BED-IIT-382: Changes in ^{18}F-fluciclovine Positron Emission Tomography (PET) in Patients with Metastatic Castration Resistant Prostate Cancer Treated with Life-Prolonging Therapies: (A Pilot Study)

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Glossary:

ADT androgen deprivation therapy

AR androgen receptor

BAT bipolar androgen therapy

CI confidence interval

CT computerized tomography

ctDNA circulating tumor deoxyribonucleic acid

DNA deoxyribonucleic acid

ECOG PS performance status

HR hazard ratio

LHRH luteinizing hormone-releasing hormone

mCRPC metastatic castration-resistant prostate cancer

NGS next-generation sequencing

PARP poly ADP ribose polymerase

PCWG3 prostate cancer working group 3

PET positron emission tomography

PSA prostate-specific antigen

RECIST response evaluation criteria in solid tumors

SBRT stereotactic body radiation therapy

Synopsis:

PROJECT TITLE:

Changes in ^{18}F-fluciclovine Positron Emission Tomography (PET) in Patients with Metastatic Castration Resistant Prostate Cancer Treated with Life-Prolonging Therapies: A Pilot Study

RATIONALE:

Prostate cancer is the most common non-cutaneous cancer in men and the second leading cause of cancer-related death in the United Sates, with 164,690 estimated cases leading to 29,430 deaths, in 2018.[1] While the incidence of localized prostate cancer has begun to decline in the last few years as a result, at least in part, due to the change in the recommendations for prostate-specific antigen (PSA) screening by the U.S. Preventive Task Force[2], the number of patients diagnosed with metastatic prostate cancer has increased over 2.7% per year after 2012.[3]

Similar to breast cancer, prostate cancer is a hormonally driven disease and androgens are key in the growth of both normal prostate and prostate cancer cells. While androgen deprivation therapy (ADT) has become the cornerstone of medical treatment for metastatic disease after the studies from Charles Huggins and Clarence Hodges in 1941, ultimately all patients eventually progress in the setting of castrate levels of serum testosterone (< 50 ng/dL) and thus develop metastatic castration-resistant prostate cancer (mCRPC).[4,5] Once mCRPC is evident, most patients receive a second-generation hormonal therapy to further suppress the synthesis of androgens (abiraterone) and to block androgen receptor (AR*)* activation, nuclear translocation and DNA binding (enzalutamide).[6,7] Abiraterone acetate (abiraterone) and enzalutamide were approved in this setting based on the results of two large phase III trial in patients with mCRPC who had not received previous chemotherapy.[8,9] Our internal data and other published data show that most responses are detectable by 12 weeks, and this is in line with published data on PSA changes at 12 weeks and overall survival, hence we emphasize this early time point as a way to assess these patients relatively early in their treatment course.[8,10]

In addition to novel hormonal therapies, life-prolonging therapies also include chemotherapy with docetaxel [11,12] and cabazitaxel[13], the alpha-emitter radium-223[14] and the autologous active cellular immunotherapy sipuleucel-T[15] based on the pivotal phase 3 trials that demonstrated an overall survival advantage in CRPC setting. More recently, the poly ADP-ribose polymerase (PARP) inhibitor olaparib has also demonstrated a survival advantage over the physician's choice of enzalutamide or abiraterone among men with mCRPC who had qualifying

alterations in homologous recombination repair genes and whose disease has progressed during previous treatment with a next generation hormonal agent.[16]

The management of patients with metastatic prostate cancer continues to rapidly change with more and more patients being offered treatment intensification with the addition of chemotherapy or novel hormonal therapy to castration in the castration-sensitive setting.[17] Consequently, and since the findings of the phase III CARD trial have shown cabazitaxel to be superior to next generation hormonal agent for mCRPC patients previously treated with docetaxel and next generation hormonal agent, the sequence of two novel hormonal therapies is being used less frequently.[18]

While data with functional imaging in the metastatic setting is lacking, conventional imaging of prostate cancer has known limitations in staging, restaging after biochemical relapse, and response assessment. Functional imaging with positron emission tomography (PET) can target various aspects of tumor biology and is clearly superior in the detection of extra-prostatic disease. A number of PET tracers are available and/or in development, including FDG, ^{18}F-NaF, ^{11}C-choline, ^{18}F-choline, ^{68}Ga-PSMA, ^{18}F-PSMA, and ^{18}F-fluciclovine (Axumin™).

^{18}F-fluciclovine is a synthetic amino acid transported across mammalian cell membranes by amino acid transporters that are upregulated in prostate cancer cells.[19,20] ^{18}F-fluciclovine was approved by the US FDA for PET imaging to identify sites of prostate cancer recurrence in men with elevated prostate specific antigen (PSA) following prior definitive treatment.[21] This approval was based on two prospective studies comparing ^{18}F-fluciclovine with histopathology results[22,23] and with ^{11}C-choline PET in patients with biochemical recurrent prostate cancer.[24] These compared the efficacy and safety of ^{18}F-fluciclovine with ^{11}C-choline PET and biopsy results, revealing a very good performance in terms of lesion detection rate for low, intermediate and high PSA levels, with higher sensitivity than ^{11}C-choline PET.

Based on the observations above and the lack of data in the advanced setting especially in the CRPC setting for disease monitoring, we propose to conduct a pilot phase II study describing the changes in ^{18}F-fluciclovine PET scan in mCRPC patients treated with life-prolonging therapies and compare these results with PSA, conventional CT and bone scans. Initially, this study was designed to include mCRPC patients treated with abiraterone-prednisone, yet the changes in the management of metastatic disease support the changes in the eligibility criteria to include other life-prolonging therapy in the CRPC setting. This study will exclude treatment with radium-223 due to the very different mechanism of action of this agent and the heterogeneous response between skeletal metastases that may exist.

The results of this study can potentially leverage further data supporting the use of ^{18}F-fluciclovine for response assessment in the metastatic setting. Furthermore, we are extremely interested in understanding disease heterogeneity and how PET scans depict both early responses and possible heterogeneous progression.

We hypothesize that using ^{18}F-fluciclovine PET scanning will allow a more sensitive assessment of mCRPC patients at the initiation of systemic therapy and changes observed in ^{18}F-fluciclovine PET will correlate better with the serologic changes in PSA, allowing superior disease monitoring, as compared to conventional imaging modalities. In addition, we hypothesize that ^{18}F-fluciclovine PET will detect heterogeneity in disease response and thus identify potential lesions amenable to targeted therapy. We hypothesize that the PET scan will detect more disease than conventional scanning and thus provide more sensitive, and earlier information about tumor response to life prolonging-therapies than conventional scanning. Exploratory objectives are to understand disease heterogeneity and possible heterogeneous progression and change in patient management as well as to compare the ^{18}F-fluciclovine PET findings with genomic alterations found in ctDNA especially in the AR gene, using an NGS assay of patients with mCRPC treated with life prolonging-therapies.

STUDY DESIGN: This is a pilot phase 2 single-arm study of men with mCRPC. Patients will have a baseline ^{18}F-fluciclovine PET scan, then treated with a life-prolonging therapy (ie, abiraterone acetate, enzalutamide, docetaxel) for mCRPC. After 12 weeks they will have a second ^{18}F-fluciclovine PET scan and then move to the follow-up phase of the study for 2 years.

TREATMENT PLAN:

We will include adult patients with mCRPC, with a detectable baseline PSA of at least 2 ng/mL. Evidence of metastatic disease is required but measurable disease (RECIST version 1.1) is not a prerequisite on conventional staging scans (CT and bone scans) done within 42 days of starting a life-prolonging therapy. The use of docetaxel in the hormone-sensitive setting is allowed.

