Protocol Title: 18F-Fluciclovine PET CT as an indicator of therapeutic response in metastatic prostate carcinoma (M1PCa).

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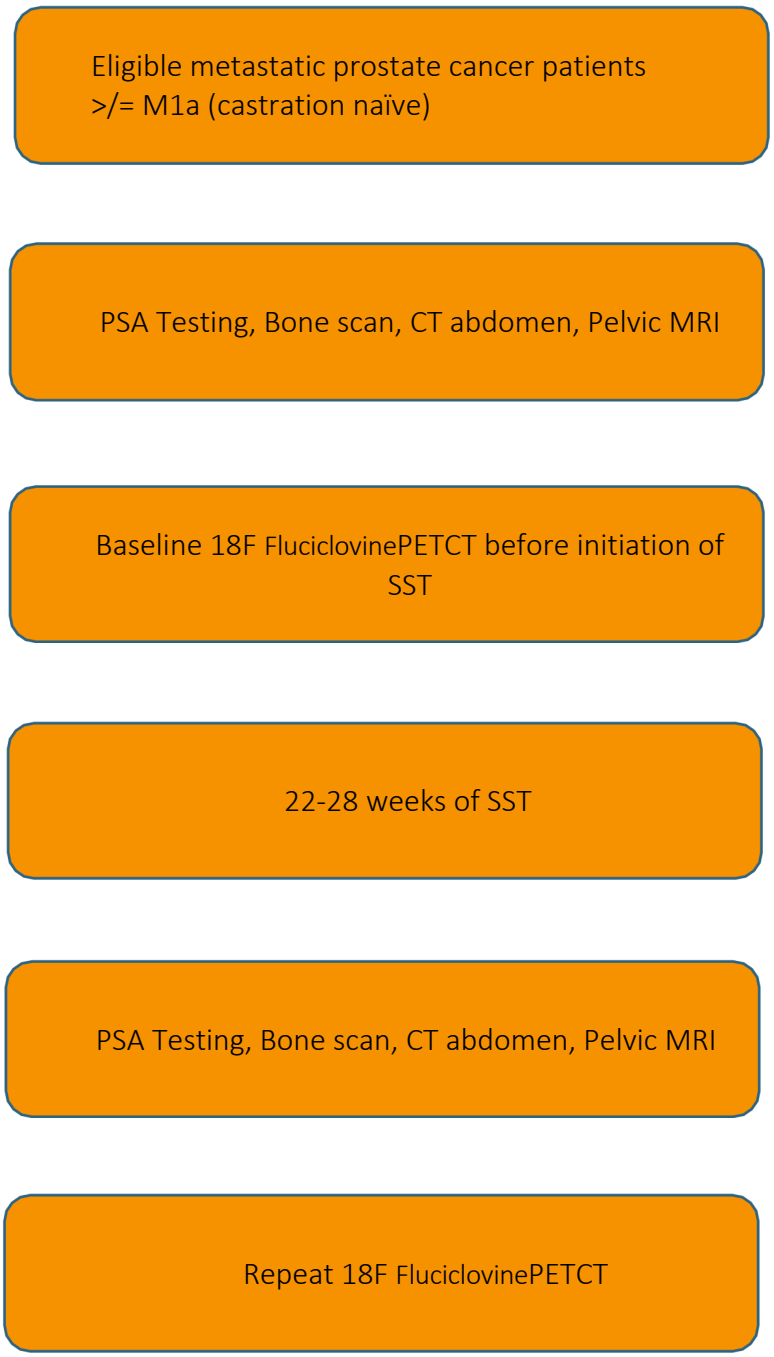
1.0 PROTOCOL OVERVIEW (SCHEMA)



