[18F]Fluciclovine Companion Imaging Study to Radium-223 and Radiotherapy in Hormone-Naïve Men with Oligometastatic Prostate Cancer to Bone (RROPE) Study: IIT Fluciclovine Prostate

Protocol Summary

IRB Approval Date of Current Version:	5/5/2022
University of Utah IRB #:	IRB_00113970
Sponsor:	HUNTSMAN CANCER INSTITUTE BLUE EARTH DIAGNOSTICS
Principal Investigator:	John Hoffman
Internal Staff and Sub-Investigators:	**Site Name** / **Staff Names** University of Utah: John Hoffman, Jonathan Tward, Kathryn Morton, Neeraj Agarwal, Kenneth Boucher, Lance Burrell, Zane Archibald, Jeffrey Yap, Matt Covington

This document was created using the ERICA Online System at the University of Utah. The document is created from study information approved by the IRB on the date listed above. Any alteration to the original content of this document may not be considered to represent the study as approved by the IRB.

Background and Introduction

This is a companion imaging study to IRB #102312 (A Phase 2 Study of Radium-223 and Radiotherapy in Hormone-Naïve Men with Oligometastatic Prostate Cancer to Bone). This companion imaging study is designed to obtain pre-therapy, mid-therapy and post-therapy [18F]Fluciclovine –PET/CT imaging assessments of prostate cancer metastatic to bone and correlate the results with standard 99mTc-MDP bone scintigraphy and CT imaging.

Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in the United States and second leading cause of cancer death. At diagnosis, approximately 10% of men will have bone metastases identified on 99mTc-MDP bone scintigraphy (Klatte et al., 2006). These bone metastases can result in skeletal related events (SREs) causing substantial morbidity (Pelger et al., 2001). Men with five or fewer prostate cancer bone metastases noted on initial bone scan have a 94%, two year survival rate, and a significantly favorable overall survival when compared to those with more lesions (Soloway et al., 1988). The current standard of care for men with overt metastatic disease is immediate androgen deprivation therapy (ADT) (NCCN Guideline, 2017). Long term androgen deprivation therapy results in a significant decrement in quality of life (Bellmunt, 2013) and a host of unfavorable side effects including but not limited to loss of libido, lack of energy, difficulty concentrating, hot flashes, decreased bone density, decreased muscle mass, and increased risk of heart attack and stroke. Although ADT will delay the appearance of tumor related symptoms in metastatic patients, there are no data that it prolongs overall survival (NCCN Guideline, 2017). Developing novel strategies to control metastatic prostate cancer with side effect profiles superior to that of ADT or other approved systemic agents is highly desirable. External beam radiation treatment is effective at controlling both primary and metastatic prostate cancers, and Radium-223 has demonstrated a survival benefit in castrate-resistant prostate cancers. Both forms of therapy have been shown to palliate painful bony lesions.

Imaging of Metastatic Prostate Cancer

Currently, standard-of-care imaging for prostate cancer staging as recommended by the National Comprehensive Cancer Network guidelines includes 99mTc-MDP bone scintigraphy and pelvic imaging with CT or MRI (NCCN Prostate Cancer Guideline 2017). This includes initial staging and subsequent re-staging often in the setting of early biochemical relapse after prostatectomy. Unfortunately, these imaging studies are generally uninformative. The prostate cancer that is present at this time is often very small and even micro-metastatic and escapes detection on conventional imaging. As a result, clinicians must often decide for or against further local therapy (e.g., salvage external beam radiation therapy for biochemical recurrence after prostatectomy) as guided by nomogram-based probabilities rather than anatomic localization. The goal in imaging is to have a much more sensitive, specific and accurate imaging procedure for initial as well as follow-up imaging of prostate cancer. A more sensitive imaging modality that could offer anatomic localization within the clinical setting of early PSA relapse would better inform treatment decisions and improve the management of patients with apparent recurrence based on PSA levels. Prostate cancer functional imaging with PET is presently used on a limited basis. Widely available, PET or PET/CT with [18F] fluorodeoxyglucose (FDG) is not standard of care imaging as FDG uptake is usually low in prostate cancer prior to the development of castration-resistant disease. [18F] sodium fluoride