After informed consent, patients will get a screening ^{18}F-fluciclovine PET scan before starting a life-prolonging therapy for CRPC and only patients with a positive PET scan (study procedure) will be included in the study. Patients will repeat both ^{18}F-fluciclovine PET scan and conventional CT and bone scans 12 weeks after starting abiraterone therapy or earlier if disease progression (by serologic or clinical criteria) is noted, per physician's discretion. All ^{18}F-

fluciclovine PET/CT scans will be interpreted by a single trained reader and with the same camera at Tulane University.

When feasible, a next generation sequencing (NGS) testing of ctDNA (Guardant360 assay) and a germline testing (Invitae assay) will be conducted at baseline; a repeated NGS testing of ctDNA will also be repeated at 12 weeks following initiation of the therapy of choice.

Patients will be treated with any of the approved life-prolonging therapies: abiraterone 1000 mg daily plus prednisone 5 mg (or dexamethasone 0.5 mg) daily, enzalutamide 160 mg daily, or docetaxel 50 mg/m2 every two weeks or 75 mg/m2 every three weeks. All patients will remain on luteinizing hormone-releasing hormone (LHRH) agonist therapy, except those who have been surgically castrated. At week 1 and 12, we will assess patients for PET-CT scan related toxicity, clinical evaluation and with standard laboratory measures including but not limited to complete blood count, complete metabolic panel, prostate specific antigen (PSA) and testosterone. The clinical evaluation will be at the discretion of the treating physician with clinical visits, imaging and laboratory tests based on routine clinical practice. Objective response for patients with measurable disease will be defined using RECIST version 1.1. PSA progression will be defined as a repeated increase in PSA of at least 2 ng/dL and 25% from nadir values, at least 1 week apart, according to PCWG3 criteria and clinical or radiographic progression by RECIST version 1.1.[25] PSA response will be defined as a ≥50% decline from baseline.

Patients may remain on their assigned therapy in the setting of PSA progression, if the treating physician believes the patient is still gaining clinical benefit. Patients with a treatment delay of longer than 4 weeks due to toxicity will be discontinued from treatment. The duration of therapy and dose adjustments is allowed at the discretion of the treating physician to ensure patient´s safety.

OBJECTIVES: The primary objective of the study is to describe the ^{18}F-fluciclovine PET findings for patients with mCRPC prior to starting treatment with first line life-prolonging therapy (i.e., abiraterone acetate, enzalutamide, docetaxel-based regimen), and at 12 weeks after therapy initiation.

Secondary objectives include a comparison of ^{18}F-fluciclovine PET with conventional CT and bone scans for patients with mCRPC prior to starting first-line mCRPC treatment, and at 12 weeks later; and to correlate these changes with PSA response and progression.

Exploratory objectives are to understand disease heterogeneity and possible heterogeneous progression and change in patient management as well as to compare the ^{18}F-fluciclovine PET

findings with genomic alterations found in ctDNA especially in the AR gene, using an NGS assay of patients with mCRPC treated with life prolonging therapies.

STUDY POPULATION: Adult patients (18 years or older) with mCRPC according to serologic, radiographic or clinical criteria, despite a castrate concentration of testosterone of ≤ 50 ng/dL.

NUMBER OF PATIENTS: 12

PATIENT SELECTION CRITERIA

INCLUSION CRITERIA

1. ECOG Performance status 0-2;
2. Age ≥ 18 years;
3. Histologically confirmed adenocarcinoma of the prostate;
4. Ongoing use of LHRH required in the absence of surgical castration and castrate concentration of testosterone (≤50 ng/dL);
5. Detectable PSA of at least 2 ng/dL;
6. Metastatic disease documented by CT or bone scan within 42 days of cycle 1 day 1
7. Life expectancy of ≥ 6 months;
8. Must have disease progression despite a castrate concentration of testosterone of ≤ 50 ng/dL based on:
    A. PSA progression defined as increase in PSA of at least 2 ng/dL and 25% from nadir values of prior therapy, determined by 2 separate measurements taken at least 1 week apart;

    And/or

    B. Radiographic disease progression based on RECIST 1.1 for soft tissue disease and/or ≥2 new bone lesions for bone-only disease;
9. No prior life-prolonging therapies for mCRPC are allowed;
10. The use of docetaxel in the mHSPC setting is allowed;
11. Low dose prednisone (10 mg or less) or equivalent is allowed;
12. Acceptable liver function (within 28 days from enrollment) defined as:
    A. Bilirubin < 2.5 times upper limit of normal (ULN), except for patients with known Gilbert disease (in such cases bilirubin < 5 times ULN)
    B. AST (SGOT) and ALT (SGPT) < 3 times ULN

13. Acceptable renal function (within 28 days from enrollment):
    A. Serum creatinine ≤ 2.0 x ULN or creatinine clearance ≥30 mL/min
14. Acceptable hematologic status (within 28 days from enrollment):
    A. Absolute neutrophil count (ANC) ≥ 1000 cell/mm^3 (1 x 10^9/L)
    B. Platelet count ≥ 100,000 platelet/mm^3 (100 x 10^9/L)
    C. Hemoglobin ≥ 9 g/dL
15. At least 2 weeks since prior radiation before starting life-prolonging therapy of choice;
16. Able to understand and willing to sign a written informed consent document;
17. Patients who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 1 week after last dose of abiraterone acetate;

EXCLUSION CRITERIA

1. Pathological findings consistent with small cell carcinoma of the prostate;
2. Treatment with radium-223;
3. Patients with normal ^{18}F-fluciclovine PET/CT scans at baseline;
4. Known allergies, hypersensitivity, or intolerance to ^{18}F-fluciclovine or their excipients;
5. Major surgery (e.g., required general anesthesia) within 2 weeks before screening;
6. Uncontrolled active infection (including hepatitis B or C or AIDS). Patients with hepatitis B/C who have disease under control and no significant liver function impairment, and undetectable viral load will be allowed to participate; Similarly, patients with known HIV and ≥ 400 CD4+ T cells are allowed to participate;
7. Evidence of other metastatic malignancies within the last year;
8. Evidence of serious and/or unstable pre-existing medical, psychiatric or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study;

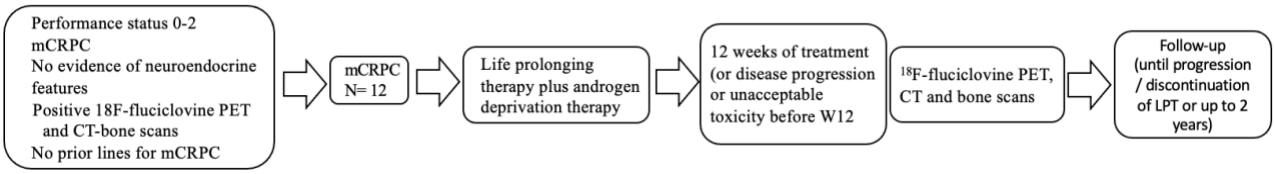
STUDY ENDPOINTS:

PRIMARY: ^{18}F-fluciclovine PET findings within 42 days prior to start of treatment with first line mCRPC life-prolonging therapy and at 12 weeks after therapy initiation;

SECONDARY: Comparison of ^{18}F-fluciclovine PET with conventional CT and bone scans, as well as PSA changes, for patients with mCRPC prior to starting treatment for mCRPC, and at 12 weeks later;
Comparison of PET scan (study procedure) findings to PSA response and progression;

EXPLORATORY: Understand disease heterogeneity and possible heterogeneous progression and change in patient management
Compare the ^{18}F-fluciclovine PET findings with genomic alterations found in ctDNA especially in the AR gene, using an NGS assay of patients with mCRPC treated with a life-prolonging therapy.

