, 1993). Radiation dose estimates were calculated for seven of the patients. Imaging revealed bone uptake and distribution into metastases similar to that seen on·Tc-99m-MDP images in the same patients. No other specific organ uptake was seen, other than very faint renal activity following radionuclide administration. The ratios of levels in lesion to normal bone varied from 1 to 15, with a typical value of about 4. Approximately 10-fold more radioactivity was absorbed by bone surface than by bone marrow; the ratio of bone to kidney radiation absorbed dose was >300-fold. Over half of the administered radioactivity localized in bone. Radioactivity concentration in bone was nearly constant over the duration of the study. Blood activity disappeared rapidly with a biexponential curve. Urinary excretion was limited. Image quality was good, despite the low level of radioactivity administered. Median bone uptake at 24 and 48 hours was 64.6% (range: 37.7%-83.8%) and 61.0% (range: 35.4%-81.5%), respectively. Eight of 10 patients had bone uptake >50% of administered dose.

#### 2.2.3.2 Phase 1/2 Dose-ranging Study

Sn-117m-DTPA has a monoenergetic gamma photon of 159 keV in 86% abundance. Sn-117m-DTPA was administered at doses ranging from 71 to 286 mcCi/dose to 47 cancer patients with painful bone metastases (Krishnamurthy *et al.*, 1997; Srivastava *et al.*, 1998). In the initial 17 patients, total body clearance of Sn-117m-DTPA showed two compartments: soft tissue and bone (Krishnamurthy *et al.*, 1997). The soft tissue component accounted for 22.4% of the dose and consisted of four subcomponents with an average biologic clearance half-life of 1.45 days.

Initial clearance was very rapid; 15 minutes after injection, the mean and standard deviation of the activity remaining in the vasculature was 14.8%±4.8% of the amount injected. The bone component accounted for 77.6% of the total dose and showed no biologic clearance. Peak uptake in normal bone was observed within 24 hours and within metastatic lesions within 3-7 days. The ratio of uptake in tumor/normal bone ranged from 2 to 9. Mean urinary excretion was 22.4% within 14 days; half of that was excreted in the first 24 hours. The distribution of activity on the bone scans was observed to be similar to that observed for a Tc-99m labeled diphosphonate bone scan. In the expanded series, including a total of 43 patients for whom biodistribution data were obtained, overall bone uptake was 69.7±14.7% (Srivastava *et al.*, 1998). Uptake was higher in prostate cancer (n=29, mean 75.8%±12.0%) as compared to breast cancer patients (n=7, mean 54.8%±15.7%).

### 2.2.4 Clinical Safety

#### 2.2.4.1 Phase 1/2 Dose-ranging Study

The phase 1/2 dose-ranging study found decrease in total white blood cell count to be the only significant toxicity (Srivastava *et al.*, 1998). While the incidence of leukopenia was highest in the highest dose group (5/12 evaluable patients, 42%), severe toxicity was uncommon. Three patients (two at 10 mCi/70 kg and one at 16 mCi/70 kg) developed grade 3 neutropenia. One patient, treated with 5 mCi/70 kg, developed grade 4 neutropenia. The investigators attributed all these instances of neutropenia to chemotherapy administered following Sn-117m-DTPA administration. No patient exhibited significant thrombocytopenia. One patient reported pruritus the day after dosing; this was controlled by antihistamines. Mean decrease in total white cell count was 1,870±1,450 cells/mcL; mean decrease in platelet count was 66,000±64,600/mcL. No dose-response trend was noted for either white cells or platelets. Nadirs were at 34±16 days (n=35) for total white blood cells and 41±26 days (n=34) for platelets.

#### 2.2.4.2 Randomized, Active-Control Study (Diatide, Inc. study 117-30)

Single doses of Sn-117m-DTPA at 5, 12.5, or 30 mCi/70 kg were administered to prostate cancer patients with painful bone metastases, compared to a standard dose (1.0-5.5 mCi, median 4 mCi) of Metastron (Sr-89-chloride) as the control (Sn-117m-DTPA Investigator's Brochure, 2020). The average number of AEs per patient was slightly higher in the 30 mCi Sn-117m-DTPA group: approximately 11 events *versus* 8 events for each of the other groups. There was no trend towards increasing overall incidence of severe AEs with dose of Sn-117m-DTPA. The SOC category "Investigations" was the most common category of AEs and consisted mainly of clinically significant changes in clinical laboratory measurements and vital signs. The 30 mCi/70 kg Sn-117m-DTPA group exhibited the highest incidence with 86% of patients experiencing adverse events compared to 68% and 69% of patients in the 5 mCi/70 kg and 12.5m Ci/70 kg Sn-117m-DTPA groups, respectively, and 53% in the Sr-89-chloride group. The 30 mCi/70 kg Sn-117m-DTPA group also had the highest incidence of gastrointestinal disorders, and GI events in this group were more likely to be considered study treatment-related. The incidence of respiratory, thoracic, and mediastinal disorders appeared to be dose-related among the Sn-117m-DTPA patients, though no such trend was noted in severe AEs in that category. Considering all Sn-117m-DTPA treatment patients together, the incidence of respiratory, thoracic, and mediastinal disorder events was comparable to the incidence in Sr-89-chloride

patients: 29% *versus* 37% respectively.

Regardless of treatment group, most events were mild or moderate in severity (Sn-117m-DTPA Investigator's Brochure, 2020). The lowest overall incidence of severe events occurred in the 30 mCi/70 kg Sn-117m-DTPA treatment group: 6 patients in that group (43%) *versus* 10 (53%) in the 5 mCi/70 kg group, 10 (63%) in the 12.5 mCi/70 kg group, and 9 (47%) in the Sr-89-chloride group experienced severe AEs. The percentage of events that were considered by investigators related to study drug (including possibly or probably related) were similar in the four treatment groups (21% to 24% of events). The MedDRA SOC with the highest incidence of related events was investigations (42%, 38%, and 43% of patients in the 5 mCi, 12.5m Ci, and 30 mCi Sn-117m-DTPA groups respectively, and 26% of patients in the Sr-89-chloride group).

Twenty of 68 patients (29%) across all treatment groups experienced SAEs (Sn-117m-DTPA Investigator's Brochure, 2020). However, only two patients had serious adverse events (SAEs) that were considered possibly related to study drug. Disorientation and spinal cord compression experienced by one patient who received 5 mCi/70 kg of Sn-117m-DTPA, and an increased white blood cell count observed in a patient treated with Sr-89-chloride, were considered possibly drug related. The latter increased WBC count was in association with chills and rigor, vomiting and diarrhea, and increased bone pain. The WBC count returned to normal following antibiotic treatment. All other SAEs were considered unrelated to study drug. Eight patients had SAEs with an outcome of death: three each in the 5 and 12.5 mCi Sn-117m-DTPA groups and two in the 30 mCi Sn-117m-DTPA group. The 12.5 mCi Sn-117m-DTPA group had the highest number and percentage of patients experiencing SAEs: 44% compared to 26%, 21%, and 26% in the 5 and 30 mCi Sn-117m-DTPA groups and the Sr-89-chloride group, respectively. Three patients exhibited clinically significant changes in vital signs following injection of study drug. One Sr-89-chloride patient experienced decreased heart rate; one 5 mCi/70 kg Sn-117m-DTPA patient experienced decreased systolic blood pressure, and one 12.5 mCi/70 kg Sn-117m-DTPA patient displayed an increase in blood pressure. These events were all considered possibly related to study drug, but they did not require treatment; all resolved without sequelae and were not considered SAEs.

### 2.2.5 Clinical Efficacy – Pain Palliation

The phase 1/2 dose-ranging study evaluated the effects of Sn-117m-DTPA administration on pain relief using daily 5-point numeric pain rating scales (Krishnamurthy *et al.*, 1997; Srivastava *et al.*, 1998). About one quarter of all patients entered had complete and an additional one third >50% relief of pain. There appeared to be a threshold in complete pain relief, though the numbers in each dose group were small. More striking was a decrease in the time to onset of pain relief, with a mean time to onset of pain relief of 22 days at the lowest dose, plateauing at 5 days for doses of 12.5 mCi/70 kg and above. Mean duration of response was 3.3 months, with a maximum of 13.4 months; complete responses generally lasted longer than partial responses. Three patients with prostate cancer received second doses upon worsening of pain. Two had complete responses and one had a partial response to the second dose. Neither radiologic time to progression nor OS was assessed in this study.

### 2.2.6 Additional Safety Considerations

Sn-117m-DTPA contains pentetic acid (pentetate), a chelating agent used for heavy metal detoxification (Klaassen, 1990). A related chelating agent, edetate, chelates serum calcium upon injection in the absence of calcium in the formulation (Sn-117m-DTPA Investigator's Brochure, 2020). Rapid injection of edetate has caused hypocalcemic tetany, although slow infusion does not, due to replenishment of serum calcium from tissue stores. As a member of the same drug class, pentetate also has the potential to cause hypocalcemic tetany if injected too rapidly. Calcium chloride is added to the Sn-117m-DTPA formulation. Some pentetate does remain free in solution, but no evidence of hypocalcemic tetany has appeared in clinical studies of Sn-117m-DTPA.

Edetate administration in large repeated-daily doses for lead detoxification has been associated with nephrotoxicity, which reverses upon cessation of the repeated administrations (Sn-117m-DTPA Investigator's Brochure, 2020). Edetate administration has also been associated with decreases in serum ALP activity due to chelation and excretion of zinc, a trace mineral component of the enzyme, though edetate is not known to interfere with clinical laboratory tests. As Sn-117m-DTPA is a member of the same family of chelating agents, it should be noted that it has the potential to cause similar events.

The medical literature contains a case report of a fatal outcome in a patient who suffered disseminated intravascular coagulation (DIC) and who received Sr-89-chloride for treatment of bone pain due to metastatic bone disease (Leong *et al.*, 1994; Sn-117m-DTPA Investigator's Brochure, 2020). Although not chemically related to Sr-89-chloride, Sn-117m-DTPA belongs to the same drug class as the former, so may have the potential to cause similar events.

Results of previous clinical studies of Sn-117m-DTPA do not suggest that patients will risk developing severe myelotoxic responses as a consequence of exposure to anticipated doses (Sn-117m-DTPA Investigator's Brochure, 2020). However, patients who have previously received cytotoxic chemotherapy may experience more marrow suppression than patients who have not previously received cytotoxic chemotherapy. Eligibility criteria for bone marrow competency must be observed when screening patients, and complete blood counts and serum chemistry will be performed regularly for enrolled patients to monitor for myelosuppression and institute any necessary treatment delays (see Sections 7 and 11).

### 2.3 Rationale

Sn-117m-DPTA localizes selectively in bone, a unique physical characteristic. In addition, a major advantage of Sn-117m-DTPA is the low energy conversion electrons emitted (0.2-0.3 mm), which minimizes the radiation dose to the bone marrow and results in deeper tissue penetration (~300 mcm). Thus, this radiopharmaceutical has low bone marrow toxicity compared to the beta and alpha emitters. Sn-117m-DTPA has a gamma photon of 158.6 keV, and its half-life is 13.6 days. Atkins *et al.* (1993) studied the whole-body distribution of Sn-117m-DTPA and showed that more than 50% of the administered activity was absorbed in the bones of patients with metastatic cancer. The red marrow absorbed dose was low compared with the bone surface dose. All other tissues received less than 1/10 of the dose received by red marrow.

A pilot study of 15 patients with painful skeletal metastases from myriad solid tumors evaluated treatment with Sn-117m-DTPA at 71-143 mcCi/kg (Atkins *et al.*, 1995). Results demonstrated pain relief without inducing bone marrow toxicity. Krishnamurthy *et al.* (1997) studied the biokinetics and imaging characteristics of Sn-117m-DTPA radioactivity in 17 patients with metastatic bone pain. Three dose levels were administered IV: 180 mcCi/kg, 229 mcCi/kg, and 285 mcCi/kg of patient body weight. Pain palliation was observed with all three doses, with responses in 60-83% of cases. The duration of pain palliation ranged from 3 to 14 months from a single administration of Sn-117m-DTPA. The majority (59%) of the administered Sn-117m-DTPA was taken up in bony metastatic lesions and peaked in three to seven days, whereas peak uptake in normal bones occurred by 24 hours. The remaining radioactivity was excreted by the urinary tract (37%).

In a phase 1/2 study, 47 patients with painful bone metastases from a variety of malignancies (including 30 patients with prostate cancer) were treated with five different levels of Sn-117m-DTPA radioactivity (Srivastava *et al.*, 1998). The dose levels, based on kg of body weight, were as follows: 2.64 MBq (71 mcCi), 5.29 MBq (143 mcCi), 6.61 MBq (179 mcCi), 8.46 MBq (229 mcCi), and 10.58 MBq (286 mcCi). Approximately 45% of patients obtained reduction of pain by at least 50%, and 30% experienced complete relief of pain for more than two weeks. There was no correlation between response rate and the dose levels. However, the time to onset of pain relief was shorter (5 ± 3 days) with doses ≥12.5 mCi/70 kg than with doses ≤10 mCi/70 kg (19 ± 15 days).

In a randomized phase 2 study of three dose levels of Sn-117m-DTPA compared to Sr-89-chloride, a dose of 30 mCi Sn-117m-DTPA was well tolerated (Data on file, Serene LLC). The study was stopped early due to commercial considerations, and only safety results were analyzed. The results of this study demonstrate, however, that a dose of at least 30 mCi/70 kg (approximately 1.73 $m^2$) could be administered safely.

Collectively, there is mounting evidence that Sn-117m-DTPA has promising palliative efficacy with minimal toxicity. Thus, additional evaluation of this agent in patients with bony metastases is urgently required.

## 2.4 Correlative Studies Background

### 2.4.1 Whole Exome Sequencing (WES)

Biologic Rationale: Gene expression profiling is an important tool to elucidate the novel biomarkers of radio-sensitivity in order to predict treatment response. Radiation induces DNA damage and thus causes cell death. Upregulation of DNA damage response pathways was associated with radiation sensitivity (Kamran and Mouw, 2018). Extent of somatic copy number alterations and increased expression of PI3K and JAK/STAT pathway components were associated with radiation resistance.

Hypothesis: We propose to test for DNA damage repair (DDR) gene alterations (*BRCA1/2* loss/mutation, *ATM*, *ATR*, *CHEK1/2* loss/mutation, *RAD50*, *PALB2*, *CDK12*, *FANCA*, *POLE* mutation), somatic mutations in MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*), replication stress

(*CCNC1*, *CCNE1*, *MYCN* amplification) and *TP53*, *PIK3CA*, *FBXW7*, and *KEAP1* mutations and will correlate with treatment outcomes. Additionally, we propose to test for germline variants such as *MLH1*, *MSH2*, *MSH6*, *PMS2* (for Lynch syndrome), and homologous recombination genes such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, and *CHEK2*. Archival tissue will be employed as available (no new baseline biopsies will be performed).

2.4.2 RNA Sequencing (RNAseq)

Biologic Rationale: Radiation-induced gene expression changes mainly involve p53 signaling, cell cycle regulation, DNA repair, and inflammatory response (Bosma *et al.*, 2020). The ability to predict tumor response to radiation therapy is a necessary avenue to improve treatment outcomes. RNAseq allows for a much broader dynamic detection of both protein-coding and non-coding RNAs that play significant roles in prostate cancer progression.

Hypothesis: We will explore the differences in RNA expression between radiosensitive and radioresistant treatment outcomes in prostate cancer patients who undergo treatment with Sn-117m-DTPA.

Relevant Preclinical Data: Young *et al.* (2014) studied novel predictive biomarkers *in vitro* by analyzing the expression of genes involved in DNA repair pathways by RNAseq in radioresistant (PC-3) and radiosensitive (LNCaP) prostate cancer cell lines. The study demonstrated that radiosensitive LNCaP cells down-regulated *BRCA1*, *FANCG*, *RAD51*, *MCM7*, *CDC6*, and *ORC1*, whereas the radioresistant PC-3 cell line up-regulated these genes.

2.4.3 Polo-like Kinase (PLK1)

Biologic Rationale: PLK1, a critical cell cycle regulator, is overexpressed in prostate cancer, and its level of expression is associated with tumorigenicity in prostate cancer (Zhang *et al.*, 2015) (**Figure 1**). PLK1-associated phosphorylation of Mre11 leads to premature DNA damage checkpoint termination and reduced DNA repair (Weichert *et al.*, 2004). Thus, cancer cells with higher levels of PLK1 tend to continue to enter mitosis with damaged DNA, resulting in a higher level of cell death.

Hypothesis: We propose to evaluate the feasibility of measuring the expression level of PLK1, a critical cell cycle regulator, to be used as a biomarker to predict the efficacy of radiotherapy. Tissues will be subjected to immunohistochemistry to measure the levels of PLK1 prior to radiotherapy. These studies will interrogate whether it is feasible to do this exploratory study, and this will help guide future biomarker studies.

