Title:

A Pilot Study of F-18 Fluciclovine-PET/CT as A Diagnostic Tool for Bone Metastases in Patients With Hormonal Sensitive and Resistant Prostate Adenocarcinoma

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Background:

Approximately one-third of men treated for primary prostate cancer (PC) will have biochemical recurrence (BCR) of prostate cancer within 10 - 15 years after initial treatment. Approximately one-third of men with BCR will develop metastatic disease within 8 years. Thus, determining the location of the recurrence is critical, since it guides the optimal choice of therapy. In other words, treating all men with BCR for potential metastatic disease would result in overtreatment of two-thirds. However, knowledge of the location of the disease for those patients who do develop recurrence and metastasis can direct salvage surgical or radiation therapy. Biochemical recurrence is most often detected through the blood test for prostate specific antigen (PSA). While the blood test can detect early recurrence, it is severely limited since it cannot localize the site of disease recurrence. Approximately 90% of the standard battery of imaging tests, including computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy, may be negative at the time of detection of BCR when PSA levels are still low and hence a new more effective detection modality is needed.

In 2016, a new positron emission tomography (PET) radiopharmaceutical was approved by the United States Food and Drug Administration for localizing BCR in prostate cancer. This new radiopharmaceutical, F-18 fluciclovine, is like amino acids which are the building blocks of proteins. When F-18 fluciclovine is injected into the bloodstream of a patient, prostate cancer cells accumulate F-18 fluciclovine, and then a PET/CT scanner is used to localize the fluciclovine and thus the cancer. This detection modality proved to be effective and safe.

Significance:

F-18 fluciclovine gained approval from strong data which accurately correlated imaging with biopsy results; however, only a small number of those biopsies were from bone. Thus, there is a need for more data on the accuracy of F-18 fluciclovine with regards to PC spreading to the bone. In addition, we see on average 180-200 patients with prostate cancer per year and hence we can accrue well for this trial.

Study Hypothesis:

1. Validation by core needle biopsy of suspected osseous metastases identified on F-18 fluciclovine-PET/CT in patients with castrate resistant prostate cancer (CRPC) in need for biopsy for molecular testing.
2. Correlate the results of blood cell free DNA mutational analysis, tissue mutational testing of the biopsy material, and results of the F-18 fluciclovine-PET/CT (standardized uptake value (SUV) of lesions and extent of disease). This can assist with the identification of targetable mutations in the future for approved drugs in prostate cancer. For example, olaparib is currently approved for the treatment of prostate adenocarcinoma harboring the following mutations: BRCA1/BRCA2/PALB2/FANCA/CHK2/ATM. This secondary aim is exploratory.

Methods:

The study will consist of prostate cancer patients who would not ordinarily obtain an Axumin-PET scan for routine standard of care but have a need for bone biopsy. This will include patients with metastatic castrate resistant prostate cancer. The current standard of care is to obtain molecular testing for patients with prostate cancer castrate resistant disease for BRCA1, BRCA2, PALB2, CHK2, FANCA, and ATM as olaparib is approved for these patients after progression on chemotherapy and targeted drugs [2]. Moreover, the FDA recently approved pembrolizumab for patients with MSI-H solid tumor, which includes patients with prostate cancer, after a clinical trial showed robust results for these patients [3]. Hence, molecular testing is recommended as part of standard of care therapy for these patients due to FDA approved drugs that can provide clinical benefit for patients. Moreover, since PC most commonly metastasizes to the bone, most of the attained biopsied specimens are from the bone. This reflects current standard of care (SOC) therapy in GU-oncology clinics. cfDNA testing (Guardant360) is used as SOC therapy in clinics to obtain potential targetable mutations, for clinical trial participation, for patients with castrate resistant prostate cancer who have been treated with SOC therapy and their disease is still progressing.

The trial will obtain correlative F-18 fluciclovine-PET/CT imaging and bone biopsy results on a total of 15 patients with prostate cancer. Patients with negative biopsies will be followed for minimum of another 12 months (SOC imaging and clinical assessment) for possibility of false negative biopsy. We will review medical records at 12 months post bone biopsy.