PET is more sensitive than standard 99mTc-MDP bone scintigraphy, but both methods are non-specific and do not image cancer outside of the skeleton. Acetate- and choline-based PET tracers have been the subject of study but are not broadly approved and available. PET or PET/CT with the experimental L-leucine analog 18F-fluciclovine has demonstrated promise and is now approved for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment (Axumin 2016).

99mTc-MDP bone scintigraphy is the most commonly used technique to assess for metastatic bone disease. 99mTc-MDP is a nonspecific marker of osteoblastic activity accumulating in response to tumor as well as degenerative joint disease, benign fractures, and inflammation (Eustace et al., 1997; Hamaoka et al., 2004; Rybak et al., 2001). Another limitation of conventional 99mTc-MDP bone scintigraphy is that it only becomes positive at a fairly advanced stage of tumor infiltration, when osteoblastic reaction to metastatic cell deposit has occurred (Daldrup-Link et al., 2001). Sensitivities for tumor detection in bone as reported in the literature range between 62 and 89%. These levels are considered acceptable (Daldrup-Link et al., 2001). A major limitation to 99mTc-MDP bone scintigraphy is the low specificity. This has led to a decreased diagnostic accuracy and this has led to concern about the procedure in the literature (Jacobson et al., 1998; Schirrmeister et al., 1999). Due to this relatively poor diagnostic accuracy, regions of increased uptake cannot be definitively characterized as negative or positive for malignancy. Phrases such as “equivocal,” “possible,” “suspicious,” “likely,” “highly suspicious,” “almost certain,” may be found in the bone scan report as it is not possible to be definitive that the osteoblastic activity is from malignancy or another etiology. Often an equivocal area of concern will be obtained to look for evidence of metastatic disease versus a benign etiology (Gosfield et al., 1993). Despite the use of the radiograph to improve specificity, the combination of 99mTc-MDP bone scintigraphy and plain film x-ray is imperfect. The diagnosis may remain equivocal after this workup. In clinical practice, a normal bone radiograph associated with an abnormal scan is highly suggestive of bone metastasis (McKillop et al., 1980).

Computed tomography (CT) is an important tool in the management of almost all tumor types. It is the primary imaging modality used to stage patients as well as assess treatment response. It provides excellent resolution of cortical and trabecular bone. It is particularly helpful in assessing the ribs which have a high cortex to marrow ratio. It is possible to use dedicated bone algorithms on the acquired images to adjust the window and width and level. The resolution of the images is such that the skeleton can be viewed in multiple planes using multi-planar reformatted images. These techniques maximize the conspicuity of bone lesions. This in turn results in higher sensitivity of CT compared to plain radiography in detecting both lytic and blastic metastases. An advantage of using CT to assess metastatic bone disease or response is that these assessments can be performed at the time of staging or restaging. CT has limited soft tissue resolution when compared to MRI, but despite this limitation, CT can demonstrate bone marrow metastases before bone destruction occurs which results in earlier diagnosis and can improve prognosis and prevent complications (Bäuerle et al., 2009).

Clinical trials have demonstrated a role for CT in evaluating the sclerotic changes within a metastatic deposit. This change occurs in response to treatment of skeletal metastases with chemo/radiotherapy. The reactive sclerosis may be quantified by calculating the change in

Hounsfield units within metastatic deposits

Computed tomography (CT) has the highest sensitivity and specificity for the detection of osteoblastic metastases with high Hounsfield units (HU), CT has limitations in the detection of osteolytic and bone marrow metastases (Lange et al., 2016, Evangelista et al., 2012).

A list of references can be located in the full protocol.