Relevant Preclinical Data: Our preliminary data showed that mice with Plk1 overexpression are much more sensitive to radiotherapy than Plk1-negative mice (**Figure 2**) (Li *et al.*, 2017).

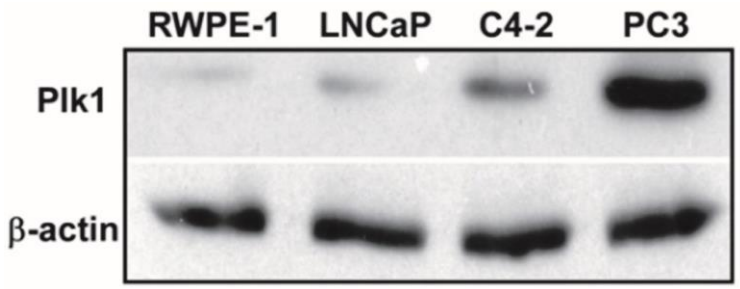



**Figure 1. PLK1 level is correlated with tumorigenicity in different prostate cell lines.** Immunoblot of PLK1 in RWPE-1, LNCaP, C4-2, and PC3 cells.

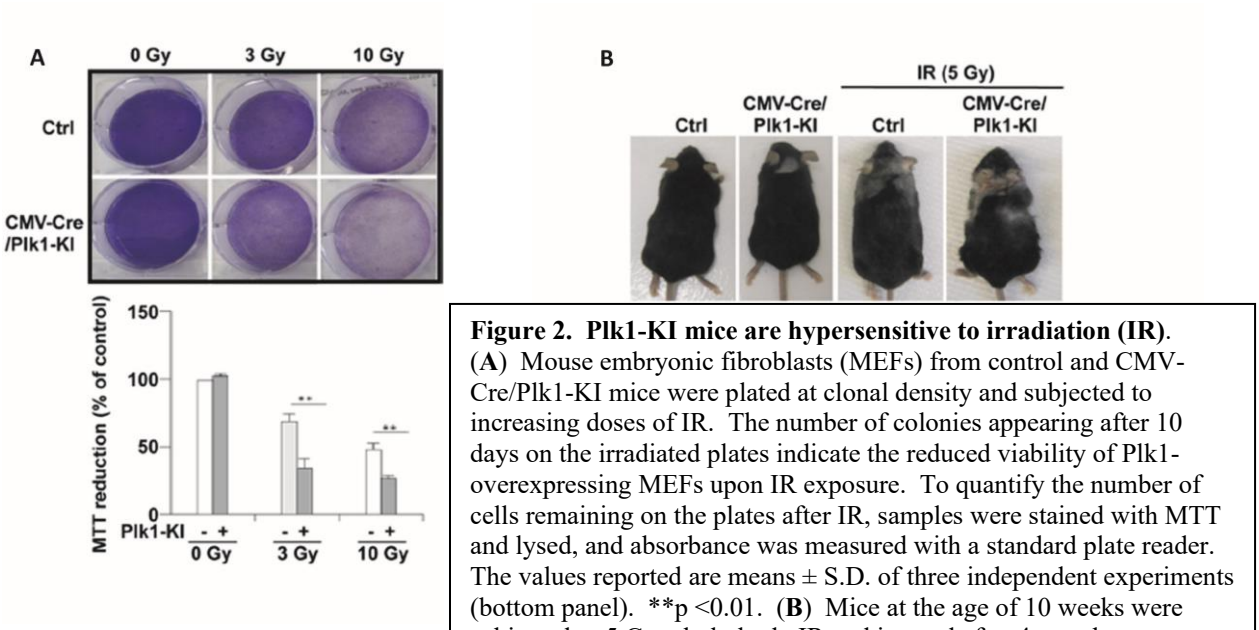



**Figure 2. Plk1-KI mice are hypersensitive to irradiation (IR)**. (**A**) Mouse embryonic fibroblasts (MEFs) from control and CMV-Cre/Plk1-KI mice were plated at clonal density and subjected to increasing doses of IR. The number of colonies appearing after 10 days on the irradiated plates indicate the reduced viability of Plk1-overexpressing MEFs upon IR exposure. To quantify the number of cells remaining on the plates after IR, samples were stained with MTT and lysed, and absorbance was measured with a standard plate reader. The values reported are means ± S.D. of three independent experiments (bottom panel). **p <0.01. (**B**) Mice at the age of 10 weeks were subjected to 5 Gy whole-body IR and imaged after 4 months.

2.4.4 Systemic Inflammatory Markers

Biologic Rationale and Relevant Preclinical Data: Our preclinical animal data studied the changes of IL-8 (pro-inflammatory cytokine) and PSA levels in tumor-bearing mice after treatment with radiotherapy (Xu *et al.*, 2012). It showed that an inverse relationship between IL-8 and PSA levels is associated with the response of PCa cells to radiation (**Figure 3**).

Hypothesis: We predict that patients with low IL-8/PSA ratios have a potential to respond to radiotherapy much better than those with high IL-8/PSA ratios. We propose to examine the irradiation-induced changes in systemic inflammatory markers such as IFN-gamma, TNF-alpha, IL-8, IL-10, and IL-17 prior to treatment *vs*. after one and two cycles of treatment, and 8 weeks after completing treatment, and correlate values/changes with treatment outcomes.

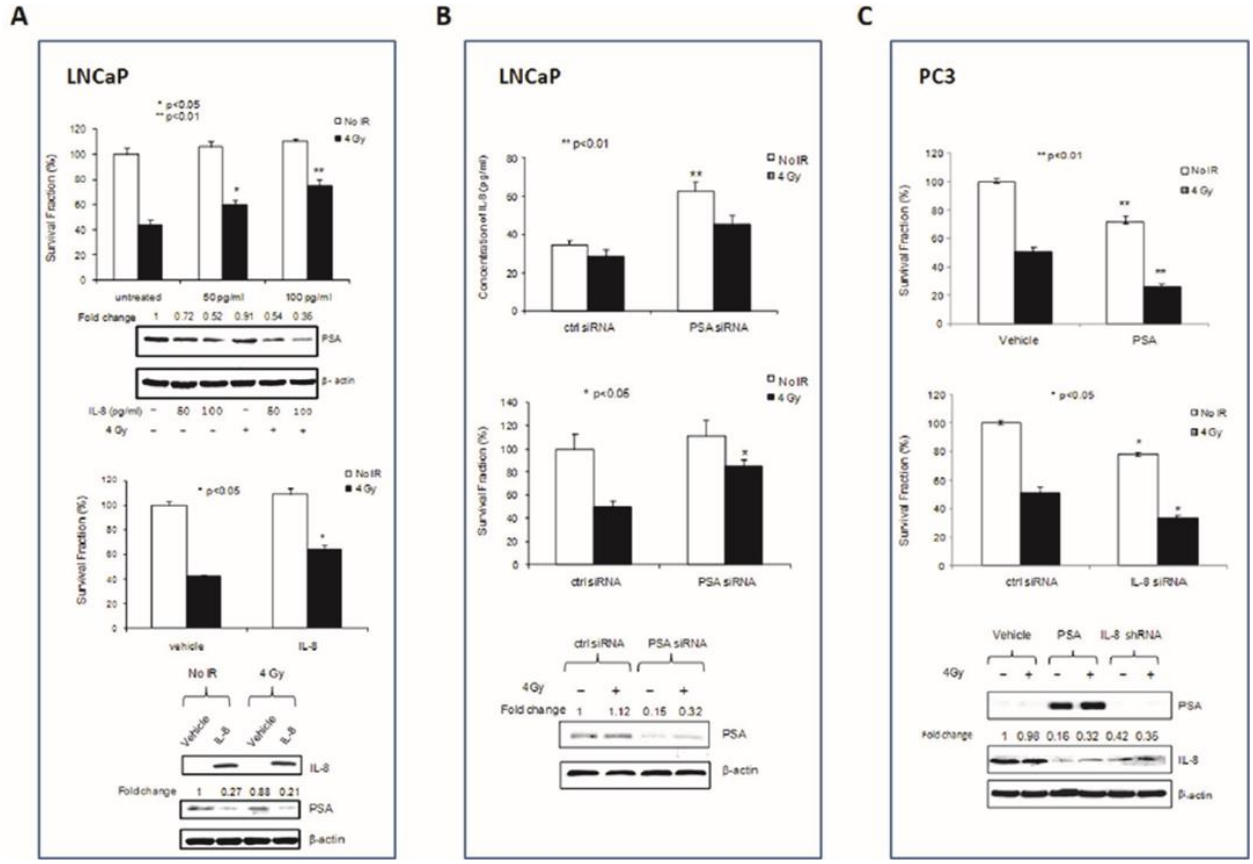



**Figure 3. The effects of PSA and IL-8 on radioresistance of PCa cells.** To determine the roles of PSA and IL-8 in radiosensitivity of PCa cells, LNCaP cells were treated with IL-8 protein or stably transfected with IL-8 cDNA (**A**) and stably transduced with PSA shRNA lentivirus (**B**). PC3 cells were stably transduced with PSA cDNA and IL-8 shRNA lentivirus (**C**). The levels of PSA were quantified by western blots, and the levels of IL-8 were quantified by either western blots or an ELISA kit.

### 2.4.5 Immune Cells

Biologic Rationale: The effects of ionizing radiation are seen not only in tumor cells but also in the tumor microenvironment. In general, lymphocytes (T cells, B cells, and natural killer [NK] cells) are among the most radiosensitive cells, followed by monocytes, macrophages, and antigen-presenting cells (APCs), specifically dendritic cells (DCs), which have a higher radio-resistance (Bauer *et al.*, 2011; Manda *et al.*, 2012). Additionally, radiation therapy can cause overproduction of inflammatory chemokines and cytokines including granulocyte colony-stimulating factor (G-CSF), macrophage CSF (M-CSF), granulocyte-macrophage CSF (GM-CSF), IL-6, IL-10, vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-beta, tumor necrosis factor (TNF)-alpha, chemokine ligand (CCL) 2, CCL5, and prostaglandin E2. The overproduction of these chemo-cytokines results in altering myelopoiesis and causing release of MDSCs. MDSCs suppress antitumor responses of T and NK cells and expand regulatory T cells, promoting cancer progression (Umansky *et al.*, 2016). IL-6 is critically important for MDSC generation and survival. There is a correlation between increased IL-6 concentrations and MDSC frequencies and their suppressive functions (Chi *et al.*, 2014). MDSCs are increasingly recognized as important contributors to immunosuppression in the

tumor micro-environment and are also closely associated with resistance to RT (Kang *et al.*, 2020).

Hypothesis: We propose to evaluate the correlation between frequencies of MDSCs, immune function markers, and treatment outcomes. The markers of immune function will be evaluated by measuring the percentage and absolute number of $CD4^+$ T helper cells, CD8 $T^+$ cytotoxic cells, NK cells, T regulatory cells, PMN-MDSCs, and M-MDSCs by flow cytometry prior to treatment *vs*. after one and two cycles of treatment, and 8 weeks after completing treatment, and correlate changes with treatment outcomes. PMN-MDSCs are defined as $CD15^+$ HLA-$DR^{low}$ $CD14^{+/-}$ and M-MDSCs are defined as $CD15^-$ HLA-$DR^{low}$ $CD14^+$ $CD11b^+$ $CD33^+$ by flow cytometry.

### 2.4.6 Patient-Reported Outcomes by Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (CTCAE) was designed for patients to report their symptomatic AEs in a complementary manner to clinician graded CTCAE AE items (https://healthcaredelivery.cancer.gov/pro-ctcae). While the measurement system has been validated, the current use of PRO-CTCAE in clinical trials remains exploratory. Clinician reported AE items remains the safety standard. There is no real-time review of the patients' responses. Patients are encouraged to report their concerning symptoms to their physicians and/or nurses.

In this study, the symptomatic AEs to be collected are nausea, vomiting, constipation, diarrhea, numbness and tingling, dizziness, general pain, joint pain, fatigue, painful urination, urinary urgency, urinary frequency, and change in usual urine color.

For any one of these items, patient may be asked 1-3 questions for the presence, frequency, severity, and level of interference. For these 5 PRO-CTCAE items, patients will be asked a total of 11 questions. These PRO-CTCAE items correspond to nausea, vomiting, constipation, diarrhea, numbness and tingling, joint pain, fatigue, painful urination, urinary urgency, urinary frequency, change in usual urine color, CTCAE items that clinicians are reporting. Patients will report every 2 weeks from the beginning of treatment until Week 28, and then every 3 months for a total of 12 months after the first Sn-117m-DTPA administration.

Studies have demonstrated that clinicians under-report symptomatic AEs compared to patient reporting of symptoms in Health-Related Quality of Life instruments. Patient reporting may provide more complete information, particularly for lower grade chronic toxicities that may impair tolerability over time. The PRO-CTCAE data will be evaluated for data quality, to characterize baseline symptom status of patients on study, to explore the development of symptomatic AEs and their change over time, and to explore the patient scores with clinician graded AEs.

## 3. PATIENT SELECTION

## 3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed adenocarcinoma of the prostate that is castration-resistant, defined as:

- A castrate serum testosterone level ≤50 ng/dL or 1.7 nmol/L
- Bilateral orchiectomy or maintenance on androgen ablation therapy with luteinizing hormone-releasing hormone (LHRH) or antiandrogen such as bicalutamide. Androgen deprivation therapy needs to be maintained throughout the study unless a patient has had orchiectomy by surgery.
- Serum PSA progression defined as two consecutive increases in PSA over a previous reference value, each measurement at least 1 week apart.

3.1.2 Progression after androgen receptor blockers (enzalutamide, apalutamide, or darolutamide) or androgen synthesis blockers (abiraterone acetate) or chemotherapy (docetaxel or cabazitaxel). There are no maximum number of prior therapies.

3.1.3 Progressive castration-resistant prostate cancer with two or more skeletal metastases identified by Tc-99m bone scintigraphy or prostate specific membrane antigen (PSMA) PET scan .

3.1.4 Patients must have self-reported moderate to severe pain at trial entry (baseline weekly average "worst pain in the past 24-hours" scores of ≥4 on an 11-point numeric rating scale [NRS], the Brief Pain Inventory – Short Form [BPI-SF] item #3 for worst pain).

3.1.5 Patients must either currently employ regular (not occasional) analgesic medication use for cancer-related bone pain or have undergone treatment with EBRT for bone pain within 4 weeks before starting study treatment.

3.1.6 Age ≥18 years. Children <18 years of age are excluded from the study as the prevalence of prostate cancer is extremely rare in this age group.

3.1.7 Patients must have a life expectancy ≥3 months.

3.1.8 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.9 Patients must have a serum PSA value ≥1 ng/mL.

3.1.10 Patients must have adequate organ and marrow function as defined below to be eligible for the <u>first</u> treatment administration:

| | |
|---|---|
| – absolute neutrophil count | ≥1,000/mcL |
| – platelets | ≥100,000/mcL |
| – hemoglobin | >10.0 g/dL |
| – total bilirubin | ≤2.5 × institutional upper limit of normal (ULN) |
| – AST(SGOT)/ALT(SGPT) | ≤5 × institutional ULN |
| – creatinine | ≤1.7 mg/dL |

OR

- glomerular filtration rate (GFR) ≥50 mL/min/1.73 $m^2$ (see Appendix B)

3.1.11 Patients receiving bisphosphonates or denosumab prior to enrollment can maintain therapy throughout all or part of the study. The bisphosphonate may be stopped or started at the discretion of the investigator throughout the study (*i.e.*, both treatment phase and follow-up). Injection of bisphosphonates should be done at least 2 hours before or after study drug administration.

3.1.12 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.13 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.14 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.15 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.16 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.1.17 The effects of Sn-117m-DTPA on the developing human fetus are unknown. For this reason and because radionuclides are known to be teratogenic, male participants and their female partners must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while her male partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of Sn-117m-DTPA administration.

3.1.18 Patients must be willing and able to comply with the protocol and agree to return to the hospital for follow-up visits and examinations.

3.1.19 Ability to understand and the willingness to sign a written informed consent document.

### 3.2 Exclusion Criteria

3.2.1 Patients must not have visceral metastases (such as liver and lung) as assessed by

abdominal/pelvic CT or chest X-ray within 12 weeks before starting study treatment.

3.2.2 Patients must not have malignant lymphadenopathy exceeding 3 cm in short-axis diameter.

3.2.3 Patients must not have imminent or established spinal cord compression based on clinical findings and/or MRI.

3.2.4 Patients who have had chemotherapy, immunotherapy, or external radiotherapy within 4 weeks prior to entering the study.

3.2.5 Patients must not have received systemic radiotherapy with radium-223, strontium-89, samarium-153, rhenium-186, or rhenium-188 for the treatment of bony metastases within 24 weeks before starting study treatment.