2.0 Background and Rationale

In screened populations, the incidence of metastatic prostate cancer (M1 PC) at diagnosis is approximately 1.5%.[1] In the general population, the incidence of M1 PC at diagnosis is approximately 5%.[2] Thus, men presenting with M1 PC at diagnosis represent close to one third of the 30,000 men dying from PC each year in the US. The treatment paradigm for M1 and clinically node positive (cN1) PC is centered on use of systemic therapies, commencing with androgen deprivation therapy (ADT) followed by secondary hormonal treatments and then chemotherapy upon the development of castrate resistance, while definitive local therapy has traditionally been reserved for treatment of localized PC.[3] However, a growing body of evidence suggests that definitive treatment of the primary tumor may improve the outcome of men with advanced disease. First, two recent prospective randomized trials have shown a survival benefit for men with locally advanced disease that received radiation therapy in addition to ADT compared to those receiving ADT alone.[4,5] Second, retrospective studies suggest overall survival (OS) and cancer specific survival (CSS) are better in patients with pathologically proven lymph node positive disease that went on to receive treatment (radiation or prostatectomy) of their primary tumor.[6-8] Third, it has been estimated that 24-44% of men treated with non-curative intent will develop symptomatic local progression requiring intervention.[9,10] Symptomatic progression of local disease is a source of intense suffering as well as health care resource spending, consumed in hospital admissions and unsatisfactory palliative procedures, and is likely to accelerate death from PC.[9] While salvage cystoprostatectomies and pelvic exenterations can offer palliation of symptoms, they carry a high rate of complications and can only be offered to a subset of men in this situation.[11,12]

From a biological perspective, recent data suggest that ADT may not provide sufficient control of the primary tumor, which may act as a continued source for additional metastatic spread and resistant clonal selection.[13-15] While there is evidence that demonstrates prostate cancer has significant heterogeneity within the multiple foci of tumors with a gland, molecular and cytogenetic data show that multiple metastases within the same patient are clonally related[16-18] suggesting that metastatic clones may arise from a selective advantage of individual clones and that further systemic therapies may select for cells with varying malignant potentials. Therefore, definitive treatment of the primary tumor may also improve outcomes by removing a major source of spread and thereby increasing freedom from local and distant progression, delaying time to castrate resistance and prolonging time to fatal metastatic burden, thus resulting in prolongation of overall survival.

In this context, it will be important to develop a potential imaging biomarker for assessing response to SST which can potentially differentiate responders vs non-responders early in the course of treatment. It is possible that SST might significantly benefit only a subset of patients and imaging biomarker could allow risk stratification and possible incorporation of alternative therapies at a time when they would be expected to be most effective.

Multiple positron emission tomography (PET) tracers are available to evaluate patients with prostatic cancer, including fluorine-18 fluorodeoxyglucose (18F-FDG), 11C-choline, PSMA and 18F FLT. However, these tracers have a limited role in the evaluation of response to therapy. Hence, there is a need for a radiotracer that can be used to more accurately assess response to therapy. 18F-fluciclovine, is a Federal Drug Administration (FDA) approved imaging agent that is used to identify disease recurrence after definitive treatment in response to a rising PSA. It is a radiolabeled leucine analog (1-amino-3- fluorocyclobutane-1-carboxylic acid in the 'anti' configuration [18F-fluciclovine]) and used to depict amino acid transportation. Amino acid transporters and amino acid metabolism are up-regulated in multiple malignancies, including prostate cancer. 18F-fluciclovine has been shown to accumulate within prostate cancer.[19,20]Although 18F-fluciclovine18F-fluciclovine has been approved for the evaluation of occult disease at the time of biochemical recurrence, this tracer also exhibited excellent in vitro uptake in the DU145 prostate carcinoma cell line and within orthotopically implanted prostate tumors in nude mice.[19] Moreover, since only a small fraction of 18F-fluciclovine is excreted through the urinary tract early after injection, its imaging characteristics are favorable in the prostate. 18F-fluciclovine has been found to be successful in the assessment of primary and metastatic prostate cancer.[21-23] In a study of 21 patients, 18F-fluciclovine uptake in patients with prostate cancer was nearly 2-fold greater than that in patients with normal tissue.[24] Schuster et al[22] found a moderate correlation between 18F-fluciclovine uptake and cancer aggressiveness. Although 18F-fluciclovine has been shown to successfully image prostate cancer, there is currently no evidence that changes in 18F-fluciclovine avidity correlate with changes in tumor burden or patient outcomes. Before 18F-fluciclovine is used for evaluation of the tumor response, the association of 18F- fluciclovine avidity and the tumor response must be established. The purpose of this pilot study is to assess the ability of 18F-fluciclovine positron emission tomography computed tomography (PET CT) to determine the therapeutic response to SST in patients with metastatic prostate cancer (M1PC).

3.0 Study Objective

Primary objective: Evaluate metabolic response by 18F-fluciclovine PET qualitatively and semi-quantitatively with standardized uptake values (SUV) following standard systemic therapy at 22-28 weeks (+/- 4 weeks) and correlate the findings with size changes as defined by conventional imaging and PSA response.