Purpose and Objectives

This is a companion imaging study to IRB #102312 (A Phase 2 Study of Radium-223 and Radiotherapy in Hormone-Naïve Men with Oligometastatic Prostate Cancer to Bone). This companion imaging study is designed to obtain pre-therapy, mid-therapy and post-therapy [18F]Fluciclovine –PET/CT imaging assessments of prostate cancer metastatic to bone and correlate the results with standard 99mTc-MDP bone scintigraphy and CT imaging.

Positron emission tomography (PET) is a molecular imaging modality that can probe various aspects of tumor function and biology using a variety of radiolabeled imaging agents ("tracers"). Oncologic PET imaging has seen a dramatic rise in clinical utilization over the past decade for cancer detection, staging, and evaluating residual or recurrent disease following therapy. These clinical scans use the FDA approved PET radiopharmaceutical [18F]fluoro-2-deoxy-D-glucose (FDG), which accumulates in cells in proportion to GLUT transporter and hexokinase activity. FDG thus provides a measure of tissue glucose metabolism. On May 27, 2016 [18F] anti-FACBC ([18F]Fluciclovine) with the brand name of Axumin was approved for detection of recurrent prostate cancer (Axumin 2016). ([18F]Fluciclovine is a synthetic L-leucine analogue that is transported into cells but is not incorporated into proteins. Prostate cancer has upregulated amino acid utilization and thus increased [18F]Fluciclovine uptake. [18F]Fluciclovine provides a measure of tumor growth related to amino acid transport and utilization (Shoup and Goodman, 1999, Akhurst et al., 2006, Meirelles et al., 2006, Oka et al., 2007, Yu 2009, Yu 2010, Oka et al., 2012).

The patients will be hormone naïve and have 5 or fewer bone lesions and have no visceral metastatic disease. Treatment will include systemic Radium-223(6 possible treatments over approximately 6 months) and hypofractionated radiotherapy to oligometastatic sites. Certain patients may have progressive disease as determined on the primary protocol and will not receive additional Radium-223 treatments but will remain on the trial (IRB #102312).

These preliminary and exploratory data will provide information regarding visual and semi-quantitative [18F]Fluciclovine uptake and correlate these variables with changes in uptake on standard 99mTc-MDP bone scintigraphy and CT imaging. This unique situation will allow us to obtain an initial experience on the performance and correlation of [18F]Fluciclovine bone uptake in various metastatic subtypes (lytic, blastic, marrow, mixed) compared to standard imaging tests.

The hypothesis of this exploratory clinical trial in patients with prostate cancer metastatic to bone is that [18F]Fluciclovine–PET/CT uptake will correlate with the type of bone metastasis present (blastic, lytic, marrow, mixed) as has been seen in pre-clinical animal models. It is expected that lytic and marrow foci will exhibit the greatest [18F]Fluciclovine–PET/CT uptake.

The primary exploratory objectives of the study are:
• Abnormal [18F]Fluciclovine uptake on visual assessment will differ by the type of metastatic lesion present (blastic, lytic, marrow, mixed).
• SUVmax and SUVmean on [18F]Fluciclovine-PET/CT imaging will differ by the type of metastatic lesion present (blastic, lytic, marrow, mixed).

Secondary Exploratory Objectives are outlined below
• Determine if a 25% or greater reduction in aveSUVmax or aveSUVmean on [18F]Fluciclovine-PET/CT imaging after completion of all radiation therapy will be predictive of increased time to biochemical failure.
• Determine the correlation between the number of lesions, their visual uptake, and semi-quantitative uptake on 99mTc-MDP bone scintigraphy and [18F]Fluciclovine- PET/CT at baseline
• Determine the correlation between the number of lesions, their visual uptake, and semi-quantitative uptake on 99mTc-MDP bone scintigraphy and [18F]Fluciclovine- PET/CT after 3 and 6 cycles of treatment.