3.2.6 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1) with the exception of alopecia.

3.2.7 Patients must not have received any investigational agents within 4 weeks before starting study treatment, nor be scheduled to receive one during the planned treatment period.

3.2.8 Patients must not have unmanageable urinary incontinence.

3.2.9 Patients must not have had known non-pathological bone fractures within 2 months before starting study treatment.

3.2.10 Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to Sn-117m-DTPA.

3.2.11 Patients must not have uncontrolled intercurrent illness, including:
- Any uncontrolled infection
- Grade 2 or greater motor or sensory neuropathy

3.2.12 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

### 3.3 Inclusion of Minorities

NIH policy requires that members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Please see

http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

## 4. REGISTRATION PROCEDURES

### 4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

| Documentation Required | IVR | NPIVR | AP | A | AB |
|---|---|---|---|---|---|
| FDA Form 1572 | ✓ | ✓ | | | |
| Financial Disclosure Form | ✓ | ✓ | ✓ | | |
| NCI Biosketch (education, training, employment, license, and certification) | ✓ | ✓ | ✓ | | |
| GCP training | ✓ | ✓ | ✓ | | |
| Agent Shipment Form (if applicable) | ✓ | | | | |
| CV (optional) | ✓ | ✓ | ✓ | | |

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

## 4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

### IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

### Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO), and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *LAO-OH007*, and protocol number *10437*,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Protocol Specific Requirements for Protocol *10437* Site Registration

- Specimen Tracking System Training Requirement:
    - The Study PI will conduct the site initiation training (SIV) for each site. Study investigators and staff must review initial site initiation slides and/or attend site initiation webinar, as well as reviewing all amendments.
    - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
    - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
    - This training will need to be completed before the first patient enrollment at a given site.
    - Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

- The following three documents must be submitted to NCIPMBTRFDOCS@mail.nih.gov (Note: please submit all documents simultaneously in a single e-mail with the subject line "NCI Protocol 10437:"
    - Upon CTEP receipt of these documents it will take **at least one week** to set-up the site and personnel.

1. A valid facility Radiation Material License (RML) approved for medical use of Sn-117m with a valid expiration date.
    - Updates to the license must be submitted throughout the course of the trial in the same fashion. Sites will not be able to enroll study subjects or submit requests for Sn-117m-DTPA without a valid facility license on file.
2. A fully completed "Sn-117m-DTPA Site On-Boarding Form" (**see Appendix K**).
    - Updates to the provided information on this form must be submitted throughout the course of the trial in the same fashion.
    - The form must:
        - Identify the targeted radiopharmaceutical treatment facility (TRF) and address to where the Sn-117m-DTPA will be shipped.
        - Document the availability of a Sn-117m calibrated dose calibrator and the date of last calibration.
        - Identify the CTEP registered physician investigator Authorized Users of Sn-117m-DTPA for medical use responsible for prescribing Sn-117m-DTPA at the Targeted Radiopharmaceutical Facility (TRF) treating site and overseeing subject therapy with this agent. One CTEP registered physician investigator Authorized User of Sn-117m-DTPA for medical use is required to be identified, but at least two are preferred for sites with adequate personnel.
        - Identify the qualified site shipping contact personnel responsible for receiving, storing, and dispensing Sn-117m-DTPA. Two CTEP registered study site personnel registered at the Associate Plus, Non-Physician Investigator or Investigator registration type are required to be identified that have been identified by the site RSO as Sn-117m-DTPA trained personnel.
        - The identified study site personnel are not mutually exclusive. CTEP registered study site personnel may be identified to serve in multiple contact roles on the On-Boarding Form.
3. A Radiation Safety Officer (RSO) provided list of individuals at the site that are Authorized Users of Sn-117m for medical use (if not included on the RML) and an RSO provided list of personnel trained and credentialed by your RSO to handle, receive, store, dispense and manage Sn-117m-DTPA waste.
    - Any updates to the provided Authorized User list or list of trained personnel must be submitted throughout the course of the trial in the same fashion.

- Each enrolling site must be aligned to a credentialed TRF provider for the protocol on the CTSU website. Sites will manage TRF provider associations via the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be associated to a credentialed TRF for the protocol to participate on this trial. Enrolling sites are responsible for ensuring appropriate agreements and IRB approvals are in place if the provider is not directly aligned

with the enrolling site. An individual with a primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

- Sites must be a qualified user of Sn-117m-DTPA for medical use prior to site activation and must attest to having a valid calibrated dose calibrator for measuring Sn-117m radioactivity upon submission of the On-Boarding Form. Sn-117m-DTPA must be added to a site's radioactive material license and document training for administration and handling of the agent. To request training (provided at the expense of Serene LLC), contact Dr. Chad Smith, F.X. Masse Associates, Inc., P.O. Box 1636, Gloucester, MA 01931; Phone 978-283-4888; Email: info@fxmasse.com.

If necessary, a calibration reference standard may be requested from IsoTherapeutics by contacting Kim Miller; Phone: (979) 848-0800; Email: orders@isotherapeutics.com. Upon receipt of the reference standard and completion of calibration of the dose calibrator, a copy of the site's calibration document with calibration date must be submitted to CTEP at the following e-mail address: NCIPMBTRFDOCS@nih.gov. Use the Subject: "NCI Protocol 10437 Calibration Documentation."

#### 4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

**Delegation of Tasks Log (DTL)**

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

CTEP will use the identified Authorized Users of Sn-117m-DTPA for medical use and identified RSO trained personnel list (along with the submitted site Radiation Material License) to create a

credentialed TRF in RSS for the trial site and an associated Sn-117m-DTPA credentialed person roster for the TRF. This roster will be used to identify Authorized Users on the Delegation of Tasks Log.

- Authorized User physician investigators of Sn-117m-DTPA for medical use must be registered with CTEP at the Investigator level and be listed on the site DTL with the task of Authorized User Prescriber. A minimum of one Authorized User Prescriber investigator is required. A minimum of two is preferred.
- Sn-117m-DTPA Study Shipping Contact sub-investigators must be listed on the site DTL with the task Authorized User Drug Mailing. A minimum of two Authorized User Drug Mailing sub-investigators are required and must be registered with the NCI as an Associate Plus, Non-Physician Investigator or Investigator.

Other site-level Authorized Users of Sn-117m-DTPA for medical use may be identified on the DTL with the task Authorized User Medical Use. There are no minimum requirements for identifying these individuals, but if identified, must be registered with the NCI as an Associate Plus, Non-Physician Investigator or Investigator. All individuals assigned to the Authorized User tasks must be identified as such by the site Radiation Material License indicating their authority as an Authorized User of Sn-117m-DTPA for medical use or site Radiation Safety Officer authorized list indicating their authority as an Authorized User of Sn-117m-DTPA for medical use or site trained personnel for Sn-117m-DTPA.

#### 4.2.4 Checking Site Registration Status

A site's registration status may be verified on the CTSU website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

### 4.3 Patient Registration

#### 4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. The IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

Sites must reserve a slot in IWRS. The multi-institution program coordinator will verify slot availabilities prior to consenting patients. The required forms, including the eligibility criteria checklist and registration form, should be provided to the study team. The study team will review the request and, once a slot is allocated, will communicate with the sub-site regarding the decision.

4.3.2 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on use of the STS can be found in Section 5.4.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN link of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.3.4 Patient Registration for Medidata Patient Cloud

**a. Medidata Patient Cloud**

This study includes the use of Medidata Patient Cloud electronic patient-reported outcomes. Patients will be allowed the paper format option if they are not comfortable using the digital app format or if it is not available. All sites will participate in the collection. After the patient is registered to the trial via OPEN, and if the patient is willing to participate in electronic data collection (or paper, which will be converted to electronic by site staff), the site staff will then complete a registration for the patient to the Patient Cloud through iMedidata. Note: Site staff must have already completed required eLearning for the Patient Cloud application to register a patient and information about the training is in the Medidata Patient Cloud Registration Appendix (Appendix H). The registration to the Patient Cloud will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from

the site staff) should be instructed to download the Patient Cloud app onto his/her own device (IOS, Android, phone, or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial.

For sites providing a shared institutional device for use by multiple patients on site:

- The site staff should assist the patient with access and registration to the Patient Cloud app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

**b. CRA Patient Registration Instructions for Medidata Patient Cloud**

Please visit the Medidata Learning Tool (https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html) for reference information on Patient Cloud for CRAs.

i. The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud Registration link for your study
ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.
iii. Now you can register your first patient. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.
iv. The subject added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

Reminder- site staff must have already completed the Medidata Patient Cloud training in order to register study participants. Please visit the Medidata Learning Tool for reference information on Patient Cloud for CRAs (https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html).

There are multiple versions of the app available. Ensure that the correct version of the app is downloaded by the patient by verifying the correct version per the study build requirements. Note: only 1 version of the app is active per protocol and this protocol is using Patient Cloud.

**Patient Cloud**

## 4.4 General Guidelines

Following registration, patients should begin protocol treatment within 30 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

## 5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

### 5.1 Summary Table for Specimen Collection

| Time Point | Specimen and Quantity | Send Specimens to: |
|---|---|---|
| **Archival** | | |
| | Formalin-fixed paraffin-embedded (FFPE) tumor rich tissue block (preferred)[1] (optional)<br><br>If archival tumor tissue block is not available, then submit:<br>• 4 (4-5 micron) unstained charged slides[1]<br>• 15-20 (10-micron) unstained uncharged slides[1]<br>• 1 H&E stained slide (3-5 micron) | EET Biobank |
| **Pre-treatment** | | |
| | • 10 mL whole blood in EDTA tube (mandatory when archival tissue or slides are submitted)<br>• 24 mL whole blood in citrate CPT (three 8 ml) tubes, processed to PBMC and plasma and frozen (optional) | EET Biobank |
| **Cycle 1, Week 8** | | |
| | • 24 mL whole blood in citrate CPT (three 8ml) tubes, processed to PBMC and plasma and frozen (optional) | EET Biobank |
| **Cycle 2, Week 8** | | |
| | • 24 mL whole blood in citrate CPT (three 8 ml) tubes, processed to PBMC and plasma and frozen (optional) | EET Biobank |
| **Week 24** | | |
| | • 24 mL whole blood in citrate CPT (three 8ml) tubes, processed to PBMC and plasma and frozen (optional) | EET Biobank |

[1]For archival tissue, **a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave**. The pathology report must be labeled with the Patient Study ID and Universal Patient ID when submitted to the Biobank. If submitting slides, then

slides must be processed in order, and numbered sequentially.

## 5.2 Summary Table(s) for Interventional Radiologist for Research Biopsies

N/A

## 5.3 Specimen Procurement Kits and Scheduling

### 5.3.1 Specimen Procurement Kits

Kits for the collection and shipment of blood in CPT tubes to the EET Biobank can be ordered online via the Kit Management system: https://kits.bpc-apps.nchri.org.

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kits per kit type per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

**Note:** Kits or supplies are only provided for specimens shipped to the Biobank. Institutional supplies must be used for all other specimen collection and processing.

### 5.3.2 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect specimens:

- Fresh blood in EDTA may be collected and shipped Monday through Friday.
- Blood in CPT processed for plasma and mononuclear cells can be collected any day and shipped on Monday through Thursday.

## 5.4 Specimen Tracking System Instructions

### 5.4.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment

patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

The Shipping List Report **must** be included with all sample submissions.

5.4.2 Specimen Labeling

5.4.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like plasma and PBMCs):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, plasma, PBMC)
- Collection date (to be added by hand)

5.4.2.2 Tissue Specimen Labels

Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

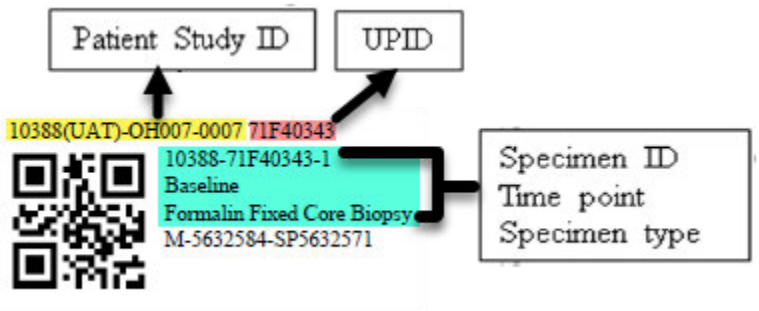
- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, *etc.*)

- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report
- Collection date (to be added by hand)
- Slide section number (only if archival tissue is submitted as slides) (to be added by hand)

5.4.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5" high and 1.28" wide.




The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

**Space is provided at the bottom of the label for the handwritten date and optional time.** The last line on the example label is for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be set up with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.4.3.2 Rave Specimen Tracking Process Steps

**Step 0**: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

**Step 1**: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

**Step 2**: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date on each label. After collection, store labeled specimens as described in Section 5.5.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports and Tissue Biopsy Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. **Do not redact SPID, block number, diagnosis, or relevant dates (such as collection date), and include the UPID and patient study ID on each document (either by adding a label or hand writing)**.

**Step 3**: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

**Step 4**: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.**

**Step 5**: Print shipping list report and prepare to ship.

- The Shipping List Report is available at the site level.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

**Step 6**: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

**Step 7:** Ship the specimen(s).

**Step 8**: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

## 5.5 Specimen Collection

### 5.5.1 Archival Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously-collected FFPE tissue will be submitted, then the following criteria must be met:

- Tissue is preferred from radical prostatectomy specimens, however, a core or excisional biopsy of a tumor lesion is acceptable.
- Tissue is preferred to be collected within 3 years prior to registration for whole genome sequencing/RNA sequencing and PLK1 immunohistochemistry staining. Archival tissues must be collected within 3 years to perform RNA squencing study. However, two decade old tissues are acceptable to use for DNA sequencing and PLK1 immunohistochemistry studies.
- Submission of either FFPE tumor tissue block(s) or unstained slides is acceptable; FFPE tumor blocks are preferred. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
    - Surface area: 25 $mm^2$ is optimal. Minimum is 5 $mm^2$.
    - Volume: 1 $mm^3$ optimal. Minimum volume is 0.2 $mm^3$, however the success of

DNA extraction decreases at suboptimal tissue volume.

If an existing block cannot be submitted, the following are requested, if available. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 72 hours from the date the slides are cut, otherwise a new sample will be requested.

- Four (4) unstained charged slides (4-5 µm)
- 15-20 (10-micron) unstained uncharged slides
- 1 H&E stained slide (3-5 µm)

Process and number slides sequentially (*e.g.*, unstained charged slides should be created first and labeled with 1 – 4, and additional unstained slides should be processed next and be labeled 5 – n).

See Section 5.4.2 for labeling instructions.

5.5.2 Blood Collection

5.5.2.1 Collection of Blood in EDTA Tubes for Shipping Whole Blood (WES baseline sample)

1. Label EDTA tubes according to the instructions in Section 5.4.2.
2. Collect 10 mL blood in EDTA tube(s) and gently invert tube to mix.
3. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
4. If blood cannot be shipped on the day of collection (*e.g.*, a late scheduled collection), then refrigerate until shipment.

5.5.2.2 Collection of Blood in CPT Sodium Citrate Tubes for Plasma and PBMC Processing (Immune Cells and Inflammatory Markers samples)

1. Label CPT sodium citrate tubes according to the instructions in Section 5.4.2.
2. Collect three (3) 8-mL samples and gently invert to mix.
3. The samples can be stored on ice up to 2 hours before processing.
4. Centrifuge the vacutainers at 3,000 rpm (approx. 1,700 x g) at 21 C for 12 minutes so as to produce plasma. The resulting plasma should be stored in 1 ml aliquots at -80 C or below.
5. The PBMC layer should be transferred to a fresh tube with sterile PBS and centrifuged at 300 x g for 15 minutes. Repeat the washing step, then cryopreserve in 10% DMSO/FBS, preferably in 0.5 mL aliquots with 2,000,000 cells per aliquot. The samples should be frozen in a “Mr. Frosty”, or similar below-freezing apparatus and stored in liquid nitrogen the next day for long term storage.
6. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
7. If blood cannot be shipped on the day of collection (*e.g.*, a late scheduled collection), then refrigerate until shipment. Ship frozen plasma and mononuclear cells according to instructions in Section 5.6.

## 5.6 Shipping Specimens from Clinical Site to the EET Biobank

### 5.6.1 General Shipping Information

When kits are provided, the shipping container sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must be sent to the EET Biobank as soon as possible and uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

#### 5.6.1.1 Required Forms for Specimen Submissions:

**Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.**

| Tissue | Required Forms |
|---|---|
| Archival Tissue | 1. Shipping List<br>2. Corresponding Pathology Report |
| Other (blood, blood product, urine, stool, etc.) | 1. Shipping List |

### 5.6.2 Specimen Shipping Instructions

Archival (FFPE) tissue may be shipped on Monday through Thursday.