Secondary objectives:

1. To correlate pelvic 18F-fluciclovine PET imaging findings with pathologic findings at radical prostatectomy and pelvic lymph node dissection to determine 18F-fluciclovine PET imaging sensitivity and specificity for pelvic lymph node cancer involvement.
2. To evaluate 18F-fluciclovine PET imaging response and its correlation with progression free survival (defined by PCWG2 criteria)
3. To determine if sites of progressive disease develop at the initial/prior site (diagnostic site) of metastases or in newly developed sites at the time of metastatic progression.
4. To evaluate metabolic response by 18F-fluciclovine PET semi-quantitatively with target to blood pool ratio (TBR) following SST at 22-28 weeks (+/- 4 weeks), and correlate the findings with size changes as defined by conventional imaging and PSA response.

4.0 Eligibility Criteria

For entry into this study, the following criteria must be met. Any exceptions from the

protocol specific selection criteria must be approved by the principal investigator, and MD Anderson Cancer Center IRB, prior to enrollment.

4.1 Inclusion Criteria

1. Male patients
2. 18 years and older
3. Histologically or cytologically proven prostate carcinoma
4. Documented evidence of M1 disease by AJCC staging by Bone scan, computed tomography (CT) or magnetic resonance imaging (MRI) 5. Castration naive disease, no prior systemic therapy for prostate cancer
Planned to receive SST
5. ECOG PS 0 or 1
6. Ability to understand and willingness to sign informed consent

4.2 Exclusion Criteria

1. Known brain metastasis
2. Small cell carcinoma of the prostate

5. 0 Research Design and Methods

5.1 Study Design

A prospective pilot study will consist of eligible patients referred from genitourinary multidisciplinary care center at the University of Texas at MD Anderson cancer Center. All eligible patients scheduled to receive SST for up to 28 weeks will be enrolled, and initial 18F-fluciclovine PET CT will be performed within four weeks before initiation of systemic therapy. The patient will receive SST for up to 28 weeks, and 18F-fluciclovine PET CT will be repeated within four weeks following SST. 18F-fluciclovine PET CT will be performed as per the standard institutional protocol (Appendix C.). Blinded image interpretation will be made by radiologists and nuclear medicine physician. All scans will be interpreted independently by two physicians. Areas of focal tracer uptake will be localized with the companion CT and classified as lesions of the prostate, pelvic nodes, extrapelvic nodes, visceral, and bone lesions. Three- dimensional regions of interest will be placed in areas of tracer uptake, and measures of 18F- fluciclovine avidity will be recorded; the measures include SUVmax (body weight), metabolic tumor volume (MTV; volume of tumor [cm3] with SUV >42% of SUVmax), SUVmean (within the MTV), and total lesion avidity (TLA; calculated as MTV x SUVmean). A background SUVmax will be documented for each examination. On both pretreatment and posttreatment scans, the lesion SUVmax will be corrected for the background as follows: corrected SUVmax = lesion SUVmax - background SUVmax. When the correct SUVmax is less than 0, 0 will be recorded. Similar corrections will be made for SUVmean. When the corrected SUVmax and the corrected SUVmean are 0 on posttreatment scans, MTV and TLA will also be recorded as 0. The percentage of change in the 18F-fluciclovine SUVmax after therapy will be calculated as follows: [(pretreatment corrected SUVmax - posttreatment corrected SUVmax)/pretreatment corrected SUVmax] x 100. Similar calculations will be performed for SUVmean, MTV, and TLA.

5.2 Reference standard

We will calculate tumor response by using RECIST 1.1 for visceral, bone and lymph node metastasis.[25] Primary tumor within the prostate gland will be assessed based on percent reduction in tumor size, changes in restricted diffusion and ADC value on mp pelvic MRI.[26-28] In patient with available pathological specimen following prostatectomy and pelvic LN dissection, the pathologic response will be used to assess tumor response as well as identification of involved lymph nodes to assess for specificity and sensitivity of F18 Fluciclovine to detect occult lymph node involvement.
Patients will be dichotomized by PSA measurement is taken at six months, PSA ≤ 4 and PSA > 4.[29]

Response assessment	
Evaluation of Target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. At least 17% increase in median ADC value within the tumor on DWI MR images.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion (s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

5.3 Investigator and Institutional Requirements

Principle investigator and co-investigators comply with institutional research procedures and policies. The study will be activated after approval by the IRB.