STUDY SCHEMA:



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1 Background and Study Rationale

1.1 Background

Metastatic Castrate Resistant Prostate Cancer

Prostate cancer, though the most common cancer among men, has proven to be an extraordinarily diverse and challenging conundrum for clinicians, researchers and patients.[1] African American men have about 60% greater incidence of being diagnosed with prostate cancer and nearly two-fold greater chance of dying from the disease than Caucasian men, yet the underlying cause for this increased mortality remains controversial.[26,2728]

Since the work of Dr. Huggins and Dr. Hodges almost 80 years ago, androgen suppression has been the mainstay of treatment for advanced prostate cancer.[29] Despite suppressed levels of testosterone, the disease invariably progresses to CRPC, usually with metastases.

Persistent activation of the androgen-AR axis underlies resistance to ADT and progression to mCRPC.[30] Once mCRPC is evident, most patients receive a second-generation hormonal therapy to further suppress the synthesis of androgens (abiraterone) and to block AR activation, nuclear translocation and DNA binding (enzalutamide), based on pivotal phase III trials showing that further inhibition of the AR pathway translates into further disease control and prolongation of overall survival.[6,7] Clinically, most patients respond to abiraterone or enzalutamide initially, but subsequent tumor progression occurs in nearly all of them, typically after 9 to 16 months with either agent.[6,7]

In addition to novel hormonal therapies, life-prolonging therapies include chemotherapy with docetaxel [11,12] and cabazitaxel[13], the alpha-emitter radium-223[14] and the autologous active cellular immunotherapy sipuleucel-T[15] based on the pivotal phase 3 trials that demonstrated an overall survival advantage in CRPC setting. More recently, the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib has also demonstrated a survival advantage over the physician's choice of enzalutamide or abiraterone among men with mCRPC who had qualifying alterations in homologous recombination repair genes and whose disease has progressed during previous treatment with a next generation hormonal agent.[16]

The management of patients with metastatic prostate cancer continues to rapidly change with more and more patients being offered treatment intensification with the addition of chemotherapy or novel hormonal therapy to castration in the castration-sensitive setting.[17] Consequently, and since the findings of the phase III CARD trial have shown cabazitaxel to be superior to next generation hormonal agent for mCRPC patients previously treated with docetaxel

and next generation hormonal agent, the sequence of two novel hormonal therapies is being used less frequently.[18]

Novel Imaging Techniques

For the first time in 1995, Hellman and Weichselbaum introduced the concept of oligo- (Greek "oligo": few) metastatic state as an intermediate state in the malignancy spectrum between localized disease and prior to disseminated disease.[31] The definition of oligometastatic prostate cancer is not consensual but usually includes patients with up to five extra-pelvic lesions on conventional imaging.[32,33]

The rise in the diagnosis of oligometastatic prostate cancer is likely due to multiple factors, that may include closer monitoring of patients, improved survival secondary to emergent agents and most of all advances in imaging techniques.[34]

Conventional imaging of prostate cancer has known limitations in staging, restaging after biochemical relapse, and response assessment. Functional imaging with PET scans (study procedure) can target various aspects of tumor biology and is clearly superior in the detection of extra-prostatic disease. A radionuclide produced from either a cyclotron or a generator is attached to a biologically active molecule to form a PET radiotracer. A number of PET tracers have been developed specifically for prostate cancer in the last few years and are now available or under investigation (^{18}F-NaF, ^{11}C-choline, ^{18}F-choline, ^{68}Ga-PSMA, ^{18}F-PSMA and ^{18}F-fluciclovine).

PSMA agents labeled with ^{68}Ga, ^{18}F and ^{18}F-fluciclovine are being increasingly used in this field. ^{18}F-fluciclovine is a synthetic amino acid transported across mammalian cell membranes by amino acid transporters that are upregulated in prostate cancer cells.[19,20] ^{18}F-Fluciclovine was recently approved by the US FDA for PET imaging to identify sites of prostate cancer recurrence in men with elevated prostate specific antigen (PSA) following prior definitive treatment.[21] This approval was based on two prospective studies comparing ^{18}F-fluciclovine (Axumin™) with histopathology results[22,23] and with ^{11}C-choline PET in patients with biochemical recurrent prostate cancer.[24] These studies compared the efficacy and safety of ^{18}F-fluciclovine with ^{11}C-choline PET/CT and biopsy results, revealing a very good performance in terms of lesion detection rate for low, intermediate and high PSA levels, with higher sensitivity than ^{11}C-choline PET.

While the benefit of ^{18}F-fluciclovine PET is established, the role of this imaging to monitor response to mCRPC therapies is largely unknown. We hypothesize that using ^{18}F-fluciclovine PET scanning will allow a more sensitive staging of mCRPC patients at time of starting systemic therapy and changes observed in ^{18}F-fluciclovine PET will correlate better with the serologic changes in PSA, allowing better disease monitoring. In addition, we hypothesize that ^{18}F-fluciclovine PET will

detect heterogeneity in disease response and thus identify potential lesions for SBRT. We hypothesize that the PET scan (study procedure) will detect more disease than conventional scanning and thus give more sensitive, and earlier, information about tumor response than conventional scanning. Lastly, we hypothesize that the functional changes observed in ^{18}F-fluciclovine PET scans will correlate with genomic alterations found in ctDNA, especially in the AR gene, using a commercially available NGS assay (Guardant) of mCRPC patients.

1.2 Patient Selection Criteria

INCLUSION CRITERIA:

1. ECOG Performance status 0-2;
2. Age ≥ 18 years;
3. Histologically confirmed adenocarcinoma of the prostate;
4. Ongoing use of LHRH required in the absence of surgical castration and castrate concentration of testosterone (≤ 50 ng/dL);
5. Detectable PSA of at least 2 ng/dL;
6. Metastatic disease documented by CT or bone scan within 42 days of cycle 1 day 1
7. Life expectancy of ≥ 6 months;
8. Must have disease progression despite a castrate concentration of testosterone of ≤ 50 ng/dL based on:
    A. PSA progression defined as increase in PSA of at least 2 ng/dL and 25% from nadir values of prior therapy, determined by 2 separate measurements taken at least 1 week apart;

    And/or

    B. Radiographic disease progression based on RECIST 1.1 for soft tissue disease and/or ≥2 new bone lesions for bone only disease;
9. No prior life-prolonging therapies for mCRPC are allowed;
10. The prior use of docetaxel in the mHSPC setting is allowed;
11. Low dose prednisone (10 mg or less) or equivalent is allowed;
12. Acceptable liver function (within 28 days from enrollment) defined as:
    A. Bilirubin < 2.5 times upper limit of normal (ULN), except for patients with known Gilbert disease (in such cases bilirubin < 5 times ULN)
    B. AST (SGOT) and ALT (SGPT) < 3 times ULN

13. Acceptable renal function (within 28 days from enrollment):
    A. Serum creatinine ≤ 2.0 x ULN or creatinine clearance ≥30 mL/min
14. Acceptable hematologic status (within 28 days from enrollment):
    A. Absolute neutrophil count (ANC) ≥ 1000 cell/mm^3 (1 x 10^9/L)
    B. Platelet count ≥ 100,000 platelet/mm^3 (100 x 10^9/L)
    C. Hemoglobin ≥ 9 g/dL
15. At least 2 weeks since prior radiation before starting life-prolonging therapy of choice;
16. Able to understand and willing to sign a written informed consent document;
17. Patients who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 1 week after last dose of abiraterone acetate.