Study Population

Age of Participants: 18+

Sample Size:

At Utah:	15
All Centers:	18

Inclusion Criteria:

- Enrollment on IRB #102312 (A Phase 2 Study of Radium-223 and Radiotherapy in Hormone-Naïve Men with Oligometastatic Prostate Cancer to Bone).
- Patients must document their willingness to be followed for up to 24 months after recruitment by signing informed consent documenting their agreement to allow access to the data obtained on IRB #102312 and information and data entered into a research database.
- All patients, or their legal guardians, must sign a written informed consent and HIPAA authorization in accordance with institutional guidelines.

Exclusion Criteria:

- Patients with known allergic or hypersensitivity reactions to previously administered radiopharmaceuticals. Patients with significant drug or other allergies or autoimmune diseases may be enrolled at the Investigator's discretion.

- Patients who require monitored anesthesia for PET scanning.
- Patients who are too claustrophobic to undergo PET scanning.

Design

Prospective Biomedical Intervention or Experiment
Open Label Trial

Study Procedures

Recruitment/Participant Identification Process:

Patients must be enrolled on the parent study, 102312, so all patients will be recruited from that pool of patients. Once a new patient enrolls, the team for this study will be notified. Patients will not be approached with the approved consent form until the physician has first discussed the trial and assessed their interest.

Information regarding this study will be posted on the Huntsman Cancer Institute web site (www.huntsmancancer.org), which could be another source of recruitment, as well as the Cancer Learning Center at the Huntsman Cancer Hospital. The HCI web site posting is automatically generated at IRB approval and utilizes the Objectives & Eligibility criteria from the ERICA application via the OnCore interface.

Informed Consent:

Description of location(s) where consent will be obtained:

Private room at a hospital or clinic within the University of Utah's covered entity

Description of the consent process(es), including the timing of consent:

The consent form is given to the patient after initially discussing the trial with the treating physician. The patient is encouraged to take the consent home. The patient is allowed as much time as needed to consider fully if they want to participate in the study. The patient is encouraged to ask questions and to take the consent form home to discuss with family members or other physicians. There is no time limit on their decision, unless it impacts an immediate treatment decision. The consent process begins when the treating physician initially discusses the clinical trial with the potential participant. The consent form document is given to the patient for review. The participant is encouraged to take home the consent form for review and given contact information to contact the investigator and study team for any questions. After the patient has indicated their desire to participate, all elements of the document are reviewed and discussed. When all of the participants' questions have been answered, his or her signature will be obtained, either in person or remotely. Due to the large geographic area that the University of Utah's Covered Entity serves, travel to the clinic may be difficult for signing a document. We will allow participants to sign the document at a remote location and send to our site (via email, fax or mail) to initiate the screening process.

Patients who sign from a remote location will return their original ICF to the study team. If the original is unavailable, the patients will be asked to and sign another original in the presence of the study team.

Procedures:

As described in the consent form:

Your participation for this study will consist of a screening visit (today), and up to three additional imaging sessions: 1) prior to any tumor-directed radiation therapy; 2) between months 3 and 4 of treatment or follow up; and 3) at approximately 6-7 months.

Screening Visit

Before the study starts, you will be asked to sign this informed consent form, and a member of the Study Staff will ask you about your general health history, treatments you have had for your prostate cancer, if you take any over-the-counter or prescription medicines, vitamins, or herbs, and if you have any drug allergies.

The Study Staff will also record information from your medical records including previous blood test results, procedures, treatments, and plans for your prostate cancer treatment.

If you agree to participate in the study and you qualify for the study, then you will be scheduled for your first scan before you receive any treatment with Radium 223. The Study Staff will tell you when and where the PET/CT scan will be performed.

Day of Imaging Session 1: Baseline

Before the dosing of [^{18}F]Fluciclovine and the PET/CT scan, a member of the Study Staff will ask you questions about any changes to your general health and medications since your screening visit.