5.4 Study Calendar (Accrual process)

Visits	Activities	Site/Person involved
Initial clinic visit	Determination of eligibility	GU multidisciplinary center
Imaging visit	Standard of care Bone scan	Diagnostic Imaging
Imaging visit	The standard of care CT abdomen	Diagnostic Imaging
Imaging visit	The standard of care pelvic MRI with endorectal coil	Diagnostic Imaging
Imaging visit	Research 18F-fluciclovine PET CT	Diagnostic Imaging

5.5 Pre-test/study evaluation

Patients with metastatic prostate cancer are seen and evaluated at genitourinary multidisciplinary care center of MDACC. Based on the past clinical volumes, we are expected to see 2-4 metastatic prostate cancer patients per month. This center is staffed by clinical faculty from urology, medical oncology, and radiation oncology departments. Before enrollment, patients will be seen in genitourinary multidisciplinary center in consultation with a medical oncologist, urologist, and radiation oncologist to ensure eligibility.

5.6 Registration Visit and Procedures

Verification of eligibility criteria, and clinical consultation notes by DI research nurse. All patients will be scheduled to undergo standard of care laboratory studies and imaging workup that include PSA, bone scan, CT abdomen and mpPelvic MRI with the endorectal coil. Informed consent will be obtained by either by a qualified research personnel or research staff.

5.7 Baseline Imaging Visits

Baseline bone scan, CT abdomen, mpPelvic MRI (or) 18F-fluciclovine PET CT will be scheduled or completed within 30 days before initiation of SST. Please refer to Appendix C. for complete imaging protocols.

5.8 Post Systemic Therapy-Imaging Visits

Patients will return following 22-28 weeks (+/- 4 weeks) of SST for follow-up imaging studies which will include MDP Bone scan, CT abdomen, MP PELVIC MRI AND 18F-FLUCICLOVINE PET CT.

5.9 Criteria for Removal from Study

Subjects must be withdrawn from the study for the following reasons:

- 5.9.1 The patient withdraws consent
- 5.9.2 The patient cannot complete all imaging tests within 30 days of time frame.
- 5.9.3 Study completed

5.10 Innovation:

This is to our knowledge the first study of using 18F-fluciclovine PET CT in the assessment of therapy response in prostate cancer. Although glucose metabolism is recognized as a key metabolic pathway for imaging, amino acid metabolism is emerging as a promising pathway for

tumor imaging.[30,31] Recent studies with ^{18}F-Fluciclovinehave shown that this tracer can accurately detect prostate cancer and regional lymph node metastases with better specificity and sensitivity.[32-34] 18F-fluciclovine have also been tried in breast cancer with positive results. A pilot study evaluated the ability of ^{18}F-fluciclovine avidity to determine neoadjuvant therapy response in 24 breast cancer patients, using histology after definitive surgical management as the gold standard.[35] Changes in ^{18}F-fluciclovine avidity strongly correlated with the percentage of reduction of tumor seen on pathology.[35] Motivated by these prior studies, we propose to evaluate the ability of 18F-fluciclovine avidity to determine neoadjuvant therapy response in M1PCa. In addition to establishing the importance of tumor response assessment with novel radio tracers, this study has the potential to combine with pelvic MRI and whole-body MRI to study high risk and metastatic prostate cancer. Also, the knowledge gained from this research will be used to design and test the utility of PET-MRI with novel tracers such as 18F-fluciclovine and PSMA. The culmination of the pilot studies will be an extramural application to conduct a multicenter trial.

5.11 End of the Study information handling

All collected information from participants will be destroyed, including patient identifiers. This information will be destroyed within 5 years from publication in accordance with UT MD Anderson Cancer Center policies.

6.0 Statistical Considerations

Objectives, Endpoints, and Study Design

The primary objective of this prospective study is to evaluate the ability of 18F Fluciclovine PET CT to determine the therapeutic response to SST. All eligible patients will be imaged by 18F Fluciclovine PET CT before and after treatment. Treatment responders were defined as the posttreatment PSA level <= 4.0 ng/mL, and >4.0 ng/mL for non-responders. The primary endpoint is the percentage change of 18F-fluciclovine SUVmax. Secondary endpoints include the size changes defined by conventional imaging; TBR; sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) when comparing 18 F Fluciclovine PET CT imaging findings with pathologic findings; progression free survival defined by PCWG2 criteria; and the types of metastatic progression sites. The accuracy of using the percentage change of 18F- Fluciclovine SUVmax to discriminate treatment responders from non-responders is evaluated using Receiver Operating Characteristic (ROC) curve analysis.