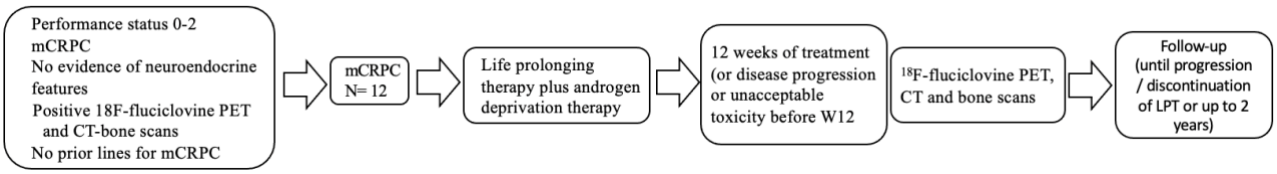
EXCLUSION CRITERIA

1. Pathological findings consistent with small cell carcinoma of the prostate;
2. Treatment with radium-223 for metastatic CRPC;
3. Patients with normal ^{18}F-fluciclovine PET/CT scans at baseline;
4. Known allergies, hypersensitivity, or intolerance to abiraterone, prednisone, ^{18}F-fluciclovine or their excipients;
5. Any chronic medical condition requiring ≥ 10 mg daily of systemic prednisone (or equivalent)
6. Major surgery (e.g., required general anesthesia) within 2 weeks before screening;
7. Uncontrolled active infection (including hepatitis B or C or AIDS). Patients with hepatitis B/C who have disease under control and no significant liver function impairment, and undetectable viral load will be allowed to participate; Similarly, patients with known HIV and ≥ 400 CD4+ T cells are allowed to participate;
8. Evidence of other metastatic malignancies within the last year;
9. Evidence of serious and/or unstable pre-existing medical, psychiatric or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study.

2 Trial Design

This is a pilot phase 2 single-arm study at Tulane University, New Orleans, of 12 men with mCRPC beginning treatment with standard of care life prolonging therapy (ie, abiraterone 1000 mg daily plus prednisone 5 mg or dexamethasone 0.5 mg daily, enzalutamide 160 mg daily, docetaxel 50 mg/m2 every two weeks or 75 mg/m2 every three weeks). This study will: 1) describe the ^{18}F-fluciclovine PET findings for patients with mCRPC prior to starting treatment with first line mCRPC life prolonging therapy, and at 12 weeks after therapy initiation with an emphasis on understanding the heterogeneity of lesions. This study will begin after approval by the Institutional Review Board at Tulane University and all accrued patients will provide informed consent. All ^{18}F-fluciclovine PET/CT scans will be interpreted by a single trained reader and with the same camera at Tulane University.

Study Design Schematic



3 Objectives of the Trial

3.1 Primary objective

- To describe the ^{18}F-fluciclovine PET findings for patients with mCRPC prior to starting treatment with first line mCRPC life-prolonging therapy and at 12 weeks later, with an emphasis on understanding the heterogeneity of lesions.

3.2 Secondary Objectives

- To compare ^{18}F-fluciclovine PET with conventional CT and bone scans, as well as PSA changes for patients with mCRPC prior to starting treatment for mCRPC, and at 12 weeks later;

- Comparison of PET results with PSA changes.

3.3 Exploratory Objectives

- Understand disease heterogeneity and possible heterogeneous progression and change in patient management
- To compare the ^{18}F-fluciclovine PET findings with genomic alterations found in ctDNA especially in the AR gene, using a commercially available NGS assay (Guardant360) in patients with mCRPC treated with first-line therapy.

4 Study Treatments, Procedures and Treatment Scheme

4.1 Study Treatment

After eligibility and informed consent procedures, patients will get a baseline ^{18}F-fluciclovine PET scan as well as the required conventional CT and bone scans (standard of care). Patients will be treated with any of the approved life-prolonging therapies: abiraterone 1000 mg daily plus prednisone 5 mg (or dexamethasone 0.5 mg) daily, enzalutamide 160 mg daily, docetaxel 50 mg/m2 every two weeks or 75 mg/m2 every three weeks. All patients will remain on luteinizing hormone-releasing hormone (LHRH) agonist therapy, except those who have been surgically castrated. We will assess patients on day one of each cycle for toxicity both clinically, and with standard laboratory measures including complete blood count, complete metabolic panel and prostate specific antigen (PSA). Patients will repeat both ^{18}F-fluciclovine PET/CT scan and conventional CT and bone scans 12 weeks after starting a life prolonging therapy or earlier if disease progression (by serologic or clinical criteria) is noted, per physician's discretion. Objective response for patients with measurable disease will be defined using RECIST version 1.1. PSA progression will be defined as a repeated increase in PSA of at least 2 ng/dL and 25% from nadir values, at least 1 week apart, according to PCWG3 criteria and clinical or radiographic progression by RECIST version 1.1.[35]

Patients may remain on therapy in the setting of PSA progression, if the treating physician believes the patient is still gaining clinical benefit. Patients with a treatment delay of longer than 4

weeks due to toxicity will be discontinued from treatment. The duration of therapy and dose adjustments is allowed at the discretion of the treating physician.

4.1.1 Treatment Scheme

Patients can remain on therapy indefinitely if clinically benefiting, at the discretion of the treating physician. Patients will have PSA level checked on day 1 of every cycle. Staging scans (CT and bone scans) as well as ^{18}F-fluciclovine PET scan will be done at baseline and then 12 weeks after starting a life prolonging therapy. Patients will remain on treatment until evidence of clinical or radiographic progression as determined by the Principal Investigator (PI), RECIST version 1.1[35] (for measurable disease) or PCWG3 criteria[25] (if no measurable disease) respectively. PSA progression will be defined as repeated increase in PSA of at least 2 ng/dL and 25% from nadir values, according to PCWG3 criteria[25]. Patients may remain on therapy in the setting of PSA progression without clinical and/or radiographic progression, per treating physician´s choice. Patients with a treatment delay of longer than 4 weeks due to toxicity will discontinue treatment and proceed to the 30-day safety follow-up visit.

4.1.1.1 Dose Adjustments

Therapy of choice will be started on day 1 of week 1 and will be taken as prescribed by the treating physician as standard of care. Patients will be evaluated for safety and tolerability of the ^{18}F-fluciclovine PET. Patients will be evaluated for safety and tolerability of their therapy per routine clinical practice.

Dose modifications are allowed according to the approved guidelines for each therapy (see package inserts).

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to study drugs and requires a dose to be held. Dose may be held for up to 4 weeks.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, patient travel, etc. may be allowed with Principal Investigator´s approval. The acceptable length of interruption will depend on agreement between the Investigator and the Principal Investigator.

4.1.2 Criteria for Removal of Patients from Study

A patient may be removed from the study for a number of reasons, including:

1. Evidence of disease progression based on radiographic or clinical criteria (worsening symptoms) as defined by the protocol;
2. Unacceptable adverse event(s), including: new or worsening pain deemed by the investigator to be due to prostate cancer progression; development of urinary outlet obstruction secondary to disease progression and requiring urinary catheterization; patients who develop seizures, pulmonary embolus or any other thromboembolic event will be removed from study; patients who develop treatment-related ≥ grade 3 toxicities, including laboratory abnormalities; patients who develop hypersensitivity or anaphylactoid reactions to abiraterone or steroids;
3. Incurrent illness that prevents further participation;
4. Experiencing a treatment delay longer than 4 weeks due to toxicity;
5. Patient refuses further treatment through the study or withdraws consent to participate;
6. Patient is noncompliant with respect to taking drugs, keeping appointments, or having tests required for evaluation of drug safety and efficacy;
7. In case a patient withdraws consent from the study, care will not be affected under any circumstance;
8. Deterioration in ECOG performance status to ≥ 3
9. If treating physician thinks that staying on study may cause increased harm to the patient or if another systemic treatment for prostate cancer is required.