Fresh blood may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

#### 5.6.2.1 Shipping of FFPE Blocks and Glass Slides

1. Before packaging blocks or slides, verify that each specimen is labeled according to Section 5.4.2.2.
2. Blocks should be placed in a hard-sided container, preferably a special block holder, to protect the specimen. Glass slides are to be placed in plastic slide holders. Place tissue paper on top of the separated slides prior to closing the slide holder to reduce slide movement during shipment.
3. Place the blocks or slides in a reinforced cardboard shipping box with appropriate packaging filler to minimize movement of specimens within the shipping box.

4. Include a copy of the corresponding pathology report, labeled with the Patient Study ID and Universal Patient ID and a shipping manifest from the Specimen Tracking System with each shipment.
5. Please include a cold pack when shipping on hot days and extra insulation on cold days.
6. Ship specimens to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.2 Shipping Blood in an Ambient Shipper

1. Before packaging specimens, verify that the collection tube is labeled according to instructions in section 5.4.2.1
2. Place the blood collection tube into a zip-lock bag.
3. Place zip-lock bag into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
4. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place the specimen(s) and a copy of the shipping manifest into a sturdy shipping container. In winter months please use an insulated container and include extra insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
6. Close the container and tape shut.
7. Attach a shipping label to the top of the shipping container.
8. Attach an Exempt Human Specimen sticker to the side of the container.
   Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.3 Shipping Frozen Specimens in a Single-Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in section 5.4.2.1 and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
4. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place frozen specimens in the kit compartment with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. When packaging specimens, ensure that you leave enough room to include at least 5 pounds of dry ice in the shipment.
6. Insert a copy of the shipping list(s) into a plastic bag and place in the kit chamber.
7. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
8. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.

9. Complete a FedEx air bill and attach to top of shipping container.
10. Complete a dry ice label.
11. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.3 Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
PH: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

**FedEx Priority Overnight** service is very strongly preferred.

**NOTE:** The EET Biobank FedEx Account will not be provided to submitting institutions. There is no central Courier account for this study. Sites are responsible for the cost of shipments to the EET Biobank.

5.6.4 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

## 5.7 Shipping of Specimens from Clinical Site to Other Laboratories

N/A

## 5.8 Biomarker Plan

### List of Biomarker Assays in Order of Priority

***Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing.***

| Priority | Biomarker Name | Assay (CLIA: Y/N) | Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose | Specimens Tested | Collection Time Points | Mandatory or Optional | Assay Laboratory and Lab PI |
|---|---|---|---|---|---|---|---|
| **Tissue-based Biomarkers** | | | | | | | |
| 1 | Whole Exome Sequencing | NGS<br>CLIA: N | Exploratory<br>Molecular characterization of the tumor | DNA from FFPE tumor | Archival | O | NCLN Genomics Laboratory<br>Mickey Williams<br>mickey.williams@nih.gov |
| 2 | RNAseq | NGS<br>CLIA: N | Exploratory<br>Molecular characterization of the tumor | RNA from FFPE tumor | Archival | O | NCLN Genomics Laboratory<br>Mickey Williams<br>mickey.williams@nih.gov |
| 3 | Polo-like Kinase (PLK) | IHC<br>CLIA: N | Exploratory<br>To evaluate efficacy in predicting response to therapy | Unstained slides from FFPE tumor | Archival | O | Liu Laboratory, University of Kentucky<br>Xiaoqi Liu<br>Xoaoqi.Liu@uky.edu |
| **Blood-based Biomarkers** | | | | | | | |

| Priority | Biomarker Name | Assay (CLIA: Y/N) | Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose | Specimens Tested | Collection Time Points | Mandatory or Optional | Assay Laboratory and Lab PI |
|---|---|---|---|---|---|---|---|
| 1 | Systemic inflammatory markers<br>(IFN-gamma, IL-6, IL-8, IL-10, IL-17, TNF-alpha) | Flow Cytometry<br>CLIA: N | Exploratory<br>To examine the irradiation induced changes in inflammatory markers of immune function | Plasma and PBMCs from CPT sodium citrate tube | Pre-treatment<br>Cycle 1 Week 8<br>Cycle 2 Week 8<br>Week 24 | O | St. Clair Laboratory, University of Kentucky<br>William H. St. Clair<br>stclair@email.uky.edu |
| 2 | Immune cells<br>(CD4+ T helper cells, CD8+ T cytotoxic cells, T regulatory cells, MDSCs) | Flow Cytometry<br>CLIA: N | Exploratory<br>To examine the irradiation induced changes in inflammatory markers of immune function | Plasma and PBMCs from CPT sodium citrate tube | Pre-treatment<br>Cycle 1 Week 8<br>Cycle 2 Week 8<br>Week 24 | O | St. Clair Laboratory, University of Kentucky<br>William H. St. Clair<br>stclair@email.uky.edu |
| 3 | Whole Exome Sequencing | NGS<br>CLIA: N | Exploratory<br>Germline Control | DNA from blood in EDTA tube | Pre-treatment | M when archival tissue or slides are submitted. | NCLN Genomics Laboratory<br>Mickey Williams<br>mickey.williams@nih.gov |

## 5.9 Exploratory/Ancillary Correlative Studies

### 5.9.1 Whole Exome Sequencing / RNA Sequencing

#### 5.9.1.1 Specimen(s) Receipt and Processing at the EET Biobank

FFPE tissue blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide. All H&E stained slides will undergo a pathology QA review and annotation for macrodissection. Following macrodissection, tumor tissue from unstained slides will be scraped for co-extraction of DNA and RNA. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of DNA and RNA will be shipped to the central sequencing laboratory for analysis.

DNA will be extracted from blood collected in the EDTA tube at pre-treatment. Blood DNA will be quantitated, and then stored in a -80°C freezer until shipping to the NCLN Genomics Laboratory for analysis.

#### 5.9.1.2 Site(s) Performing Correlative Study

WES and RNAseq will be conducted in the NCLN Genomics Laboratory under the leadership of Mickey Williams, Ph.D.

#### 5.9.1.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:
NCLN Genomics Laboratory at The University of Texas MD Anderson Cancer Center
Attn: Jincy Veliyathu or Khushali Rajendra Patel
Zayed Building
CTLU Z3.4020
6565 MD Anderson Blvd
Houston, TX 77030

#### 5.9.1.4 Contact information for notification of specimen shipment

Thomas Forbes
NCLNGenomicsReceiving@nih.gov

### 5.9.2 Polo-like Kinase

#### 5.9.2.1 Specimen(s) Receipt and Processing at the EET Biobank

Unstained slides will be shipped for this assay. Archival tumor tissue slides will be stored at room temperature until shipment. If archival blocks are received, then slides will be sectioned for distribution.

5.9.2.2 Site Performing Correlative Study

Immunohistochemistry for PLK1 will be performed in the laboratory of Xiaoqi Liu, Ph.D., at the University of Kentucky.

5.9.2.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:
Markey Biospecimen SRF
Dana Napier
744 Rose Street, Combs 107
Lexington, KY 40506
Phone: 859-323-7374

5.9.2.4 Contact information for notification of specimen shipment

Please send an email notification of shipment, including protocol ID, patient study ID, study visit, and tracking number to Dana Napier at the Markey Biospecimen SRF (markey.bstp@uky.edu)

5.9.3 Systemic Inflammatory Markers

5.9.3.1 Specimen(s) Receipt and Processing at the EET Biobank

Frozen plasma and PBMC samples will be accessioned and stored at -80°C until shipment to the laboratory for analysis once all timepoints for a patient are collected.

5.9.3.2 Site Performing Correlative Study

Systemic inflammatory marker changes will be analyzed in the laboratory of William H. St. Clair, M.D., Ph.D., at the University of Kentucky.

5.9.3.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:
Markey Biospecimen SRF
Dana Napier
744 Rose Street, Combs 107
Lexington, KY 40506
Phone: 859-323-7374

5.9.3.4 Contact information for notification of specimen shipment

Please send an email notification of shipment, including protocol ID, patient study ID, study visit, and tracking number to: Dana Napier at the Markey Biospecimen SRF

(markey.bstp@uky.edu)

5.9.4 Immune Cells

5.9.4.1 Specimen(s) Receipt and Processing at the EET Biobank

Frozen plasma and PBMC samples will be accessioned and stored at -80°C until shipment to the laboratory for analysis once all timepoints for a patient are collected.

5.9.4.2 Site Performing Correlative Study

Immune cell population changes will be analyzed in the laboratory of William H. St. Clair, M.D., Ph.D., at the University of Kentucky.

5.9.4.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:
Markey Biospecimen SRF
Dana Napier
744 Rose Street, Combs 107
Lexington, KY 40506
Phone: 859-323-7374

5.9.4.4 Contact information for notification of specimen shipment

Please send an email notification of shipment, including protocol ID, patient study ID, study visit, and tracking number to: Dana Napier at the Markey Biospecimen SRF (markey.bstp@uky.edu)

## 5.10 Special Studies

5.10.1 Sn-117m-DTPA Dosimetry

5.10.1.1 Outcome Measure

Sn-117m-DTPA activity will be evaluated as a primary correlative of radioactivity distribution. Tin is an avid bone seeker, and its biodistribution is nearly identical to that of Tc-99m-MDP (Swailem *et al.*, 1998). The highest tin distribution is seen in bone surfaces (82%) with increased uptake in bone metastases. Other normal physiological tissue retention can be seen in liver, lungs, spleen, heart, and kidneys, and their uptake varies with the rates of clearance.

5.10.1.2 Assessment

5.10.1.2.1 Method of Assessment

Sn-117m-DTPA activity will be assessed by gamma camera dosimetry outlined here and in

Appendix J. A positive Sn-117m-DTPA scan is defined as tumor uptake ≥ normal liver uptake observed on planar imaging. Focal and heterogeneous Sn-117m-DTPA bone uptake will be correlated with the baseline Tc-99m-MDP dosimetry results.

5.10.1.2.2 Timing of Assessment

Serial whole-body (head to mid-thigh) planar images in the anterior and posterior projections will be acquired during the first cycle only, 1 hour, 4 hours (or within 4-6 hours), 24 hours (or within 16-24 hours), 48 hours (or within 40-48 hours), 72 hours (or within 60-72 hours), 1 week (±2 days), and 4 weeks (±2 days) after the first Sn-117m-DTPA dose (see the table below). If one or more images are not performed at the correct time, make-up whole-body scans are not needed, especially for patients that live in the vicinity of the clinic.

Table: Dosimetry image acquisition timelines

| Timing (Target range) | Imaging |
|---|---|
| 1 hr | Whole body scan * |
| 4 hrs (4-6 hrs) | Whole body scan |
| 24 hrs (16-24 hrs) | Whole body scan + SPECT/CT |
| 48 hrs (40-48 hrs) | Whole body scan + SPECT/CT |
| 72 hr (60-72 hrs) | Whole body scan |
| 1 week (+/- 2 days) | Whole body scan |
| 4 weeks (+/- 2 days) | Whole body scan |
| *No voiding between radiopharmaceutical infusion and 1st imaging. | |

SPECT/CT: single-photon emission computed tomography/computed tomography

Dosimetry reference standard preparation and utilization

After each therapeutic session, the residual activity in the vial will be measured in a dose calibrator, labelled as a reference standard, and kept for further imaging. The reference standard will be placed at the inferior part within the field of view of whole-body scans at all time points. Caution will be taken for the standard reference not to touch the patient during imaging. Optional 3D SPECT scans will be performed at 24 hours and 48 hours in the upper abdomen to include kidneys, liver, and spleen. Extending coverage can be done to include regions determined by the planar imaging.

5.10.1.3 Data Recording

5.10.1.3.1 Method of Recording

We will compare radiopharmaceutical whole-body retention rates of our patients to the previously reported values. Image based dosimetry analysis will be performed.

1) Equipment: Large-field-of-view dual-head gamma camera will be used.
2) Energy window: 20% window centered at 159 KeV
3) Collimator: Low-energy high-resolution parallel-hole (LHRP) collimator

Image Analysis:

Geometric mean will be calculated from anterior and posterior images for both whole-body. Counts in whole-body images will be normalized at the first image, scanning the patient with 100% of the injected activity at 1 hour before patient void or by subtracting the percent of injected activity eliminated in the urine before the first image acquisition.

Patient-specific organ mass (liver, spleen, and kidneys) will be obtained by measuring organ volume using CT scan and assuming liver, spleen, and kidney density as 1.03 g/cc. Regions of interest (ROIs) will be placed over whole body, liver, spleen, and kidneys, as well as the dosimetry reference standard on both anterior and posterior planar whole body images. Both total counts and number of pixels will be recorded for each ROI. Target organ radiation absorbed dose will be calculated using the MIRD schema or related methodology.

5.10.1.3.2 Timing of Recording

Dosimetry scans will be assessed within one week of Sn-117m-DTPA administration.

5.10.2 Sn-117m-DTPA Palliative Pain Effect

5.10.2.1 Outcome Measure

The effect of Sn-117m-DTPA treatment on cancer-related bone pain will be assessed via patient reports of pain intensity and changes in analgesic use to manage pain. Patients will be asked to complete the BPI-SF questionnaire, which rates several aspects of pain and the effects of pain on common activities, on an 11-point scale; a "0" represents "no pain/no pain relief/does not interfere", and an "11" represents "pain as bad as you can imagine/complete relief/completely interferes". Patients will also be asked to complete a simple analgesic use log by choosing among the options of "decreased", "stable", or "increased" use of any pain medication.

5.10.2.2 Assessment

5.10.2.2.1 Method of Assessment

The Sn-117m-DTPA palliative pain effect will be measured by using a pain index as described in the table below (Nilsson *et al.*, 2012).

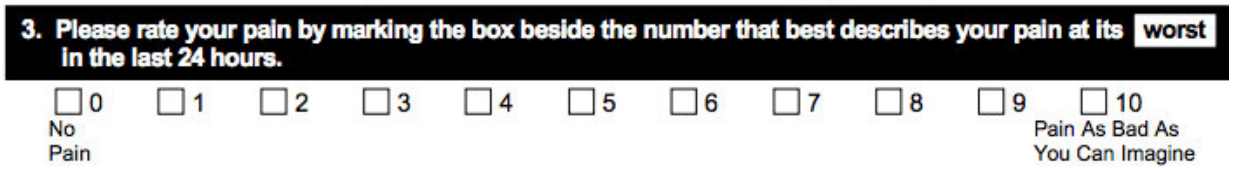
**Classification of pain index based on diary pain intensity rating and analgesic intake**

| **Pain response** | **Pain index** | **Diary pain rating change from baseline** | **Analgesic intake compared with baseline** |
|---|---|---|---|
| Complete | 1 | Decrease ≥90% | Stable or reduced |
| Marked | 2 | Decrease ≥50% to <90% | Stable or reduced |
| Moderate | 3 | Decrease >33% to <50% | Stable or reduced |
| Minimal | 4 | Decrease ≥20% or increase <33% | Stable |
| None | 5 | Decrease <20% or increase <20% | Stable |

| | | | |
|---|---|---|---|
| Pain progression | 6 | Increase ≥20% | Stable or increased |
| | | Decrease <20% or increase <20% | Increased |
| | | Decrease ≥20% | Increased |

This pain index is derived from a combination of the following 11-point pain intensity scale and analgesic consumption categorized according to the World Health Organization (WHO) analgesic ladder.

**Pain intensity scale (Item #3 on the BPI-SF, worst pain)**




**Analgesic Use/Consumption**

| PATIENT-REPORTED ANALGESIC LOG | | |
|---|---|---|
| Decrease | Stable | Increase |

Both narcotic and non-narcotic analgesic use and pain intensity scales will be captured using the Medidata Patient Cloud where patients will be able to complete the submission of their worst pain score and analgesic log electronically. A paper format option is allowable in case a digital collection format is not available or the patient is not comfortable using the app (Appendix E). Clinical research coordinators will verify the medication and fill out the pain medication list (Appendix F) with every clinic visit.

5.10.2.2.2 Timing of Assessment

Pain at baseline and analgesic use (pre-treatment, Week 0) will be measured via serial (daily) assessments in a 7-day run-in period. Patients will be considered evaluable if they complete assessments on ≥4 days within the 7-day run-in period. During treatment, pain and analgesic use will be measured every 2 weeks through Week 28, followed by routine clinic follow-up until 1 year or when patients experience new pain. Complete pain assessments via the full BPI-SF (Appendix D) will be collected at baseline, after Cycle 1, after Cycle 2, and at Week 28. Pain assessments will be halted at the patient's request or if the patient discontinues study treatment for reasons other than disease progression.

5.10.2.3 Data Recording

5.10.2.3.1 Method of Recording

- Pain assessments and analgesic logs will be post-processed using Medidata Rave EDC (electronic data capture). Data collection for this study will be done through Medidata

Rave.