The following tests will be performed before dosing:

- Measurement of your height and weight
- Assessment of vital signs (blood pressure, heart rate, and temperature)

PET/CT Scan [^{18}F]Fluciclovine

The Study Staff will place an IV catheter (long, thin tube) into a vein in your arm. You will receive the [^{18}F]Fluciclovine injection through the catheter in your arm immediately before the scan. During the scan, you will lie on your back on the scanning bed. The bed will move slowly through the PET/CT scanner. The CT portion of the scan usually takes about 1 minute, and sends X-rays through your body that are measured by the CT camera. The PET portion of the scan begins immediately after the CT scan and will last about 60 minutes.

You should not exercise the day before the scan and until the scan is finished. Do not eat or drink for at least 8 hours before the scan; sips of water to take medication are permitted.

This entire visit should require approximately 2 to 3 hours of your time.

Immediately Following Each Scan

Immediately following the scan, a member of the study staff will obtain your vital signs, including your blood pressure, heart rate, and temperature.

Day after Each Scan (or up to 3 days after scan)

You will be contacted by a member of the Study Staff to discuss whether you have had any side effects within the 24 hours after you received the [^{18}F]Fluciclovine.

Day of Imaging Sessions 2 and 3: During Treatment and After Treatment with Radium 223

Similarly, prior to imaging sessions 2 and 3, a member of the Study Staff will ask you questions about any changes to your general health and medications since your screening visit.

The following tests will be performed before dosing:

- Measurement of your height and weight
- Assessment of vital signs (blood pressure, heart rate, and temperature)

PET/CT Scan [^{18}F]Fluciclovine

The process of placing an IV catheter, receiving the [^{18}F]Fluciclovine injection, and the approximate 60 minute scan will remain the same as described in the baseline imaging. You should not exercise the day before the scan and until the scan is finished. Do not eat or drink for at least 8 hours before the scan; sips of water to take medications are permitted.

This entire visit should require approximately 2 to 3 hours of your time.

Immediately Following Each Scan

Immediately following each scan, a member of the study staff will obtain your vital signs, including your blood pressure, heart rate, and temperature.

Day after Each Scan (or up to 3 days after scan)

You will be contacted by a member of the Study Staff to discuss whether you have had any side effects within the 24 hours after you received the [^{18}F]Fluciclovine.

Follow-up

You will be followed up for 24 months after you sign the consent form. This will be done by reviewing your medical records.

Procedures performed for research purposes only:

Statistical Methods, Data Analysis and Interpretation

Data Analysis

Qualitative and Visual Assessment. The images for the standard ^{99m}Tc-MDP bone scintigraphy and the [^{18}F]Fluciclovine-PET/CT will be visually assessed for any artifacts. The images will then be independently scored as described earlier for each imaging modality based on the level of uptake and confidence of tumor presence. The concordance of the agreement will be assessed and compared with the CT determination of metastasis type (lytic, blastic, mixed). Data will then be assessed and tabulated on a lesion by lesion basis for all of the imaging modalities over time as to the presence and the confidence of metastatic prostate cancer. Bland-Altman plots will be prepared.

Semi- and Fully-Quantitative Assessments.

The primary analysis of SUV_{max} and SUV_{mean} will be *t*-tests comparing the osteoblastic and osteolytic lesions. An additional analysis of the primary objective will be one way ANOVA with Tukey's post hoc analysis comparing all four lesion types (osteoblastic, osteolytic, marrow and mixed). As a secondary sensitivity analysis mixed effects models with a fixed effect for lesion type and a random patient effect will also be fit.

Spearman correlation of lesion uptake on ^{99m}Tc-MDP bone scintigraphy and [^{18}F]Fluciclovine- PET/CT at baseline and after 3 cycles of Radium 223 will be calculated. The number of lesions identified by ^{99m}Tc-MDP bone scintigraphy alone, [^{18}F]Fluciclovine-PET/CT alone, and both ^{99m}Tc-MDP bone scintigraphy and [^{18}F]Fluciclovine- PET/CT will be tabulated.