4.1.3 Concomitant therapy

The use of any concurrent medication from date of informed consent and while on study, whether prescription or over-the-counter, will be recorded on the patient's CRF along with the reason the medication was taken, on week one and week 12.

Concurrent use of another investigational drug or device while on study is prohibited. Supportive care medications are allowed with their use following institutional guidelines. The following supportive care medications are considered permissible during the study:

- Conventional vitamins, selenium and soy supplements
- Additional systemic glucocorticoid administration such as “stress dose” glucocorticoid is permitted if clinically indicated for a life-threatening medical condition, and in such cases, the use of steroids will be documented as concomitant drug
- Bone modifying agents (denosumab or bisphosphonates)
- Transfusions and hematopoietic growth factors per institutional practice guidelines

- External beam radiation therapy (including radiosurgery) per the investigator's discretion
- LHRH agonist or antagonist

5 Study Activities

5.1 Screening Period

All patients must sign a written informed consent form before study specific screening procedures are performed. Screening procedures to evaluate patient eligibility will be performed within 28 days prior to Cycle 1 Week 1 (day of start life prolonging therapy), with the exception of radiological assessments (CT and bone scans) which can be performed within 42 days of Cycle 1 Week 1. If the patient meets all eligibility and screening requirements, he will have blood drawn for an NGS testing of ctDNA (Guardant360 assay) and a germline testing (Invitae assay), whenever feasible (at baseline, Cycle 1 Week 1, or within 28 days after starting life prolonging therapy). Prior NGS testing results available through routine care and within the screening window will also be accepted. Patient will return to the site for the Cycle 1 Week 1 visit and start therapy. All subsequent visits, study procedures and assessments must be done within ± 7 days of the specified study visit date following the first dose of therapy.

5.1.1 Initial Registration Process

Eligible patients will be registered on study at Tulane Cancer Center by the Research Team. The Research Team will review the documents to confirm eligibility, including eligibility checklist and related source documents, and assign a patient identifier (number). Patients found to be ineligible for participation after being consented will be considered screen failures and documented as such. Screen-failures will be replaced by other eligible patients to ensure that each cohort will consist of 12 patients. Each patient identifier is unique and will not be repeated in the case of screen failure.

5.1.2 Screening Studies (performed within 28 days before Cycle 1 Day 1, except staging imaging)

- Vitals including height (screening only), weight, body mass index, blood pressure, pulse, respiratory rate, and temperature
- Comprehensive medical history

- Prior and concomitant medications (including up to 30 days prior to signing the ICF)Physical examination
- ECOG performance status
- Comprehensive metabolic panel (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, total protein, total albumin, AST, ALT, alkaline phosphatase, LDH)
- CBC with differential (white blood cell count, red blood cell count, platelets, hemoglobin, hematocrit)
- Serum PSA
- Total testosterone
- Research blood including NGS ctDNA and germline assay, when feasible (at baseline or within 28 days after starting therapy)
- ^{18}F-fluciclovine PET scan
- Staging imaging with CT of the chest, abdomen, and pelvis with contrast (unless contraindicated), bone scan, within 42 days before starting life-prolonging therapy.

5.2 Treatment Period

All required treatment and post-treatment study procedures and assessments must be done within ± 7 days of the specified study visit date following initiation of life-prolonging therapy.

During the initial 12 weeks following initiation of life-prolonging therapy, subjects will have a clinic visit on week 1 of study and at week 12 or at time of treatment discontinuation. During the study visits patients will undergo the following study assessments:

- Physical examination
- Update concomitant medications
- Adverse event assessment related with ^{18}F-fluciclovine PET/CT scan
- Vital signs
- ECOG performance status

- Comprehensive metabolic panel (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, total protein, total albumin, AST, ALT, alkaline phosphatase, LDH)
- CBC with differential (white blood cell count, red blood cell count, platelets, hemoglobin, hematocrit)
- Serum PSA
- Research blood including NGS ctDNA and germline assay, when feasible (at baseline, or within 28 days after starting life-prolonging therapy)

In addition to study visits, patients will be regularly seen by the treating physician as standard of care visits that include clinical visits, laboratory tests and scans.

5.3 Week 12 Visit or at time of treatment discontinuation, whichever occurs earlier

After 12 weeks of treatment with life prolonging therapy or at time of treatment discontinuation due to progressive disease (clinical or radiographic) or adverse events, whichever occurs earlier, the following assessments will be performed:

- Physical examination
- Update concomitant medications
- Adverse event assessment related with ^{18}F-fluciclovine PET/CT scan
- Vital signs
- ECOG performance status
- Comprehensive metabolic panel (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, total protein, total albumin, AST, ALT, alkaline phosphatase, LDH)
- CBC with differential (white blood cell count, red blood cell count, platelets, hemoglobin, hematocrit)
- Serum PSA
- Total testosterone

- Patients must also have CT, bone scan, and ^{18}F-fluciclovine PET/CT scan
- Blood drawn for cfDNA NGS testing, when feasible

Patients with serologic progression on life-prolonging therapy are allowed to continue on treatment and/or switch prednisone for dexamethasone or discontinue treatment, at the discretion of the treating physician to ensure that safety of the patient is prioritized. Patients with radiographic progression within 12 weeks after initiating therapy may also continue on study and will have confirmatory CT and bone scans at least 6 weeks later per PCWG3. Patients may remain on therapy if radiographic progression is confirmed if the treating physician thinks that patient still benefits from treatment.

5.4 30-day Safety Follow-up

Subjects on study will come back to the clinic for a 30-day safety follow-up 30 days (+ 7 day window) following the time of the second PET/CT scan. The following assessments will be performed:

- Vital signs
- Adverse event assessment related with ^{18}F-fluciclovine PET/CT scan
- ECOG performance status
- Comprehensive metabolic panel (sodium, potassium, chloride, BUN, creatinine, glucose, calcium, total protein, total albumin, AST, ALT, alkaline phosphatase, LDH)
- CBC with differential (white blood cell count, red blood cell count, platelets, hemoglobin, hematocrit)
- Serum PSA
- Record life-prolonging therapy status and/or additional systemic anti-cancer therapies received

5.5 Follow-up Visits

Subjects will be followed for survival as well as treatment duration with life-prolonging therapy and information about the next subsequent systemic therapy following discontinuation of therapy on study. Follow-up visits will occur every 12 weeks (+/- 30 days. Visits can be done in clinic (preferred) or via phone and will continue for a maximum of 2 years from the week 12 visit (or discontinuation visit prior to 12 weeks), until progression or discontinuation of therapy, whichever occurs earlier.