5.10.2.3.2 Timing of Recording

- The pain score and analgesic data will be assessed for inclusion determination during the pre-screening period within 2 weeks of a patient's enrollment.

## 6. TREATMENT PLAN

### 6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described in Sections 6.1 and 6.3 may be administered with the intent to treat the patient's malignancy.

| **Study Regimen Description** | | | | |
|---|---|---|---|---|
| **Agent** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Sn-117m-DTPA | 20 mCi/70 kg (0.28 mCi/kg) | Slow IV injection over 10 min | Day 1 | 8 weeks* |

*Treatment continues for 2 cycles.

**Retreatment** after 2 cycles is allowed after an evaluation of AEs if:

- pain (≥4 on 11-point intensity scale) recurs within 6 months after a 16-week pain observation period
  AND
- no disease progression on bone scans (≤2 new bone lesions), or evidence of clinical progression (such as development of cancer-related symptoms)

Patients will be administered two additional cycles (8 weeks apart) if they meet the retreatment criteria. The maximum treatment dose per patient is four injections in this study.

Patients will be instructed to maintain a high fluid intake (drink at least two to three quarts of fluid every 24 hours) for 2 weeks after each Sn-117m-DTPA treatment to minimize a concentrated radioactive excretion. In general, drinking alcoholic beverages should be kept to a minimum or avoided completely. Patients will be educated on hygiene instruction/precautions on post-therapy treatment (see Appendix I).

Required Criteria for Each Re-Treatment:

Patients must have adequate organ and marrow function as defined below to be eligible for subsequent treatments after the first treatment administration:

- leukocytes ≥2,000/mcL
- absolute neutrophil count ≥1,000/mcL
- platelets ≥75,000/mcL
- hemoglobin ≥8.0 g/dL
- total bilirubin ≤ 2.5 × institutional ULN
- AST(SGOT)/ALT(SGPT) ≤5 × institutional ULN
- creatinine* ≤1.7 mg/dL
  OR
- glomerular filtration rate (GFR) ≥50 mL/min/1.73 $m^2$ (see Appendix B)

*Should a 40% increase over the baseline serum creatinine value occur during the course of treatment, with a concomitant decrease of over 40% in creatinine clearance as calculated from serum creatinine concentrations according to Cockroft's method (see Appendix B), patients must also have a measured creatinine clearance (or GFR) performed, unless resolved within 16 weeks.

6.1.1 CTEP IND Agent

6.1.1.1 Sn-117m-DTPA

Visually inspect solution for particulate matter or discoloration prior to administration. Sn-117m-DTPA solution is not to be diluted or mixed with any other solutions. Sn-117m-DTPA doses are administered by slow intravenous injection over 10 minutes into a free-flowing IV line containing 0.9% sodium chloride. The intravenous access line is to be flushed with 0.9% sodium chloride after injection of Sn-117m-DTPA. Doses must be administered by Authorized Users in a designated clinical setting licensed accordingly for medical use of Sn-117m-DTPA.

Vials are to be assayed immediately prior to and after withdrawal of the subject dose. Record radioactive activity administered according to institutional protocol and on the NCI Drug Accountability Record Form. The actual radioactivity administered must be within the tolerance limits of ± 10% of the calculated radioactivity.

Administration is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

Sn-117m-DTPA should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. Follow normal working procedures for the handling of radiopharmaceuticals and use universal precautions for handling and administration such as gloves and barrier gowns and when handling blood and bodily fluids to avoid contamination.

In keeping with the As Low As Reasonably Achievable (ALARA) principle for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials

used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

Sn-117m-DTPA must be added to a site's radioactive material license and document training for administration and handling of the agent. To request training (provided at the expense of Serene LLC), contact Dr. Chad Smith:

Chad A. Smith, Ph.D., CHP
F.X. Massé Associates, Inc.
Health and Medical Physics Consultants
PO Box 1636
Gloucester, MA 01931
Phone: 978-283-4888
Fax: 978-281-6702
Email: info@fxmasse.com

## 6.2 Definition of Dose-Limiting Toxicity

Toxicity will be assessed using the NCI's CTCAE version 5.0. A DLT is defined as an AE or abnormal laboratory value assessed as being at least possibly related to the study medication, which occurs within 60 days after the second cycle of Sn-117m-DTPA.

A DLT is defined as:

**Hematologic DLT**
- Grade ≥3 neutropenia or thrombocytopenia lasting ≥14 days
- Grade ≥3 thrombocytopenia with bleeding lasting ≥14 days

**Non-hematologic DLT**
- Grade 3 or 4 toxicity at least possibly related to study treatment and not reversible to grade ≤1 within 24 hours, spontaneously or with standard supportive measures (*e.g.*, antiemetics, electrolyte replacement), EXCEPT:
    - Grade 3 nausea/vomiting or diarrhea that lasts <72 hours
    - Grade 3 fatigue that lasts <7 days
    - Grade ≥3 electrolyte abnormality that lasts <72 hours, unless the patient has clinical symptoms, in which case all grade 3 electrolyte abnormalities count as DLT.
    - Grade 3 amylase or lipase elevation without associated symptoms or clinical manifestations of pancreatitis

## 6.3 General Concomitant Medication and Supportive Care Guidelines

### 6.3.1 Concomitant Prostate Cancer Therapy

- Patients receiving bisphosphonates or denosumab prior to enrollment can maintain therapy throughout all or part of the study. The bisphosphonate may be stopped or

started at the discretion of the investigator throughout the study (*i.e.*, both treatment phase and follow-up). Injection of bisphosphonates should be done at least 2 hours before or after study drug administration.
- Patients who have not undergone bilateral orchiectomy are allowed and should receive LHRH agonists or antiandrogen such as bicalutamide throughout the study (*i.e.*, both treatment phase and follow-up).
- Cytotoxic chemotherapy, androgen receptor blockers, androgen biosynthesis inhibitors, other systemic radioisotopes, hemi-body external radiotherapy, and other investigational drugs should not be used during the treatment period. These treatments can be given if at least 8 weeks after the last injection.
- Colony stimulating factors (*e.g.*, erythropoietin and granulocyte colony stimulating factors) and transfusions products (*e.g.*, red blood cell transfusion, and/or platelet transfusion) as dictated by standard practice are acceptable while the subject is enrolled in the study.

#### 6.3.2 Analgesic Use

Use of all analgesic medications is allowed throughout the study, including all opioid types.

#### 6.3.3 Drug-Drug Interactions

Because there is a potential for interaction of Sn-117m-DTPA with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

### 6.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 2 cycles or until one of the following criteria applies. Re-treatment is allowed upon AE evaluation if pain re-occurs within 6 months after a 16-week pain observation period.

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), defined as DLT in Section 6.2
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance

- Termination of the study by sponsor

- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

If a patient is withdrawn from the study during the treatment period (and will not return for any more visits), he will be encouraged to come to safety follow-up visits at 4 weeks and 12 weeks after his last Sn-117m-DTPA administration.

### 6.5 Duration of Follow-Up

Patients will be followed every 2 weeks during treatment (16 weeks), then every 4 weeks until Week 28, and then every 3 months or as clinically indicated for 12 months after the first Sn-117m-DTPA dose or until death, whichever occurs first. After the 1-year follow-up period, dates of death will be collected for all patients until the final patient completes his 1-year follow-up. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

## 7. DOSING DELAYS/DOSE MODIFICATIONS

No Sn-117m-DTPA dose modification is allowed. Patients will be monitored continuously for AEs throughout the study. Patients must be instructed to notify their physician immediately for any and all side effects. Treatment interval is scheduled every 8 weeks or every 56 days with a window period of +/- 7 days for all time points. If the treatment needs to be delayed due to an adverse event, study drug administration can be delayed up to 8 weeks for recovery, with the following conditions:

- Hematological toxicities must resolve to CTCAE grade 1 or less (or, if abnormal at baseline, not more than one grade above baseline) prior to administration of the next Sn-117m-DTPA dose. In the absence of recovery after 4 weeks, patients are to discontinue further study drug administrations.
- Non-hematological toxicities must resolve to CTCAE grade 2 (gastrointestinal events) or grade 3 (other toxicities) prior to administration of the next dose.
- If patients experience spinal cord compression during the treatment phase, Sn-117m-DTPA administration can continue with up to a 4-week delay if the patient is adequately treated with steroids, local SBRT, or surgery.
- If patients experience traumatic fracture in weight-bearing bones during the treatment phase, the study drug administration should be delayed 4 weeks from the fracture.

As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity.

### 7.1 PRO-CTCAE

PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol-directed action.

## 8. PHARMACEUTICAL AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 10.1.

### 8.1 CTEP IND Agent

8.1.1 Sn-117m-DTPA (NSC 824376)

# Stannic-117m Pentetate (Sn-117m-DTPA)
## (NSC 824376)

**Chemical Name:** Stannic-117m pentetate; Sn-117m-diethylenetriaminepentaacetic acid

**Other Names:** Sn-117m-DTPA

**Classification:** Conversion electron emitting radiopharmaceutical

**Molecular Formula:** $^{117m}SnHC_{14}H_{18}N_3O_{10}$ **M.W.:** 508.01 g/mole

**Mode of Action:** Tin binds to bone and especially to hypermetabolic areas in bone, such as bone adjacent to tumor metastases, similarly to calcium. Stannic-117m pentetate produces conversion electrons with finite penetration, to 300 μm, resulting in irradiation of tissues only to that distance, sparing bone marrow and other tissues adjacent to the bone-tumor interface. The isotope also produces gamma radiation, enabling imaging.

**Description:** Stannic-117m pentetate is a ligand metal chelate consisting of the radionuclide Sn-117m in the +4 oxidative state complexed to pentetate (DTPA), the chelating agent. The formulation is prepared using a 20:1 molar ratio of DTPA to Sn. Calcium chloride is added to the formulation as an excipient to combine with 80% of the excess (un-complexed) DTPA present in the formulation to minimize DTPA-related toxicity. Stannic-117m pentetate is a low energy conversion electron emitter with also energy emitted as gamma-radiation. Stannic-117m pentetate has a half-life of 14 days and decays to stable Sn-117.

**How Supplied:** Stannic-117m pentetate is supplied by Serene, LLC and distributed to clinical trial sites by IsoTherapeutics Group, Angleton, TX. under a DCTD, NCI-sponsored IND.

Stannic-117m pentetate will be distributed by IsoTherapeutics Group in single-use vials prepared for the subject's planned dose as a sterile, aqueous solution. The solution has a pH between 3 and 5 and contains the following excipients: calcium chloride and water for injection. The solution may contain sodium chloride for pH adjustment. Vials are shipped in a lead container and transported as a Type A radioactive package according to international transportation guidelines for radioactive materials.

Vials will only be shipped to Authorized Users at appropriately licensed facilities with a Radioactive Materials License approved for medical use of Stannic-117m pentetate.

**Preparation:** Stannic-117m pentetate solution is not to be diluted or mixed with any other solutions. Vials are to be assayed in a Stannic-117m pentetate calibrated dose calibrator that has been calibrated with a NIST traceable Stannic-117m pentetate reference standard. Dose calibrators are to be calibrated at time of commissioning, after any maintenance procedures and at intervals of no greater than one year. Vials are to be assayed immediately prior to and after withdrawal of the subject dose. Record radioactive activity administered according to institutional protocol and on the NCI Drug Accountability Record Form. The actual radioactivity administered must be within the tolerance limits of ± 10% of the calculated radioactivity.

A minimum of three (3) records of Stannic-117m pentetate radioactivity MUST be kept and submitted in RAVE for each individual patient administration: (1) radioactivity at initial dose shipment from IsoTherpaeutics, (2) radioactivity upon Site receipt, and (3) radioactivity at Site upon administration to the patient confirmed by radioactivity in the vial measured immediately prior to and after withdrawal of the subject dose.

**Storage:** Store vials at room temperature (between 15-30°C). Store vials in the radiation shielding container until use.

**Stability:** Vials will be labeled with an expiration date, which will be 14 days from the date of calibration prior to shipment.

**Route and Method of Administration:** Visually inspect solution for particulate matter or discoloration prior to administration. Stannic-117m pentetate doses are administered by slow intravenous injection over 10 minutes into a free-flowing IV line containing 0.9% sodium chloride. The intravenous access line is to be flushed with 0.9% sodium chloride after injection of Stannic-117m pentetate. Doses must be administered by Authorized Users in a designated clinical setting licensed accordingly for medical use of Stannic-117m pentetate.

**Special Handling and Precautions:**

Stannic-117m pentetate (a conversion electron emitting pharmaceutical) should be received, used and administered only by persons authorized to handle radiopharmaceuticals in designated clinical settings. The receipt, storage, use, transfer and disposal of Stannic-117m pentetate are subject to the regulations and/or appropriate licenses of the competent official organization (Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State). Administration may be associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

Stannic-117m pentetate should be handled by the user in a manner which satisfies both radiation

safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. In keeping with the As Low As Reasonably Achievable (ALARA) principle for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding.

Any unused drug product or materials used in connection with the dispensing or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations. Unused doses and waste may be destroyed following applicable agreement state and federal regulations for decay in storage for Stannic-117m pentetate following 10 half-lives.

Radiation protection precautions are to be followed in accordance with national and local regulations. Follow normal working procedures for the handling of radiopharmaceuticals and use universal precautions for handling and administration such as gloves and barrier gowns when handling blood and bodily fluids to avoid contamination.

**Patient Care Implications:** Fertile men study participants and their partners must abstain or use effective contraception (including barrier method) while receiving study treatment and for at least 6 months after the last dose of Stannic-117m pentetate. For at least 10-days after each dose, subjects should avoid close contact with others, should flush toilet several times after each use, and should avoid preparing food for others. Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing.

Provide subject with instructions regarding hygiene precautions to abide by at time of therapy completion in accordance with local institutional policies and guidelines for radiation protection.

**Availability**

Sn-117m-DTPA is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Sn-117m-DTPA is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.5).

8.1.2 Agent Ordering and Agent Accountability

**8.1.2.1** Sn-117m-DTPA is supplied by Serene LLC and distributed by IsoTherapeutics under a DCTD, NCI-sponsored IND.

- All requests for Sn-117m-DTPA must be submitted to IsoTherapeutics using the attached order request form attached in **Appendix L**. Complete all requested fields on the order request form. Obtain subject's weight prior to each dose. Requests must be submitted to IsoTherapeutics at least one week in advance of the planned administration date and must be shipped to the authorized facility address as identified on the Site On-Boarding Form and to a site shipping contact as identified on the Site On-Boarding Form. A copy of the completed order request form must be retained as a study record.

- Unused doses are to be accounted for on the NCI DARF. Unused doses may be destroyed following applicable agreement state and federal regulations for decay in storage for Sn-117m-DTPA.

The Authorized User investigator prescribing Sn-117m-DTPA must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF), and be designated as such on the Site On-Boarding Form and the Delegation of Task Log.

**8.1.2.2** Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received using the NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol. **All Shipping Declaration Forms received with the Sn-117m-DTPA shipments are considered IND records and must be retained by the site along with the NCI Drug Accountability Records for the trial.**

8.1.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

## 9. STATISTICAL CONSIDERATIONS

### 9.1 Study Design/Endpoints

This is a single-arm, open-label phase 2 study to evaluate the efficacy of Sn-117m-DTPA on

sustained pain response in patients with CRPC metastatic to at least two bone sites, with at least one clinically meaningful pain at baseline (≥4 on an 11-point pain intensity scale). Sustained pain-response is defined as: 1) achieving pain index ≤3 within a 12-week period and 2) maintaining that pain index ≤3 over a 16-week time period (beginning when the pain index ≤3 is initially achieved). The maximum duration of follow-up required to declare a patient a responder is 28 weeks, representing a patient who initially achieves pain index ≤3 toward the end of the 12-week period and is followed for an additional 16 weeks to confirm maintenance of pain index ≤3.

Eligible patients will be assigned to receive Sn-117m-DTPA at 20 mCi/70 kg (0.28 mCi/kg) every 8 weeks for two cycles. Treatment will last for 16 weeks with two treatment injections given at 8-week intervals. The study utilizes a mini-max Simon two-stage design to assess anti-tumor activity and pain benefit of Sn-117m-DTPA.

Patients are not allowed to receive external radiation within 12 weeks from the start of treatment administration. If their pain index does not reach ≤3 after 12 weeks, they are not meeting the primary endpoint, and they can then get external radiation for pain control.