Spearman correlation of lesion uptake on ^{99m}Tc-MDP bone scintigraphy and [^{18}F]Fluciclovine- PET/CT at baseline and after 6 cycles will be calculated (6-7 months for those individuals who progressed). The number of lesions identified by ^{99m}Tc-MDP bone scintigraphy alone, [^{18}F]Fluciclovine- PET/CT alone, and both ^{99m}Tc-MDP bone scintigraphy and [^{18}F]Fluciclovine- PET/CT will be tabulated.

Time to biochemical failure will be analyzed using standard survival analysis methods. Two binary variables will be constructed, by dividing the cohort into those that did and did not achieve a 25% or greater reduction in $aveSUV_{max}$ or $aveSUV_{mean}$ on [^{18}F]Fluciclovine-PET/CT imaging after completion of all radiation therapy. Here $aveSUV_{max}$ and $aveSUV_{mean}$ are defined as the average SUV_{max} and the average SUV_{mean} across all identified lesions. Kaplan-Meier methods will be used for plotting and log rank tests will be used to

determine whether either of these binary variable is predictive of increased time to biochemical failure.

Justification of Sample Size

(Sample size calculations were prepared by Kenneth Boucher, Ph.D. of the HCI Biostatistics Resource)

This is a companion study to IRB #102312 (A Phase 2 Study of Radium-223 and Radiotherapy in Hormone-Naïve Men with Oligometastatic Prostate Cancer to Bone). The primary outcome of IRB #102312 is progression require ADT therapy. The planned accrual time is 12-24 months with an additional 24 months of follow up. We provide sample size justifications for the primary objective.

We focus on separate comparisons of the difference in SUV_{max} and SUV_{mean} in osteolytic vs osteoblastic lesions. Both SUV_{max} and SUV_{mean} are expected to be appreciably higher in osteolytic lesions. The data available for assessment of power is sparse. Oka reported tumor to background (T/BG) ratios of approximately 3 ± 1.0 and 4.5 ± 1.0 (mean $\pm$ SD) for ^{14}C-fluciclovine uptake in osteoblastic and osteolytic lesions respectively in bone metastasis models in mice (Oka et al. 2017). A recent human study by Janssen provides some information that can be used in the current study to determine the sample size (Janssen et al 2017). The study assessed [^{68}Ga]PSMA-HBED-CC uptake in osteolytic, osteoblastic, and bone marrow metastases in prostate cancer patients. It is expected that the [^{68}Ga]PSMA-HBED-CC and [^{18}F]Fluciclovine will behave similarly for the detection of bone metastases depending on the type (blastic, lytic, marrow, mixed). As reported in table 3 of that manuscript, a median SUV_{max} for [^{68}Ga]PSMA-HBED-CC imaging of 10.6 ± 7.1 and 24.0 ± 19.3 in osteoblastic and osteolytic bone metastases in prostate cancer patients with at least one bone metastasis (Janssen et al 2017, The number of osteolytic and osteoblastic lesions in the study were 21/154 (13.6%) and 80/154 (51.9%) respectively, and there were approximately 5 lesions per subject (154 lesions in 30 patients).

Guided by the data in Janssen (Janssen et al., 2017) we assume:

1. 5 lesions per subject. As in Janssen (Janssen et al., 2017) uptake of lesions in the same patient is assumed to be independent.
2. A standard deviation of 14.5 for mean SUV_{max} or SUV_{mean}.
3. The proportion of osteoblastic and osteolytic lesions will be 50% and 13% respectively.
4. The use of separate two sample *t*- tests at the one sided 0.05 significance level for comparison of SUV_{max} and SUV_{mean} between osteoblastic and osteolytic lesions.

With these assumptions a sample size of 18 evaluable subjects will provide 80% power to detect a difference of 14.7 in mean SUV_{max} or SUV_{mean} between osteolytic and osteoblastic lesions.