Visit assessments will include:

- Survival Status
- Record life-prolonging therapy status and/or additional systemic anti-cancer therapy received
- PSA
- Radiographic imaging, only if performed as part of routine care (at the time of progression, discontinuation of therapy, or end of 2 years, whichever comes first)

6 Study Assessments

6.1 PSA Response assessment

PSA response will be defined according to PCWG3 with some modifications:

- Patients with PSA progression will have a sequence of rising values of at least 2 ng/dL and 25% above baseline, at least 1 week apart;
- Patients with PSA decreases >50% below pretreatment baseline while on abiraterone will be considered a PSA responder;
- Patients with an increasing PSA that then declines from peak levels but does not drop >50% below baseline will not be considered a PSA responder;
- Patients with an increasing PSA that subsequently declines from peak levels to > 50% below baseline will be considered a PSA responder;

6.2 Radiographic Response assessment

Patients tumor response will be evaluated using CT, bone scans and ^{18}F-fluciclovine PET at 12 weeks following week 1 day 1. Progression for soft tissue lesions will be based on RECIST v. 1.1

(>20% increase in the sum of target lesions) and for bone lesions based on PCWG3 criteria (≥ 2 new metastatic bone lesions). At 12 weeks, if radiographic progression is noted, patients will have a confirmatory CT and bone scan performed at least six weeks later as standard of care. Regardless, subjects will still complete study and come back to clinic for 30 Day safety follow-up visit.

6.3 Correlative Studies

6.3.1 *AR*-genomic alterations studies

As described in the background section, we aim to serially evaluate the genomic aberrations in *AR* that commonly occur with life-prolonging therapy and establish a strategy for assessing clonal evolution and correlate with radiographic and functional (PET) changes.

To fulfil this objective, we will use a commercially available targeted ctDNA assay. cfDNA NGS will be performed by Guardant Health (Guardant360; Redwood City, California), a Clinical Laboratory Improvement Amendments (CLIA)-licensed, College of American Pathologists-accredited, New York State Department of Health-approved clinical laboratory, using their standard collection protocol. This comprehensive genomic test performs complete exon sequencing of all critical exons (those with known hotspots) and reports all 4 major classes of GAs (single-nucleotide variants [SNVs] in 73 genes, indels in 23 genes, fusions in 6 genes, and copy number amplifications [CNAs] in 18 genes). As per Guardant360's standard protocol, blood is collected in two 10-mL Streck tubes to obtain 5.0 ng to 30.0 ng of cfDNA from plasma and analyzed as described previously.[36]

7 Statistical considerations

This pilot study is designed to accrue 12 patients and gather preliminary data on the use of ^{18}F-fluciclovine PET scan findings to monitor response to FDA-approved life-prolonging therapies compared with conventional CT and bone scans. Therefore, no formal statistics are required, and this study is mainly descriptive.

8 Standard of Care Therapies

8.1 Abiraterone acetate

Abiraterone is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with mCRPC. The patients included in the study may be scheduled for standard treatment with commercially available abiraterone acetate according to institutional practice and the approved product information (see the most up to date version of the abiraterone prescribing information for detailed information on this agent www.zytigahcp.com).

Supplier
Commercial supplies of abiraterone will be used and charged to the patient and/or his insurance company.

Summary of Adverse Events Associated with Abiraterone
The most common adverse reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

The following warnings are associated with the use of abiraterone (from the April 2017 prescribing information):
• Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: Abiraterone may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with abiraterone. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use abiraterone with caution in patients with a history of cardiovascular disease. The

safety of abiraterone in patients with LVEF < 50% or NYHA Class III to IV heart failure is not established.

• Adrenocortical insufficiency: Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking abiraterone and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving abiraterone in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone.

• Hepatotoxicity: In post-marketing experience, there has been abiraterone-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths. In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received abiraterone, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking abiraterone. No deaths clearly related to abiraterone were reported due to hepatotoxicity events. The safety of abiraterone re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Prednisone and dexamethasone

Prednisone and dexamethasone are synthetic adrenoglucocorticoids. They are commercially available as generics in tablet form for oral administration. They are indicated for a variety of medical conditions, including cancer.

Summary of Adverse Events Associated with Prednisone/dexamethasone

See reference for a more complete summary of AEs associated with glucocorticoids.[37] The side effects from systemic glucocorticoids are usually dose and duration dependent and can impact virtually all body systems. Common side effects include thinning of the skin, purpura, Cushingoid appearance, weight gain, sleep disturbance and mood changes. Hyperglycemia is common if these agents are used in patients with pre-existing diabetes or those at risk of diabetes for other reasons.

Cataracts are also common with prolonged (>1 year) of glucocorticoids. Other risks of concern with glucocorticoids include an increased risk of cardiovascular disease and hypertension (particularly when glucocorticoids are prescribed in patients with pre-existing cardiac or renal disease), increased risk of peptic ulcer disease and gastritis (especially when patients are also taking nonsteroidal anti-inflammatory agents), osteoporosis, increased fracture risk, osteonecrosis, myopathy, edema, and immunosuppression with an increased risk of infection. With the exception of cataracts and some of the cardiac and bone toxicities, adverse effects from glucocorticoids are at least partially reversible upon discontinuation.[38]

8.2 Enzalutamide

Enzalutamide is an AR inhibitor indicated for the treatment of patients with mCRPC.
The patients included in the study may be scheduled for standard treatment with commercially available enzalutamide according to institutional practice and the approved product information (see the most up to date version of the enzalutamide prescribing information for detailed information on this agent (www.xtandi.com).

Supplier
Commercial supplies of enzalutamide will be used and charged to the patient and/or his insurance company.

Summary of Adverse Events Associated with Enzalutamide
The most common adverse reactions (≥10%) reported in the two randomized placebo-controlled clinical trials that occurred more commonly (>2% over placebo) in the enzalutamide arm were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weigh decreased, headache, hypertension, and dizziness/vertigo. The following warnings are associated with the use of enzalutamide (from the October 2016 prescribing information):
• Seizure: Seizure occurred in 0.5% of patients receiving enzalutamide in clinical studies. Seizure occurred from 31 to 603 days after initiation of enzalutamide. Patients experiencing seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering enzalutamide to patients who experienced seizure. Limited safety data

are available in patients with predisposing factors for seizure because these patients were generally excluded from the trials. Because of the risk of seizure associated with enzalutamide use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

• Posterior Reversible Encephalopathy Syndrome (PRES): There have been reports of PRES in patients receiving enzalutamide. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI.

8.3 Docetaxel

Docetaxel is an anti-neoplastic chemotherapeutic agent which acts by disrupting the microtubular network that is essential for mitotic and interphase cellular functions.

The patients included in the study may be scheduled for standard treatment with commercially available docetaxel according to institutional practice and the approved product information (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/201525s002lbl.pdf)

Solution preparation

Docetaxel comes at a 10 mg/mL solution that must be diluted prior to administration in at least 250 mL of normal saline or D5W

Route of administration:

• _Administer intravenous infusion over 1 hour through non-sorbing polyethylene lined (non-DEHP) tubing

• _Some formulations contain alcohol; use caution in patients who should avoid/minimize alcohol intake

• _Irritant with vesicant-like properties; assure proper needle or catheter position prior to administration to avoid extravasation

− _If extravasation occurs, stop infusion immediately and disconnect, gently aspirate extravasated solution, remove needle/cannula, and elevate extremity

Agent ordering/Availability: May use commercial supply

Adverse Events

Common Adverse Events: edema, hair loss, rash, pruritus, vomiting, nausea, diarrhea, constipation, infection, fever, myelosuppression, fatigue, peripheral neuropathy, pain.

Hypersensitivity reactions include anaphylactic-like reactions. Tachycardia, bronchoconstriction, hypotension, facial edema and erythema may occur and should be treated with antihistamine, corticosteroids, and epinephrine as per institutional hypersensitivity management protocol. These reactions typically occur in patients with prior exposure to the drug. If appropriate based on the discretion of the treating Physician to continue with treatment then desensitization required for future doses, pretreat with the same medications for at least 24-hour and at time of infusion.

Please refer to the package insert for additional AEs.