The sustained pain response rate under null hypothesis is $p_0$=0.1 and the alternative hypothesis is $p_1$=0.3. The literature on sustained pain-relieving benefit with radiopharmaceutical drugs in prostate cancer with bone metastases is limited. Nilsson *et al*. studied the dose-response relationship and pain-relieving effect of radium-223 (Nilsson *et al.*, 2012). Pain response at Week 8 was seen in 40% of patients. The null hypothesis for sustained pain response in the absence of effective therapy and a strong literature support would assume 10%. We propose that the sustained pain response with Sn-117mDTPA would achieve 30%. Using the mini-max Simon's two-stage design, the total sample size is 25 patients, with 10 patients for the first stage and 15 patients for the second stage. If 1 or 0 patients achieve sustained pain response in the first stage, the study will be stopped early for futility; otherwise the trial continues to the second stage. If 5 or fewer patients achieve sustained pain-response, then no further investigation of the study treatment is warranted. This design has an estimated 5% type I error rate and 80% power. The planned sample size and interim analysis has a 3.28% actual type I error rate and 80.17% actual power. The probability of stopping at the end of the first stage is about 55% under the null hypothesis. Study enrollment will be interrupted for the interim efficacy analysis.

The efficacy primary endpoint will also be summarized by the point estimation of the ORR with the corresponding 95% confidence intervals. Patients who received any amount of study drug will be included in the denominator for the calculation of ORR.

Summary statistics on safety endpoints will be calculated and reviewed at the interim analysis or anytime during the study at the investigator's discretion. If there is statistically significant evidence that the DLT probability exceeds 30%, the study should be suspended for further review. A 95% exact binominal confidence interval will be calculated for the DLT rate. If the observed lower bound of the confidence interval exceeds 30%, we consider it statistically significant evidence that the DLT probability exceeds 30%.

## 9.2 Sample Size/Accrual Rate

The total sample size is 25 patients, with 10 patients for the first stage and 15 patients for the second stage. An interim analysis for efficacy will be conducted after the first 10 patients have become evaluable for the primary endpoints. Study enrollment will be interrupted for the interim analysis. Patients will be accrued at an anticipated rate of 1-2 patients per month.

**PLANNED ENROLLMENT REPORT**

| DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT) | | | | | |
|---|---|---|---|---|---|
| Racial Categories | Ethnic Categories | | | | Total |
| | Not Hispanic or Latino | | Hispanic or Latino | | |
| | Female | Male | Female | Male | |
| American Indian/ Alaska Native | 0 | 0 | 0 | 0 | **0** |
| Asian | 0 | 0 | 0 | 0 | **0** |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | **0** |
| Black or African American | 0 | 3 | 0 | 0 | **3** |
| White | 0 | 22 | 0 | 0 | **22** |
| More Than One Race | 0 | 0 | 0 | 0 | **0** |
| **Total** | **0** | **25** | **0** | **0** | **25** |

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**Stopping Criteria**

Stopping criteria will be applied if 1) there is evidence of treatment related AEs or 2) lack of efficacy.

1) We will review safety data at interim analysis or at any point if there are reasons for concern about safety. If there is strong evidence that the DLT rate is unacceptably high (>30%), we will suspend the study.

2) An interim analysis for efficacy will be conducted after the first 10 patients have become evaluable. If 1 or 0 patients achieve the primary endpoint, then the study will be stopped early for futility.

## 9.3 Stratification Factors

This is a single-arm phase 2 study with no stratification factors.

## 9.4 Analysis of Secondary Endpoints

Secondary endpoints will be summarized depending on data type. Categorical endpoints will be summarized by frequency and percent. Continuous variables will be summarized by mean and standard deviation at each assessment time point. Time-to-event endpoints will be summarized by Kaplan-Meier Methods. Safety and toxicity will be assessed through the frequency and percent of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interests (AESIs). Toxicity will be assessed using Common Terminology Criteria for Adverse

Events v 5.0 (CTCAE). Safety and toxicity will also be assessed by patient-reported outcomes and adverse events (PRO-CTCAE) captured by digital instruments during treatment and 8 weeks after the last injection to monitor for acute toxicity and every 2-4 weeks for 6 months post-therapy for monitoring of long-term toxicity. CTCAE grades for the corresponding time period will be presented in conjunction with PRO-CTCAE scores. PSA and ALP response rates will be calculated for each of the above defined categories with the corresponding confidence intervals. *Post-hoc* analysis on PSA and ALP levels may be conducted to explore possible trends in PSA and ALP levels. Time to the first symptomatic skeletal event will be analyzed using the Kaplan-Meier method. Estimation and confidence intervals for the median time to first symptomatic skeletal event will be provided. Patients who did not have a symptomatic skeletal event will be censored at the last study visit. PFS will be analyzed in a similar manner as the time to first skeletal event. Patients who did not have observed clinical progression will be censored at the last assessment.

### 9.4.1 Sn-117m-DTPA Activity

Gamma camera dosimetry will be used to evaluate whole-body distribution of Sn-117m-DTPA. Tin is an avid bone seeker, and its biodistribution is nearly identical to Tc-99m-MDP (Swailem *et al.*, 1998). The highest tin distribution is seen in bone surfaces (82%) with increased uptake in bone metastases. Focal and heterogenous bone uptake in Sn-117m-DTPA will be correlated with baseline Tc-99m-MDP. Other normal physiological tissue retention can be seen in liver, lungs, spleen, heart, and kidneys, and their uptake varies with the rates of clearance. The tumor uptake observed using the Sn-117m-DTPA scan must be ≥ normal liver uptake observed on planar imaging.

Statistical Plan:

The Pearson's correlation coefficient method will be used to assess the correlation between the baseline technetium-99 bone scintigraphy measurement and the Sn-117m-DTPA uptake. If the observed data distribution is not appropriate to calculate the Pearson's correlation, *post hoc* analysis will be conducted using non-parametric methods or other methods suitable to the observed data distribution.

The gamma dosimetry scan measurements will be reported descriptively as the average and standard deviation of dosimetry scan measurements and plotted over time and grouped by organ systems.

### 9.4.2 Overall Response Rate

A Fisher's exact 95% confidence interval will be calculated for the overall response rate. The denominator will include all patients who received at least one dose of study treatment and do not have major protocol deviations. Patients who do not have observed clinical response will be counted as negative responses.

### 9.4.3 Time to First Symptomatic Skeletal Event

The time from study enrollment to 1) the first use of external-beam radiation therapy to relieve skeletal symptoms, 2) new symptomatic pathologic vertebral or non-vertebral bone fractures, 3) spinal cord compression, or 4) tumor-related orthopedic surgical intervention will be evaluated.

### 9.4.4 Overall Pain Response Rate

The rate of achievement of pain index ≤3 within 12 weeks from the first Sn-117m-DTPA will be evaluated.

### 9.4.5 Duration of Pain Response

The time from the achievement of pain response (pain index ≤3) to the recurrence of pain (pain index ≥4) will be evaluated.

### 9.4.6 Serum Prostate-Specific Antigen and Alkaline Phosphatase Responses

Levels of serum PSA and ALP will be measured at 4-week intervals and used to determine response rates for each molecular marker.

PSA response rates will be determined for the following benchmarks:

- ≥30% reduction of the blood level, compared to the baseline value
- ≥50% reduction of the blood level, compared to the baseline value
- Confirmed PSA response: ≥50% reduction of the blood level, compared to the baseline value, and confirmed by a second PSA value approximately 4 or more weeks later

ALP response rates will be determined for the following benchmarks:

- ≥50% reduction of the blood level, compared to the baseline value
- Confirmed ALP response: ≥50% reduction of the blood level, compared to the baseline value, and confirmed by a second ALP value approximately 4 or more weeks later

### 9.4.7 Patient-Reported Outcomes and Adverse Events

Safety and toxicity will be assessed by PROs and AEs (PRO-CTCAE) captured by digital instruments every 2 weeks through Week 28 for acute and long-term toxicity.

The PRO-CTCAE data will be evaluated for data quality, to evaluate the symptoms' changes over time on study, to explore the development of symptomatic AEs and the change over time, and to explore the patient scores with clinician graded AEs. PRO-CTCAE data will be summarized descriptively as the number (percent) of patients reporting each grade for individual items.

### 9.4.8 Clinical Progression-Free Survival

Clinical PFS will be calculated from the time of study enrollment until disease progression, which is defined as 1) symptomatic progression (increasing pain from a metastatic lesion); 2) progression of bone lesions assessed per PCWG3 criteria; or 3) progression of soft-tissue lesions

assessed per RECIST v1.1 criteria. PSA progression without progression on bone lesions nor symptomatic is not considered as clinical progression. Clinical PFS will be censored if clinical progression is not observed.

9.4.9 Overall Survival

OS will be calculated from the time of the first study treatment until the date of death. OS data will be censored if death is not observed.

## 9.5 Analysis of Exploratory Endpoints

9.5.1 Tumor Genomic Alterations

9.5.2 Changes in Systemic Inflammatory Markers and Immune Cell Populations

9.5.3 PLK Immunohistochemistry

Immunohistochemistry for PLK1 will be performed using a PLK1 mouse monoclonal antibody manufactured by Sigma Aldrich (Cat#05-844). Staining will be performed on 5-micron sections obtained from formalin-fixed, paraffin-embedded tissue, with the appropriate antigen retrieval method, blocking step, and dilution as recently determined (manuscript in submission). PLK1 will be scored utilizing a modified Quickscore Method as follows:

| Intensity | Score |
|---|---|
| No staining | 0 |
| Light staining | 1 |
| Moderate staining | 2 |
| Strong staining | 3 |
| Proportion | Score |
| 0-4% | 1 |
| 5-20% | 2 |
| 21-40% | 3 |
| 41-60% | 3 |
| 61-80% | 5 |
| 81-100% | 6 |

Expression Scores will be calculated as Intensity Score × Proportion Score and classified as one of three score tiers:

- Low Expression: 1-3
- Moderate Expression: 3-5
- High Expression: ≥6

Statistical Plan:
Correlative endpoints such as systemic inflammatory, immune markers, and expression of PLK and changes from pre- to post-treatment will be summarized using descriptive statistics.

Changes from baseline *vs.* follow-up time points will be assessed using paired test methodologies. WES data will be processed using the data processing and data analysis pipelines from the Biostatistics and Bioinformatics shared resource of Markey Cancer Center to identify candidate mutated genes with adjustment for false discovery rate.

## 9.6 Reporting and Exclusions

### 9.6.1 Evaluation of Toxicity

The Safety Population is defined as all patients who received at least one dose of study treatment. Analyses of safety and toxicity will be based on the Safety Population. Safety and toxicity will be assessed through the frequency and percent of AEs, SAEs, DLT, and AEs of special interest (AESIs). Toxicity will be assessed using Common Terminology Criteria for Adverse Events v 5.0 (CTCAE). Safety and toxicity will also be assessed by patient-reported outcomes and adverse events (PRO-CTCAE) captured by digital instruments every 2 weeks until Week 28 for acute toxicity for monitoring of acute and long-term toxicity.

### 9.6.2 Evaluation of Response

The Per Protocol Population is defined as all patients who are in the Safety Population and have no major protocol violations that could influence the assessment of efficacy. Efficacy analysis, including the analysis of primary and secondary endpoints (excluding safety and toxicity), will be based on the Per Protocol Population.

Responses to treatment will be evaluated per PCWG3 criteria as described in Section 12.1 (for bone lesions).

# 10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer to the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

## 10.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

10.1.1 CAEPR for CTEP IND Agent

10.1.1.1 CAEPR for Sn-117m-DTPA

**Comprehensive Adverse Events and Potential Risks list (CAEPR)**
**for**
**Stannic-117m Pentetate (Sn-117m-DTPA, NSC 824376)**

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Stannic-117m Pentetate (Sn-117m-DTPA).

**NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 1.0, July 24, 2020[1]**

| **Adverse Events with Possible Relationship to Stannic-117m Pentetate (Sn-117m-DTPA) (CTCAE 5.0 Term)** | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|
| GASTROINTESTINAL DISORDERS | |
| Nausea | ***Nausea (Gr 2)*** |
| INVESTIGATIONS | |
| Lymphocyte count decreased | ***Lymphocyte count decreased (Gr 2)*** |
| Neutrophil count decreased | |
| Platelet count decreased | |
| White blood cell decreased | ***White blood cell decreased (Gr 2)*** |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

**Note**: Stannic-117m Pentetate (Sn-117m-DTPA) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

## 10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that require expedited reporting are outlined in Section 10.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

## 10.3 Expedited Adverse Event Reporting

### 10.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A

report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

### 10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

### 10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.**

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

**Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]**

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**
**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

| Hospitalization | Grade 1 and Grade 2 Timeframes | Grade 3-5 Timeframes |
|---|---|---|
| Resulting in Hospitalization ≥ 24 hrs | 10 Calendar Days | 24-Hour 5 Calendar Days |
| Not resulting in Hospitalization ≥ 24 hrs | Not required | |

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

**Expedited AE reporting timelines are defined as:**

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

### 10.3.4 Adverse Events of Special Interest

Grade 3 or higher renal and genitourinary AEs will be reported as expedited AEs, including but not limited to:

- Renal failure (ranging from significantly reduced measured or estimated creatinine clearance to clinically overt renal failure other than that of obvious non-investigational agent-induced origin
- Suspected radiation nephropathy of any type, such as radiation-induced thrombotic microangiopathy, manifesting as:
    - Proteinuria
    - Hypertension
    - Edema
    - Anemia
    - Decreased serum haptoglobin
- General symptoms and signs of acute radiation toxicity, such as:
    - Increased frequency/urgency of urination
    - Nocturia
    - Dysuria
    - Bladder spasm
    - Bladder obstruction
    - Genitourinary ulceration of necrosis

Grade 3 or higher bone marrow toxicities will also be reported as expedited AEs.

## 10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.4.1 Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items, but no protocol directed action will be taken. Study specific PRO-CTCAE items for this protocol can be found in Appendix G.

10.4.2 PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting.

10.4.3 Symptomatic Adverse Events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine AE data.

10.4.4 PRO-CTCAE Items

Attribute acronyms: F=Frequency, S=Severity, I=Interference, P=Presence/Absence/Amount

| CTCAE Item version 5.0 | PRO-CTCAE Item (Attributes) version 1.0 |
|---|---|
| Constipation | Constipation (S) |
| Diarrhea | Loose or watery stools (F) |
| General Pain | General Pain (FSI) |
| Fatigue | Fatigue (SI) |
| Numbness and Tingling | Numbness and Tingling (SI) |
| Nausea | Nausea (FS) |
| Vomiting | Vomiting (FS) |
| Dizziness | Dizziness (FS) |
| Painful urination | Painful urination (FS) |
| Urinary urgency | Urinary urgency (FS) |
| Urinary frequency | Urinary frequency (FS) |
| Change in urine color | Change in urine color (FS) |
| Joint pain | Joint pain (FS) |

## 10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

## 10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

## 10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

## 11. STUDY CALENDAR

Baseline evaluations are to be conducted within 4 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤8 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Visit dates and scans can be within ±7 days of planned dates. Study treatment must start within 30 days of registration.

| | Pre-study | Cycle 1 (8 weeks or 56 days) | | | | | Cycle 2 (8 weeks or 56 days) | | | | | Post-treatment | | | | | | Follow-up[a] | Off-study visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W2 | W4 | W6 | W8 | W1 | W2 | W4 | W6 | W8 | 18 weeks | 20 weeks | 22 weeks | 24 weeks | 26 weeks | 28 weeks | | |
| Sn-117m-DTPA | | A | | | | | A | | | | | | | | | | | A* | |
| Informed consent | X | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | |
| Pain medication** | X | X | X | X | X | X | | X | X | X | X | | X | | X | | X | X (every 3 months) | X |
| Physical Exam | X | X | | X | | X | | | X | | X | | X | | X | | X | X | X |
| Vital signs | X | X | | X | | X | | | X | | X | | X | | X | | X | X | X |
| Height | X | | | | | | | | | | | | | | | | | | |
| Weight | X | X | | X | | X | | | X | | X | | X | | X | | X | X | |
| Performance status | X | | | | | | | | | | | | | | | | | X | |
| CBC/diff, platelets | X | X | X | X | X | X[i] | | X | X | X | X | | X | | X | | X | X | X |
| Serum chemistry[b] | X | X | X | X | X | X[i] | | X | X | X | X | | X | | X | | X | X | X |
| PSA | X | | | X | | X | | | X | | X | | X | | X | | X | X | X |
| Adverse Events | | X---------- | | | | | | | | | | | | | | | ----------X | | |
| Patient-reported pain intensity scale and analgesic use[c] | X | | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient-reported CTCAE[d] | | | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X |
| Sn-117m-DTPA dosimetry (optional)[e] | | X | X | X | | | | | | | | | | | | | | | |
| Urine collection for urinalysis[f] | X | | | | | | X | | | | | | | | | | | | |

| | Pre-study | Cycle 1 (8 weeks or 56 days) | | | | | Cycle 2 (8 weeks or 56 days) | | | | | Post-treatment | | | | | | Follow-up[a] | Off-study visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W2 | W4 | W6 | W8 | W1 | W2 | W4 | W6 | W8 | 18 weeks | 20 weeks | 22 weeks | 24 weeks | 26 weeks | 28 weeks | | |
| Radiologic evaluation (CT of abdomen/pelvis and bone scan) and chest X-ray[g] or PSMA PET CT scan | X | | | | | X | | | | | X | | | | X | | | X (every 3 months) | |
| Research blood for genomic whole exome sequencing (mandatory when archival tissue or slides are submitted) | X | | | | | | | | | | | | | | | | | | |
| Research blood for exploratory studies (optional)[h] | X | | | | | X[h] | | | | | X[h] | | | | X | | | | |
| Archival tissue for genomic sequencing and exploratory PLK1 stain (optional) | X | | | | | | | | | | | | | | | | | | |