Sample Size and Power Calculation

We wish to enroll 41 evaluable patients. With an overall sample size of 41 and an estimated 70% response rate, we expect approximately 28 responders and 13 non-responders. With these numbers, we will have 83% power to detect a difference of 0.26 between the area under the ROC curve (AUC) under the null hypothesis of 0.50 and an AUC under the alternative hypothesis of 0.76 using a two-sided z-test at a significance level of 0.05. Considering a drop-out rate of 10%, the total sample size required is 45.

Analysis Plan

Patient characteristics and clinical outcomes will be summarized using frequencies, mean, standard deviation, median, and range. Accuracy of predicting responders using the percentage changes of SUVmax or the size changes by conventional imaging will be analyzed by ROC curves. AUC will be compared using the nonparametric method described by Delong (1988). Optimal cut- off points for dichotomizing the percentage changes of SUVmax or the size changes will be selected by maximizing the Youden's index. Dichotomized values will be compared using the McNemar's test. Sensitivity, specificity, PPV, and NPV to correlate dichotomized 18 F Fluciclovine PET CT imaging findings with pathologic findings will be estimated along with 95% confidence intervals.
Kaplan-Meier method will be used to estimate progression free survival (PFS). Log-rank test will be used to compare PFS between imaging response groups. Frequencies will be estimated for different types of metastatic progression sites. Other statistical analyses will be carried out as appropriate.

7.0 Adverse Events; Safety Issues

Adverse event reporting and safety issues will be reported as per the MDACC procedures and policies. In addition to reporting of Serious Adverse Events (SAEs) to the responsible IRB and Health Authority, the PI is required to promptly notify Blue Earth Diagnostics (BED) in the event of (SAEs) that occur following receipt of [18F]fluciclovine (whether or not related to study drug).
Such SAEs must be reported within 24 hours of Principal Investigator or designee becoming aware of the event. All SAE information must be recorded and faxed or scanned and emailed to:

Blue Earth Diagnostics SAE E mail:	Drugsafety@pharsafer.com
Tel:	1 855 AXUMIN1 (1 855 298 6461)
Fax:	+44 (0) 1483 212178.

If BED receives any individually identifiable health information collected or produced in the study, BED shall use and disclose only for the purpose of complying with applicable laws, provided that all such uses are disclosed in the IRB-approved informed consent form. BED will use all reasonable efforts to protect the privacy and security of individually identifiable health information and will require its business partners to do so also. BED will not contact any study subjects, unless permitted by the informed consent form There are no expectations of BED contacting the participants.

F18 Fluciclovine (Axumin)

The recommended dose is 370 MBq (10 mCi) administered as an intravenous bolus injection. The (radiation absorbed) effective dose resulting from this dose of Axumin is 8 mSv. The clinical trial database for Axumin includes data from 877 subjects including 797 males diagnosed with prostate cancer. Most patients received a single administration of F18 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). Adverse reactions were reported in ≤1% of subjects during clinical studies with F18 fluciclovine. The most common adverse reactions were injection site pain, injection site erythema and dysgeusia.

8.0 Ethical Considerations (Including Informed Consent)

Informed consent and ethical consideration will be in compliance with MDACC procedures and policies.

9.0 Data Management; Administrative Issues

Imaging data will be stored in MDACC PACS. Confidentiality of personal health information (PHI) will be maintained throughout the study. Data will be stored in password-protected database maintained by research information system and technology service server at MDACC. The investigators do realize that a risk to patient PHI confidentiality exists whereby personal information could be accidentally be released, however, all necessary precautions will be taken to prevent this from happening. Unique patient identifier will be available only to the investigators for the study and will be kept in a password-protected database and locked file cabinet. Paper records (data forms, list of patient names, and unique identifiers, etc.) will be kept in a locked file cabinet with access granted only to study investigators. No identifying personal health information will be used in any publication from this study. Collected information (including patient identifiers) will be destroyed within 5 years after publication. The protected health information used in this study will not be reused or disclosed to any person or entity outside of the investigator nor will it be used for other research.

10.0 Budget

Research staff support from DI-Office of Clinical and Translational Research
DICRC funding for scan time (PET/CT (CABI): $790/hr x 45 patients x 2 time points =$71,100)
Blue Earth Diagnostics (BED) will provide the dose upon completion research agreement with MDACC (18F-Fluciclovine: $6200/dose x 45 patients x 2 time points =$558,000)

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