9 ^{18}F-Fluciclovine PET/CT Scan

9.1 Administration

The recommended dose is 370 MBq (10 mCi) administered as an intravenous bolus injection. The (radiation absorbed) effective dose resulting from this dose of ^{18}F-fluciclovine is 8 mSv. The clinical trial database for ^{18}F-fluciclovine includes data from 877 subjects including 797 males diagnosed with prostate cancer. Most patients received a single administration of ^{18}F-fluciclovine, a small number of subjects (n = 50) received up to five administrations of the drug. The mean administered activity was 370 MBq (range, 163 to 485 MBq).

9.2 Pharmacology

Three studies have evaluated biodistribution and radiation dosimetry in healthy volunteers[39-41]. In general, the results of these studies are consistent. The primary evidence on the biodistribution and radiation dosimetry from the phase I study conducted by GE Healthcare[41,42] is reviewed in more detail below. This trial (GE-148-001) in 6 healthy volunteers and 6 subjects with biopsy-proven prostate cancer started in June 2009 and the clinical phase was completed in November 2009. The first part of the trial investigated the safety, biodistribution, and internal radiation dosimetry of ^{18}F-

fluciclovine injection in 6 healthy volunteers (3 males and 3 females). Overall, there was no evidence indicating that ^{18}F-fluciclovine is metabolized *in vivo*.

Qualitative assessment of the distribution of ^{18}F-fluciclovine activity in all 6 subjects showed that the distribution was largely uniform throughout the body with the exception of the liver, pancreas, lung, red bone marrow, and heart wall. The initial uptake of ^{18}F-fluciclovine in each subject was assessed at the first imaging time point, on average 7.9 mins (6.5 to 10.2 mins) post injection. Initial uptake of ^{18}F-fluciclovine activity in the liver, pancreas, and the red bone marrow of the thoracic and lumbar vertebrae and skull was immediately evident in all subjects. There was very little brain uptake, 1.6% (0.7% to 2.2%). With increasing time post injection, distributed uptake was apparent and, on the basis of the anatomical distribution, was mostly associated with skeletal muscle. This uptake could not be isolated for quantification as it was not possible to segment the muscle in the whole-body image. Hence, muscle was included in the "remaining tissues" category. Uptake in the spleen was apparent in some subjects. Uptake in the uterus was apparent in some female subjects and initial activity uptake in the uterus was limited, 1.2% (0.3% to1.7%). It was assumed, based on the general skeletal muscle uptake, to be associated with the muscle of the uterine wall. The four organs with the highest initial uptake of ^{18}F-fluciclovine were the liver at 13.8% (8.3% to 17.1%), red bone marrow at 11.1% (4.8% to 20.4%), lung at 7.1% (5.2% to 8.6%), and pancreas at 4.2% (3.4% to 5.2%). Based on comparison with washout of activity from the whole-blood samples, washout of activity from the lung was consistent with washout of activity from the pulmonary blood content. Excretion of ^{18}F-fluciclovine activity was limited and was only found for the renal pathway, reaching 3.2% (1.1% to 7.4%) at the last imaging time point an average of 4.2 hours post injection (3.8 to 4.7 hours). The small amount of activity entering the gastrointestinal (GI) tract could not be clearly identified due to the surrounding activity in muscle and mesentery. On the basis of activity washout from the liver and the pancreas, and assuming that all of this activity was to enter the duodenum through hepatobiliary and pancreatic transport, the activity excreted via the GI tract was estimated to be of the order of 10 % or less.

Although this could not be accurately quantified, any activity present in the contents of the GI tract was grouped within the "remaining tissues" category for evaluation of internal radiation dosimetry. No differences considered to be of likely clinical significance were noted between the 3 males and the 3 females.

9.3 Safety

According to clinical review of ^{18}F-fluciclovine by the US FDA (Reference ID: 3897370) that supported the approval of ^{18}F-fluciclovine for patient with recurrent prostate cancer, no deaths were reported in any of the studies evaluated in this review. Two serious adverse events were reported for the BED001 study; one subject was from the Norway site and one was from the Bologna site. Table 1 summarizes the treatment emergent adverse events and adverse reactions in healthy volunteers (N=12). Moreover, adverse reactions were reported in ≤1% of subjects during clinical studies with ^{18}F-fluciclovine. The most common adverse reactions were injection site pain, injection site erythema and dysgeusia.

	Study	
	GE-148-001 N = 6	NMK36-P1 N = 6
MedDRA SOC **MedDRA Preferred Term**	**Subjects (n (%))**	**Subjects (n (%))**
Any AE	2 (33.3)	2 (33.3)
General disorders and administration site conditions	0	1 (16.7)
Injection site erythema	0	1 (16.7)
Investigations	2 (33.3)	1 (16.7)
Decreased blood fibrinogen	0	1 (16.7)
Blood calcium decreased	1 (16.7)	0
INR increased	1 (16.7)	0

Table 1 - Treatment Emergent Adverse Events and Adverse Reactions of healthy volunteers (n=12) (adapted from CDER Clinical Review version date: June 25, 2015)

10 Study calendar

	Screening[1]	Week 1 Day 1 visit	Week 12 visit or at time of treatment discontinuation	30-day Safety Follow-up	Follow-up[4]
Informed consent	X				
History and physical exam	X	X	X		
Eligibility review	X	X			
Adverse event assessment[9]	X	X	X	X	
Concomitant medications		X	X		
Vital Signs[7]	X	X	X	X	
ECOG performance status	X	X	X	X	
CBC w/ differential[2]	X	X	X	X	
CMP[2]	X	X	X	X	
Serum PSA	X	X	X	X	X
Total testosterone	X		X		
Bone Scan[3]	X		X[5]		X[6]
CT of C/A/P w/ contrast[3]	X		X[5]		X[6]
18F-Fluciclovine PET/CT	X		X[5]		
ctNGS blood collection[8]	X		X		
Survival status	X	X	X	X	X
Cancer therapy assessment				X	X

[1] Within 28 days prior to Week 1 Day 1
[2] CBC to include white blood cell count, red blood cell count, platelets, hemoglobin, hematocrit, and differential. Chemistry to include sodium, potassium, chloride, BUN, creatinine, glucose, calcium, total protein, total albumin, AST, ALT, alkaline phosphatase, and LDH.
[3]Within 42 days prior to Week 1 Day 1, within 7 days of all other cycles at which they are required. IV contrast may be omitted if contraindicated.
[4]Follow-up visits should take place as standard of care, usually every 12 weeks +/- 30 days and should be measured from the date of the Week 12 or time of treatment discontinuation visit, whichever occurred earlier. Subject follow-up will occur until disease progression, discontinuation of study therapy, initiation of subsequent systemic anti-cancer therapy, or a maximum of 2 years, whichever comes first.)
[5]Week 12 assessments (CT, bone, and 18F-fluciclovine PET/CT scans) should be performed irrespective of treatment delays.
[6]Standard of care CT scan and bone scan should be completed at the time of progression (serologic, radiographic or clinical), at the time of discontinuation of life-prolonging therapy or at the end of 2 years, whichever comes first. Imaging is optional at these timepoints, and will only be collected if completed as part of standard of care
[7] Vitals to include height (screening only), weight, body mass index, blood pressure, pulse, respiratory rate, and temperature
[8]Collected only as feasible. Baseline assessment may occur at Screening, week 1 Day 1, or within 28 days after starting life-prolonging therapy.
[9]Adverse events occurring within 2 days from imaging test and related with 18F-fluciclovine PET/CT scans will be collected

11 Data Monitoring and reporting requirements

Data Monitoring of this protocol will occur at every six months. The protocol will be monitored internally at Tulane University by the Principal Investigator and Research Team accordant with Institutional guidelines. Trial monitoring and reporting will be done through the Principal Investigator and Research Team.