A: Sn-117m-DTPA: 20 mCi/70 kg (0.28 mCi/kg) slow IV injection over 10 min on C1D1 and C2D1
*Patients can be retreated if pain recurs within 6 months after 16-week pain observation period

a: Follow-up visit evaluation. Every 3 months or as clinically indicated up to one year from the first dose injection or disease progression

b: Albumin, ALP, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, sodium, potassium, total protein, SGOT [AST], SGPT [ALT].

c: Pre-treatment daily baseline pain and analgesic use for 7 days (at least 4 out of 7 days) is required before treatment initiation. Patients will be asked to report their pain at its worst in the last 24 hours and analgesic use (stable/reduced/increased) by digital version every 2 weeks through Week 28, followed by routine clinic follow up or when they experience new pain during off-visit. **A full short version of brief pain inventory (BPI) will be asked at baseline, after Cycle 1, after Cycle 2, and at Week 24.**

d: PRO-CTCAE survey items will be assessed by digital instruments. Beginning at Week 28, surveys are requested every 3 months for 6 months after the last study treatment administration.

e: Serial DTPA dosimetry scans (optional) will be obtained at 1 hour, 4 hours (or within 4-6 hours), 24 hours (or within 16-24 hours), 48 hours (or within 36-48 hours), 72 hours ( or within 60-72 hours), 1 week (+/2 days), and 4 weeks (+/2 days) post-infusion. The dosimetry scan will only be performed with first cycle of injection.

f: Urine collection for urinalysis will be collected at the indicated time points or as clinically indicated to monitor for microscopic or macroscopic hematuria as part of genitourinary toxicity monitoring.

g: Imaging: Follow up tumor response will be evaluated by CT scan of abdomen and pelvis, bone scan and chest X-ray. If Chest X-ray shows abnormal or clinically symptomatic, then CT chest should be obtained. Follow-up scans at every 8 weeks will be performed as clinically indicated, per institutional standards. PSMA PET CT scan at baseline is also acceptable.

h: Blood collections for research during Cycles 1 and 2 should be collected on the last day of each cycle.

i: CBC and serum chemistry should be performed 1 week before the start of Cycle 2.

** Study coordinator/research nurse will require to ask pain medications list including names, dosage and frequency and also is required to fill out pain medication list form during every clinic visit.

# 12. MEASUREMENT OF EFFECT AND DISEASE PROGRESSION

## 12.1 Antitumor Effect – Bone and PSA Response Parameters

### 12.1.1 Prostate Cancer Working Group 3 (PCWG3) Criteria

The sections of the PCWG3 Criteria that apply to this trial are the criteria for PSA response and progression, and the criteria for bone lesion (non-target) "prevent/delay end points (progression)," described in the table below. See Scher *et al.* (2016) for more details.

| Variable | PCWG3 (2016) |
|---|---|
| PSA | • Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug<br>• Monitor PSA by cycle but plan to continue through early rises for a minimum for 12 weeks unless other evidence of progression<br>• Ignore early rises (prior to 12 weeks) in determining PSA response<br><br>Decline from baseline:<br>• Record time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (*i.e.*, a confirmed rising trend)<br><br>No decline from baseline:<br>• PSA progression ≥25% and ≥2 ng/mL after 12 weeks |
| Bone | For control/relieve eliminate end points:<br>• Record changes as new lesions or no new lesions<br>• Changes in intensity of uptake alone do not constitute progression or regression<br>• **First schedule reassessment:**<br>  • No new lesions: continue therapy<br>  • New lesions: perform a confirmatory scan 6 or more weeks later<br>• **Confirmatory scan:**<br>  • No new lesions: continue therapy<br>  • Additional ≥2 new lesions: progression<br>• **Subsequent scheduled reassessments:**<br>  • No new lesions: continue<br>  • New lesions: progression<br><br>• For delay/prevent end points (Progression)<br>• Exclude pseudo-progression in the absence of symptoms or other signs of progression<br>• At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)<br>• If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented. |

| | |
|---|---|
| | ○ For all scans after the first post-treatment scan, at least two new lesions<br>○ Date of progression is the date of the scan that first documents the second lesion |
| Frequency of assessment of bone scan or other CT scans | Every 8 to 9 weeks for the first 24 weeks, then every 12 weeks |

## 12.2 Disease Progression in Soft Tissue Lesions

Patients should be re-evaluated for response/disease progression every 8 weeks for the first 24 weeks, and then every 12 weeks. No confirmatory scan is required for soft tissue lesions following initial documentation of objective response.

Response and progression in soft-tissue lesions will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

### 12.2.1 Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Sn-117m-DTPA.

Evaluable for Objective Response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

### 12.2.2 Disease Parameters

Measurable Disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-Target Lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-Ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for PSA response (in recurrent prostate cancer)

have been published [*J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008].

12.2.4 Response Criteria

12.2.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.2.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.2.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will

depend on the achievement of both measurement and confirmation criteria.

**For Patients with Measurable Disease (*i.e.*, Target Disease)**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is Required* |
|---|---|---|---|---|
| CR | CR | No | CR | ≥4 wks. Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥4 wks. Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥4 wks. from baseline** |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD | Yes or No | PD | |
| Any | Any | Yes | PD | |

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

**For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)**

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.2.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.2.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.2.7 Response Review

N/A

## 13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

### 13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

### 13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

  Rave role requirements:
  - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
  - Rave Investigator role, must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR), and
  - Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

### 13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site

audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.2.3 Data Submission for PRO-CTCAE Assessments

Electronic collection of PRO-CTCAE through the Patient Cloud app is source documentation. The surveys are not stored on the devices. Rather, each survey is available for the timeframe set by the protocol. Once a patient submits the responses, the data goes directly from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules. For paper collection of PRO-CTCAE items, the CRA will need to manually enter the data into Rave at the site.

## 13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

## 13.4 CTEP Multicenter Guidelines

N/A

## 13.5 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI

under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group

studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

### 13.6 Genomic Data Sharing Plan

The investigators and statistician and/or bioinformaticians for the study will have access to all data on mutations and variants stored in the Theradex Data Base and GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals.

### 13.7 Incidental/Secondary Findings Disclosure Procedure

Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following disclosure procedure, consistent with the recommendations of the American College of Medical and Genomics (ACMG) (Green *et al.*, 2013 and Kalia *et al.*, 2016)

The NCLN Genomics Laboratory will review the mutations/variants once at the time of initial

specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review.

For each participant with a pathogenic or likely pathogenic germline and/or somatic variant detected in the WES of blood (as defined in the ACMG guidance), the NCLN Genomics Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding.

If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a Clinical laboratory Improvement Amendments (CLIA)-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling.

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## APPENDIX A 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 B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

| Race and Sex | Serum Creatinine (SCr), *µmol/L (mg/dL)* | Equation |
|---|---|---|
| **Black** | | |
| Female | ≤62 (≤0.7) | $GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$ |
| | >62 (>0.7) | $GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$ |
| Male | ≤80 (≤0.9) | $GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$ |
| | >80 (>0.9) | $GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$ |
| **White or other** | | |
| Female | ≤62 (≤0.7) | $GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$ |
| | >62 (>0.7) | $GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$ |
| Male | ≤80 (≤0.9) | $GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$ |
| | >80 (>0.9) | $GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$ |

SCr in mg/dL; Output is in mL/min/1.73 $m^2$ and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al.*, 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 $m^2$ and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

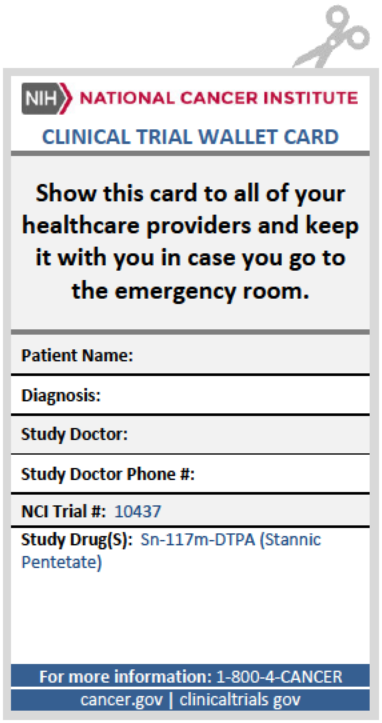
$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 $m^2$ with the patient's body surface area (BSA).

References

1. Levey, A.S., L.A. Stevens, C.H. Schmid, *et al*. (2009). A new equation to estimate glomerular filtration rate. *Ann Inter Med*. 150:604-612.
2. Levey, A.S., J. Coresh, T. Greene, *et al*. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 145:247-254.
3. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.

## APPENDIX C PATIENT CLINCAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

**Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.**

**Patient Name:**

**Diagnosis:**

**Study Doctor:**

**Study Doctor Phone #:**

**NCI Trial #:** 10437

**Study Drug(S):** Sn-117m-DTPA (Stannic Pentetate)

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials gov

## APPENDIX D BRIEF PAIN INVENTORY (SHORT FORM)

The Brief Pain Inventory (Short Form) is provided beginning on the next page.

1903

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject's Initials : _____

Study Subject #: ☐☐☐☐

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

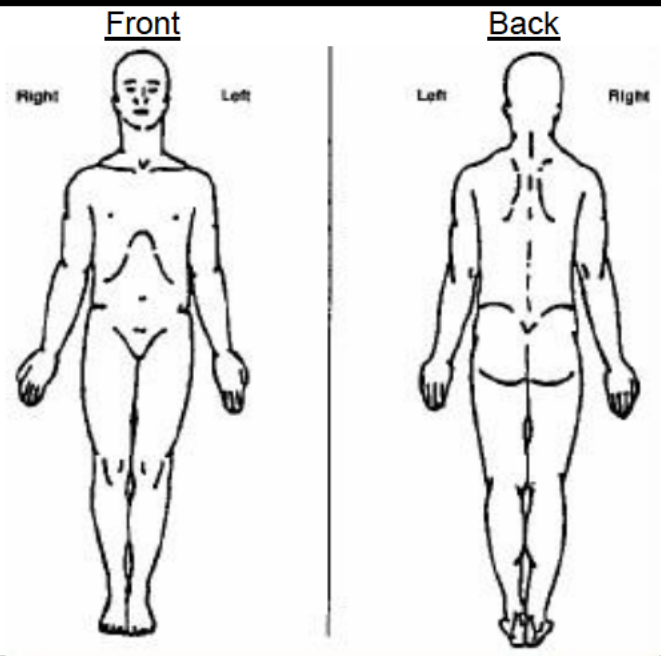
PLEASE USE BLACK INK PEN

# Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.




3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. **Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

1903

Date: (month) / (day) / (year)

Subject's Initials : _____

Study Subject #:

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

PLEASE USE BLACK INK PEN

## 7. What treatments or medications are you receiving for your pain?

## 8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0% ☐ No Relief | 10% ☐ | 20% ☐ | 30% ☐ | 40% ☐ | 50% ☐ | 60% ☐ | 70% ☐ | 80% ☐ | 90% ☐ | 100% ☐ Complete Relief

## 9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

**A. General Activity**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**B. Mood**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**C. Walking ability**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**D. Normal Work (includes both work outside the home and housework)**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**E. Relations with other people**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**F. Sleep**

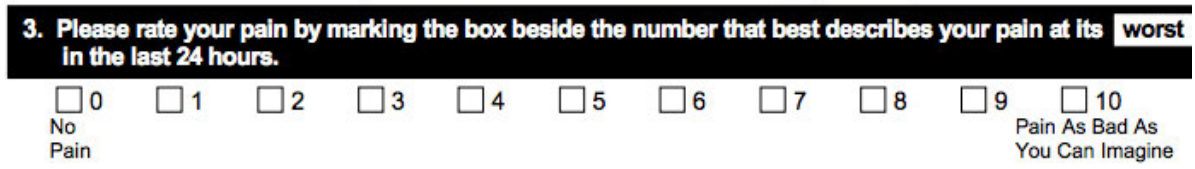
☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

**G. Enjoyment of life**

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

## APPENDIX E PATIENT PAIN INVENTORY AND ANALGESIC USE FORMS, PAPER FORMAT (IF DIGITAL IS NOT USED

**Pain intensity scale (Item #3 on the BPI-SF, worst pain)**




| Date | Pain scale |
|---|---|
| 09/19/20<br>(for example) | 6 |
| | |
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| | |

Analgesic use/consumption

| PATIENT-REPORTED ANALGESIC LOG | | | |
|---|---|---|---|
| Date | Decrease | Stable | increase |
| 09/19/20<br>(for example) | | X | |
| | | | |
| | | | |
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**APPENDIX F PATIENT'S PAIN MEDICATION LIST**

| Date | Medicine | Dose | How often taken in 24 hours |
|---|---|---|---|
| 09/19/20<br>(for example) | Oxycodone<br>Ibuprofen | 5 mg<br>400 mg | 5 times<br>3 times |
| | | | |
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## APPENDIX G TABLE OF PRO-CTCAE AND CTCAE ITEMS FOR COLLECTION

| System Organ Class | Sn-117m-DTPA - CAEPR | Possible Related PRO-CTCAE Items | Attributes |
|---|---|---|---|
| Gastrointestinal Disorders | | Constipation | Severity |
| | | Diarrhea | Frequency |
| | Nausea | Nausea | Frequency & Severity |
| | | Vomiting | Frequency & Severity |
| General Disorders and Administration Site Conditions | | Fatigue | Severity & Interference |
| Musculoskeletal and Connective Tissue Disorders | | General Pain | Frequency, Severity, Interference |
| | | Joint pain | Frequency & Severity |
| Nervous System Disorders | | Numbness and tingling | Severity & Interference |
| | | Dizziness | Frequency & Severity |
| Genitourinary System General | | Painful urination | Frequency & Severity |
| | | Urinary urgency | Frequency & Severity |
| | | Urinary frequency | Frequency & Severity |
| | | Change in usual urine color | Frequency & Severity |

# APPENDIX H MEDIDATA PATIENT CLOUD REGISTRATION

## a. Introduction

Electronic collection of patient-reported outcomes through Medidata Patient Cloud is preferred but not mandatory. Patients who will be submitting PRO data via Patient Cloud must be registered to Patient Cloud by an authorized site staff after the patient has been registered to the study. Patients may use their own device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to Patient Cloud with their passwords or their PIN codes on the same device.

## b. Patient Cloud Application Download

Note that there are multiple versions of the Medidata Patient Cloud Application. Patients should be instructed by the study team to download the Patient Cloud version. The patient will receive an error if the wrong version is downloaded.

**Patient Cloud ePRO**

**Patient Cloud**

## c. CRA Site Users

Site staff require access to the Patient Cloud application. This access is granted through the iMedidata, and is similar to the process of obtaining access to Rave studies. Site staff will receive an invitation to the Patient Cloud application which they must accept in order to begin registering patients. Staff that have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Medidata Account Activation and Study Invitation Acceptance instructions are located on the CTSU members' website under Data Management > Rave Resource Materials. Site staff will not be able to access the study in the Patient Cloud application until all required Rave and study specific trainings (eLearnings assigned in iMedidata) are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the Data Management tab and further under the Rave subtab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

## d. CRA Instructions for Setting the Patient Cloud App to Multi-User Mode

Sites conducting studies entirely on-premises, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to Patient Cloud with their passwords or their PIN codes on the same device. If

patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the Patient Cloud app to the device and set the Patient Cloud App to multi-user mode if applicable. **Verify the correct version is downloaded per the study build requirements. Note only 1 version of the app is active per protocol.

To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

**Note:** If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.
For a video demonstration, see Show Me How to Switch to Multi-User Mode.

**e. Patient Users**

To use the Patient Cloud application, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and data will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log into the Patient Cloud application with their passwords or their PIN codes on the same device. **Refer to Appendix H Section d on Setting the Patient Cloud App to Multi-User Mode.**

**f. Patient Instructions for Accessing the Patient Cloud Using Your Personal Device**

**Downloading the Patient Cloud App**

If you are using your personal device, and you do not have the Patient Cloud app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud app is already on the device, or if you are using a provider's device, you can skip this section. There are multiple versions of the app available. Ensure that the correct version of the Patient Cloud app is downloaded by the patient.
You will need an email address that you agree to use for this purpose. The e-mail address is needed to uniquely identify you on the Patient Cloud Application, and to reset your password if needed. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.
If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud app.
2. Tap the *App Store* icon.
3. Search for the appropriate Medidata Patient Cloud application and follow the installation instructions.