Additionally, scheduled meetings will take place every three months and will include the principal investigator, co-investigators, research coordinators and when appropriate, the collaborators and sub-investigators involved with the conduct of the protocol. During these meetings the investigators will discuss the safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives. Criteria for stopping or ending the clinical trial will include determination of unexpected, significant, or unacceptable risk to patients; or insufficient compliance to protocol requirements.

Monitoring plan has been established in a separate document, which will be filed in the electronic study file.

11.1 Case Report Form Submission

Electronic Case Report Forms (eCRFs) will be provided by Principal Investigator (PI) and should be handled in accordance with instructions from PI. The investigator is responsible for maintaining adequate and accurate eCRFs which have been designed to record all observations and other data pertinent to the clinical investigation. Each eCRF should be filled out completely by the investigator or delegate as stated in the Site Delegation List. All data captured for the study is planned to be electronic.

11.2 Adverse Event Monitoring and Reporting

An Adverse Event (AE) is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. As patients will be treated with standard of care while the intervention is the ^{18}F-fluciclovine PET/CT at two time points, AEs occurring until two days after the imaging test and related with ^{18}F-fluciclovine PET/CT will be reported. This can include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as

nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment. Laboratory abnormalities will only be reported as AEs when deemed clinically significant by the site's investigator.

An Adverse Drug Reaction (ADR) is defined as any response to a medical product, that is noxious and/or unexpected, related to any dose. Response to a medicinal product (used in the above definition) means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

An Unexpected Adverse Drug Reaction is any adverse reaction for which the nature or severity is not consistent with the applicable product information (e.g., Investigators' Brochure).

A Serious Adverse Event (SAE) is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a Serious Adverse Drug Reaction (SADR).

Adverse events and adverse drug reactions which are considered as serious are those which result in: death; a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed); hospitalization or prolongation of hospitalization; persistent or significant disability/incapacity; a congenital anomaly/birth defect; any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

11.2.1 Evaluating Adverse Events

Adverse events will be reported in the context of ^{18}F-fluciclovine PET scan that is being used off label. The event term, grade and severity of the event will be determined using the DCT/NCI Common Terminology Criteria, CTCAE version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. Study staff must use one of the CTCAE criteria to define the event. Adverse events not included in the CTCAE v.5.0 should be reported and graded under the "Other" adverse event within the appropriate category and grade 1 to 5 according to the general grade definitions, mild, moderate, severe, life-threatening, fatal or disabling, as provided in the CTCAE.

The event will be determined to be expected or unexpected. The determination of whether an AE is expected is based on agent-specific adverse event information provided in Section 8 Pharmaceutical

Information. Unexpected AEs are those not listed in the agent-specific adverse event information provided in Section 9 Pharmaceutical Information.
The event will be evaluated for relationship to the medical treatment or procedure. The Investigator should document his/her opinion of the relationship of the event to the imaging agent (^{18}F-fluciclovine) as follows:

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

Based on this information, a decision will be made whether an adverse event should be reported as an expedited report in addition to the routinely reported clinical data. All expedited adverse event reports should be submitted to the Institutional Review Board (IRB) and to the FDA.

11.2.2 Documenting Adverse Events

The investigator is responsible for ensuring that all adverse events (as defined in Section 10.2 and as further specified below) observed by the investigator or reported by subjects are collected and recorded in the subjects' medical records and in the CRF. These adverse events will include the following:

- All serious and non-serious adverse events (as defined in Section 10.2) that occur after the subject has signed the informed consent form and for 2 days after each ^{18}F-fluciclovine PET/CT scan will be documented.

The following serious adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to ^{18}F-fluciclovine PET scan; and action taken. The investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records.

For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event (e.g. ^{18}F-fluciclovine PET scan or other cause). The relationship of the adverse event to the imaging study will be assessed as described at 10.2.1.

In addition, all SAEs should be reported to Blue Earth Diagnostics via any of the contact routes below. **Email:** drugsafetyUS@blueearthdx.com

Phone: +1 855 Axumin1 (1-855-298-6461); option 1

Fax: +1 609 514 2522

11.2.3 Expedited Reporting of Serious Adverse Events

Serious adverse events and protocol problems will be reported in compliance with Tulane University Human Research Protections Office Standard Operating Procedures (revised 6/25/20). A copy of this document is available at https://research.tulane.edu/hrpo/policies

All study investigators will be notified by the Principal Investigator of all SAEs that are unexpected (i.e., not previously described in the characterization of ^{18}F-fluciclovine PET scan in section 9 of this protocol), and definitely or possibly related to the ^{18}F-fluciclovine PET scan.

The Sponsor-Investigator is responsible for safety reporting and to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to the local regulatory authorities and Blue Earth Diagnostics, as required by local regulations (for regulatory reporting) and as required by the ISS agreement (for reporting to Blue Earth Diagnostics).

The following reportable events must be submitted to Blue Earth Diagnostics within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided. The Principal Investigator will assume responsibility for submitting the reportable event(s) to Blue Earth Diagnostics as well as ensuring that any local reporting requirements are completed in parallel.

Serious adverse events defined by at least one of the following:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another medically important event

11.3 Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the site IRB before implementation.

11.4 Informed Consent

Written informed consent will be obtained by a study investigator or study research coordinator working on this study. An explanation of the nature of study, its purpose, procedures involved, expected duration, potential risks and benefits will be provided to each participant by the investigator or the research nurse. Each participant will be informed that participation in the study is voluntary and that he may withdraw from the study at any time, and that withdrawal of consent will not affect his subsequent medical treatment. Participants will be informed that de-identified images and medical data may be shared with our study collaborator (Blue Earth Diagnostics). Participants will be allowed time needed to make an informed decision. Participants will be encouraged to ask questions about the study and the consent form before signing the consent form. Consent forms will be filed with the Clinical Research Office and copies stored securely with the study coordinator. No patient will enter the study before his informed consent has been obtained.

12 Ethical considerations

12.1 Patient protection

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki. National Ethics Committee will approve the protocol.

12.2 Subject identification

Data collected during this study may be used for research purposes. All data collection during the study will abide by all relevant data protection laws. The patient's name, however, will not be disclosed outside the hospital. They will be known by a unique patient number. Patients will be assigned a number by the study team, when their eligibility is confirmed. Assigned number will go in sequence, every number is unique, and screen failed patients will get a number, which will not be re-used for the next patient.

The results of this study may be used by Investigators that have ensured an adequate level of protection for personal data.

13 Publication Policy

The primary investigator will be involved in all steps of the trial, including enrollment, safety meetings, data analysis and presentation of trial results. Dr. Pedro Barata will be first-author and present study results at major oncology national meetings, including the Annual Meeting of American Society Clinical Oncology (ASCO), ASCO Genitourinary Symposium, European Society of Clinical Oncology and American Association of Clinical Research. At least four abstracts at national meetings and two original publications in a peer-review indexed journal are expected, within 6 years from enrollment start date.

Co-authors of all research abstracts and publications will involve co-investigators and members of the research team included in this protocol. Additional co-authors may be added according to their contribution to the completion of the study.

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15 Appendix

15.1 ECOG Performance Status / Karnofsky Performance Scale

Performance Status Criteria[43]

WHO 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.
3	In bed >50% of the time. Capable of only limited self-care, confined in bed or chair more than 50% of waking hours.	50	Requires considerable assistance and frequent medical care.
		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	Deceased.	0	Deceased.