Note: Patient Cloud is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud app
2. Tap the *Play Store* icon.
3. Search for the appropriate Medidata Patient Cloud application and follow the installation instructions.

**Registering**

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud application.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud app.

1. If registering from the Patient Cloud, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your response to the security questions.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud app. You can then proceed to log in with the credentials you created.

**Logging in to the App**

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

**Setting a PIN Code**

The first time you log in to the Patient Cloud app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

**Resetting Your Password**

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

**Completing and Submitting Forms**

Once logged in, forms related to your study are displayed on the Tasks List page. Select a form, and complete and submit the form. New forms can appear on the Tasks List page at any time, depending on how the study is designed.
There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

To complete and submit form(s):

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you may be given the opportunity to review and change your responses prior to submitting.
3. If given the opportunity to review and update, review your responses by scrolling down the list; if you need to change an answer, tap the question to go back and change the answer.
4. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

**g. Patient Compliance**

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

**h. Security**

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.
The data will only reside on the device for a short period of time. Once the user clicks "Submit," the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The patient's email links the device (used) and (Patient Cloud) account to where the data is stored. The patient's email is not visible to anyone in the system.
The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.
The Patient Cloud application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).
Messages and information communicated to and from the Patient Cloud are encrypted and therefore this information cannot be read if intercepted while in transit.

**i. Site checklist for activities prior to consenting a patient**

Accept study invitation at iMedidata.com
- Site staff must be rostered in RSS and have received an invitation to Patient Cloud

Site staff must have already completed required eLearning assigned in iMedidata for the Patient Cloud application before gaining access to the study in Rave. See last bullet with hyperlink to training video library. Contact the LPO to request appropriate Rave access to register patients in Patient Cloud.
Verify the IOS or Android operating system is using the most current version
Verify the correct Patient Cloud app is being used. Note only 1 version of the app is active per protocol.
If using institutional shared devices, for the first patient only: Verify the Patient Cloud application is in Multi-User mode
Refer to Review Quick Reference Guides for videos and other procedural information

Note: Sites should consider copying this site checklist and placing it in the clinic or area where site is consenting patients to Patient Cloud and also copy the correct image and name of the app version with it to help remind staff and patients the correct version being used in the protocol.

*Select one*

**1.Patient Cloud ePRO**

**2. Patient Cloud**

## APPENDIX I HYGIENE/SAFETY INSTRUCTIONS FOR TREATMENT WITH SN-117M-DTPA

Patient Name _____
Date of Birth _____
Medical Record Number ____

You have received radioactive Tin DTPA to treat bone pain. After treatment, please follow the instructions below for the time indicated. These actions will keep you and your family safe.

| | |
|---|---|
| **10 Days** | **Contact with people:**<br>❑ Try to stay at least 3 feet away from others.<br>❑ Do not kiss anyone and do not have sex.<br>**Handling food and eating:**<br>❑ If you fix food for others, wash your hands well and wear gloves when doing so.<br>❑ Use separate eating utensils. Wash separately with soap and water.<br>❑ Drink at least two to three quarts of fluid every 24 hours for 14 days<br>❑ In general, drinking alcoholic beverages should be kept to a minimum or avoided completely.<br>**Washing and cleaning up:**<br>❑ Sit while you urinate. With the lid down, flush twice after each use.<br>❑ Wipe the toilet seat after each use.<br>❑ Cover your mouth and nose when you cough or sneeze.<br>❑ Wash your hands often. Always wash them after you use the toilet, cough, or sneeze.<br>❑ Wash your hands with soap and water. Do not use hand sanitizers or such products.<br>❑ Bathe or shower daily. Rinse out the sink, tub, and shower well after each use.<br>❑ Use separate towels and bed linens. Wash them separately. Do not share them.<br>❑ If you smoke, throw cigarettes into the toilet and flush away. Do not share cigarettes. |
| **30 Days** | **Contact with people:**<br>❑ Sleep in a separate bed.<br>❑ Avoid prolonged contact with others - a brief hug is OK.<br>❑ Do not nap with children or hold infants or children for extended periods of time.<br>❑ Avoid long (more than 4 hours) trips where you have to sit near others. |
| **6 Months** | ❑ If you plan to travel by air within 6 months after radioactive therapy, please inform the Radiation Safety Officer during the interview or call 859-257-7128 thereafter. |
| **Comments (if any):** | |

**If you have questions about these instructions, please call the Radiation Safety Officer at 859-257-7128. I understand and agree to follow these instructions.**

Patient/Guardian:_____Date/Time:____

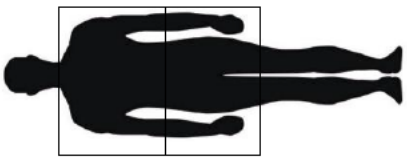
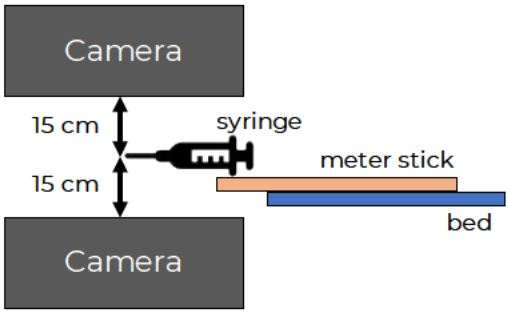
Radiation Safety Officer/Physician:_____Date/Time:_____

# APPENDIX J QUANTITATIVE IMAGING AND DOSIMETRY OF SN-117M-DTPA

| National Cancer Institute<br>Division of Cancer Treatment and Diagnosis<br>**Cancer Therapy Evaluation Program (CTEP)**<br>**Investigational Drug Branch** | Project Group: | |
|---|---|---|
| | National Cancer Institute (NCI) | Date Submitted: |
| | Cancer Therapy Evaluation Program (CTEP)<br>Investigational Drug Branch (IDB) | 20 August 2020 |
| 1. STANDARD OPERATING PROCEDURE: Quantitative Imaging and Dosimetry of Sn-117m-DTPA V1.0 | | |

Protocol items to incorporate as an Imaging & Dosimetry Appendix to NCI protocol #10437:

| | | |
|---|---|---|
| Characteristics of Sn-117m-DTPA | Tin(Sn)-117m(4+)-DTPA is primarily a conversion electron emitter (13.9-day half-life) with a monoenergetic gamma photon of 159 keV in 86% abundance. The gamma component allows for the *in vivo* quantification of total-body uptake and retention imaging. | |
| Purpose of imaging procedure | Secondary Objective: To measure Sn-117m-DTPA activity by gamma-camera dosimetry scans (serial chest, abdomen & pelvis planar images) obtained at 1 hour, 4 hours (or within 4-6 hours), 24 hours (or within 16-24 hours), 48 hours (or within 36-48 hours), 72 hours (or within 60-72 hours), 1 week (± days), and 4 weeks (±2 days) after the first agent injection. | |
| Dosage level | 20 mCi (first Sn-117m-DTPA injection) | |
| Radiation dose to main organs in men[1] (Gy/MBq) | Adrenals | 0.000164 |
| | Brain | 0.000180 |
| | Breasts | 0.000068 |
| | Gallbladder wall | 0.000086 |
| | Lower large intestine wall | 0.000124 |
| | Small intestine wall | 0.000102 |
| | Stomach wall | 0.000080 |
| | Upper large intestine wall | 0.000094 |
| | Heart wall | 0.000101 |
| | Kidneys | 0.000159 |
| | Liver | 0.000091 |
| | Lungs | 0.000112 |
| | Muscle | 0.000122 |
| | Ovaries | 0.000000 |
| | Pancreas | 0.000111 |
| | Red marrow | 0.006108 |
| | Osteogenic cells (bone surface) | 0.054864 |
| | Skin | 0.000087 |
| | Spleen | 0.000092 |
| | Testes | 0.000079 |
| | Thymus | 0.000091 |
| | Thyroid | 0.000122 |
| | Urinary bladder wall | 0.000170 |
| | Uterus | 0.000000 |
| | Whole body | 0.000535 |
| Patient preparation[2] | Patient should be asked to void prior to Sn-117m-DTPA injection in order to avoid the need to void within two hours of the start of the procedure.<br><br>Place an indwelling venous catheter in each arm, one for the Sn-117m-DTPA injection and the other for blood withdrawal. | |
| Field of views (FOVs) taken[2] | Anterior and posterior Whole Body Sweep. Chest, Abdomen & Pelvis—if there are relevant lesions, then additional views could be collected, as needed. After the first field is collected, the patient should remain on the couch without moving for subsequent imaging, if possible. | |

| | |
|---|---|
| |  |
| Imaging Time points (post-injection)[2] | 1 hour, 4 hours (or within 4-6 hours), 24 hours (or within 16-24 hours), 48 hours (or within 36-48 hours), 72 hours (or within 60-72 hours), 1 week (± days), and 4 weeks (±2 days) |
| Acquisition parameters for Whole Body Sweep | Collimator: low-energy, high-resolution parallel-hole collimators<br>Matrix: 256 x 1024<br># of projection views: 2, anterior and posterior whole body sweep<br>Scan rate: 10 cm per minute<br>Energy window setting (keV): 159 keV with a 20% window |
| Acquisition parameters for SPECT | Collimator: low-energy, high-resolution parallel-hole collimators<br>Matrix: 128 X 128<br>Time / view: 20 seconds per projection<br># of projection views: 64 projections per head with dual head system (128 total)<br>Angle range: 180 degrees with dual head system, 360 with single<br>Energy window setting (keV): 159 keV with a 20% window |
| Computed Tomography (CT) acquisition parameters for SPECT/CT[2] | CT scans should be low dose for attenuation mode and anatomic localization. Routine institutional parameters may be applied for these scans. |
| Quality control (QC) | Standard camera QC, as specified by the vendor, should be up to date on all cameras used for this study. Typical QCs include uniformity, linearity/spatial resolution, and center of rotation alignment. Dose calibrator QCs should also be routinely performed and documented (accuracy, consistency, linearity, and geometry). Sensitivity needs to be measured daily.<br><br>Suspend a calibration source (with known amount of Sn-117m-DTPA – 1 mCi) between the two camera heads (by taping it to a yard stick, and, supporting the stick on the bed). The source should be such that there are no attenuating materials between, including the bed or meter stick, between the source and collimator. Position the source so it is 15 ± 0.5 cm from the face of each collimator and collect a five (5) minute dual head single view scan (256x1024 matrix, same collimator/energy windows as above).<br><br>  |
| Recommended phantom calibration | It is recommended that a phantom calibration scan with either a NEMA PET IEC Body Phantom or an ACR Phantom be collected for each camera that may be used for Sn-117m-DTPA patient imaging. This scan is collected once prior to the use of the camera. The body of the phantom should be filled with water at room temperature removing as much of the air as possible. All spheres must be removed except the largest. The activity and measurement time of the syringe prepared earlier should be recorded. All the activity (1 mCi) contained in the syringe should be injected into the largest sphere (a long needle might be needed). Both, activity and measurement time after the injection (with needle on) must be recorded. The rest of the large sphere can be completely filled with water, using a new syringe and needle.<br><br>The image technician must make sure that the largest sphere is in place before putting the lid on the phantom and hand-tightening of the screws. The phantom should be placed flat side down on the bed (pad can be removed, if necessary) and in the middle of the camera field of view. SPECT and CT images should be acquired using pre-defined patient imaging protocol(s) and parameters used should be recorded. |

| | |
|---|---|
| Reporting requirements | Regions of interest will be drawn over normal bone and metastatic foci, and decay-corrected counts of pixels will be drawn from all seven Sn-117m-DTPA scans. Counts per pixels will be plotted against time. Time to peak will be noted for both normal and metastatic bone lesions. The slope of the curve will be monitored for washout. |
| Interpretation for dosimetry (or any other purpose) | No action. Results will be analyzed and used for publication to evaluate patient to patient variability and impact of tumor burden. Study will also provide accurate SPECT-imaging based dosimetry. |
| Step by step imaging procedure | Routine SPECT/CT imaging procedure in clinical practices should be used with the parameters specified above. |
| Data to send | Whole Body planar imaging, SPECT projections, attenuation map, and all CT slices (in DICOM format) |
| Calculation | The geometric mean counts from the planar anterior and posterior view counts (including the standard) in the first scan (1-hour post-injection prior to voiding) will be obtained as the square root of the anterior x posterior counts. The geometric mean counts of the standard will be subtracted from the total counts in the image, and, the net counts will be considered as 100% of the injected dosage. The net counts from subsequent scans will be corrected for physical decay. The geometric mean counts will be divided by the counts from the first study, and the results will be expressed as the percent injected dose retained. All results will be expressed as mean percent of injected dose ± standard deviation. The mean values will be analyzed by statistical t-tests using statistical software. Dosimetry software may be used. |
| Reference | 1. Atkins HL, Mausner LF, Srivastava SC, Meinken GE, Straub RF, Cabahug CJ, Weber DA, Wong CTC, Sacker DF, Madajewicz S, Park TL, Meek AG. Biodistribution of Sn-117m(4+)DTPA for palliative therapy of painful osseous metastases. *Radiology* 1993;186:279-283.<br>2. Krishnamurthy GT, Swailen FM, Srivastava SC, Atkins HL, Simpson LJ, Walsh TK, Ahman FR, Meinken GE, and Shah JH. Tin-117m(4+)DTPA: Pharmacokinetics and imaging characteristics in patients with metastatic bone pain. *J Nuc Med* 1997;38(2):230-237. |

**APPENDIX K Sn-117m-DTPA SITE ON-BOARDING FORM**
(see next page)

# ***Stannic-117m Pentetate (Sn-117m-DTPA) Site On-Boarding Form***

**Return Completed Form to the NCI Pharmaceutical Management Branch at:**
NCIPMBTRFDOCS@mail.nih.gov

| **Institution site name (to where Sn-117m-DTPA will be shipped):** | |
|---|---|
| **NCI Protocol Number:** | **CTEP TRF site code (to be completed by CTEP):** |

**Radiopharmaceutical Shipping Address (Street address):**

_____

**City** _____, **State** _____ **Zip** _____

**RADIOACTIVE MATERIAL LICENSE**

| **RAM license number:** | **RAM license attached (REQUIRED):** ☐<br><br>**Expiration Date:** **(DD-MMM-YYYY)** |
|---|---|

**If your RAM license does not list Authorized User personnel, submit an RSO provided list, along with this form and RAM license, of Authorized Users of Sn-177m-DTPA for medical use at your site; including, an RSO provided list of other personnel trained and credentialed by your RSO to handle, receive, store, dispense and destroy Sn-177m-DTPA waste.**

**Note: The RAM License, RSO provided Authorized User list and RSO provided Sn-177m-DTPA trained personnel list must contain the individuals identified in the following two subsections (Authorized User Physician Study Investigator and Study Shipping Contacts)**

**Validated Dose Calibrator for Sn-177m-DTPA:** ☐ **YES** ☐ **NO**

**Date of last calibration for Sn-177m-DTPA:** _____ **(DD-MMM-YYYY)**

**Attestor:** _____

**Sn-177m-DTPA AUTHORIZED USER (AU) PHYSICIAN STUDY INVESTIGATOR**

| **Primary AU Study Investigator Name (REQUIRED):** | **Address:** |
|---|---|

| | |
|---|---|
| **Phone Number:** | **E-Mail:** |
| **Secondary AU Study Investigator Name (OPTIONAL):** | **Address:** |
| **Phone Number:** | **E-Mail:** |
| **Sn-177m-DTPA STUDY SHIPPING CONTACTS** | |
| **Primary Shipping Contact Name (REQUIRED):** | **Address:** |
| **Phone Number:** | **E-Mail:** |
| **Secondary Shipping Contact Name (REQUIRED):** | **Address:** |
| **Phone Number:** | **E-Mail:** |

# Comments or Notes

**APPENDIX L Sn-117m-DTA ORDER FORM**
(see next page)

**Sn-117m-DTPA Order form**
**NCI Protocol 10437**

Send order to:

Kim Miller at
orders@isotherapeutics.com
(979) 848-0800
(receipt of order will be confirmed by Kim Miller)

Patient study ID# (OPEN-assigned study ID): _____

Date of birth: _____

Date order placed: _____

Weight of patient (kg): _____

Planned injected dose (0.28 mCi/kg): _____ mCi

Date to be received: _____

Date to be injected: _____

Send dose to (shipping address of authorized location):

_____
_____
_____
_____

Attn: _____
Tel: _____
Email: _____

**Submit order request at least one week prior to planned administration date.**