As standard of care, mutational analyses of the biopsy material (CARISx) and blood cell free DNA (Guardant360) will be obtained. These results will also be compared with SUV of lesions and extent of disease as potential imaging biomarkers of certain mutations or disease aggressiveness.

Statistical Considerations:

The study will calculate sensitivity, specificity, true positive and false positive rate of positive bone findings on F-18 fluciclovine-PET/CT scan compared to gold standard of bone biopsy. The study will also estimate the differences in the SUV parameters using a 95% confidence interval.

Risk to Participants:

Subjects are going to have bone biopsies as standard of care, therefore there is no additional risk being a participant in this study.

Subjects will receive the additional radiation from the non-standard of care F-18 fluciclovine-PET/CT scan.

PET/CT scan: A PET/CT scan with F-18 fluciclovine injection is a nuclear imaging test that scans the body from head to thigh and detects cancer. The risks to the subject associated with PET/CT scans that are part of normal cancer care are small. A radiotracer chemical is used in PET/CT scans; the amount of radiation the subject is exposed to is low and is considered so small that it does not affect the normal processes of the body. There is a rare risk of a major allergic reaction to the radiotracer.

Number of patients whose PET images will be analyzed:

15 men .

Data and Safety Monitoring Plan:

1. Identification of the DSMB obligated for oversight responsibilities:
The University of Arizona Cancer Center Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for this trial. This study has been assigned a Low Risk level by the DSMB.

2. Identification of the entity obligated for routine monitoring duties:
Routine monitoring will be provided by the Quality Assurance/Quality Control (QA/QC) Program to ensure that the investigation is conducted according to protocol design and regulatory requirements.

This trial will also undergo real-time monitoring by the PI and study team, including documentation of real-time monitoring of any new or ongoing safety issues.

The trial will have a AE/SAE log that will be reviewed and signed by the PI in a timely manner of the knowledge and documentation of an AE occurring. SAEs will be reviewed within 24 hours of notification of event.

3. Monitoring progress and data review process:
Routine monitoring of subject data will be conducted at least quarterly.

The first routine monitoring visit will include at a minimum:

- Informed consent – 50% of cases enrolled;
- Subject eligibility – 10% of cases, up to two subjects;
- Data review – 10% of cases, up to two subjects.

All subsequent monitoring visits will consist of randomly selected subject cases based on current enrollment and include continuing review of previously selected cases, as applicable.

A monitoring visit report and follow-up letter will be completed approximately two weeks after the routine monitoring visit; a copy will be maintained in the study file. The monitor will request additional source documentation, clarification, information, or corrections to the CRF and/or regulatory records from the Clinical Research Coordinator (CRC) or other applicable staff responsible for the study and resolution of queries/findings. Documentation of such a request will be maintained with a copy of the monitor's visit report for follow-up at the next monitoring visit. Electronic records will be available in the institutional database or provided by the QA/QC Program staff.

The Principal Investigator will ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Form (CRF), or other acceptable data formats. Source documentation supporting the study data should indicate the subject's participation in the trial and should document the dates and details of study procedures, adverse events, and patient status.

Case report forms, which include the inclusion/exclusion criteria form, adverse event forms and serious adverse event forms *[other forms, depending on study]* should be completed via the institution database or other acceptable data formats. Trials using paper CRFs will have the data entered with a black ball-point pen or typed. Corrections to the forms should not obscure the original entry and should be made by striking the incorrect information with a single line. Each strike should be accompanied by the initials of the corrector and the correction date. All subject forms and study files will be stored in a secure area limited to authorized staff.

Note: Routine monitoring of regulatory documents will be conducted at least annually.

4. Process to implement study closure when significant risks or benefits are identified:

We do not anticipate any additional significant risks or benefits associated with the research. If there is a reason to close the study before the planned study end, there are no additional risks to the subjects for sudden withdrawal. The subject care would continue with the standard of care plan in the event we closed the study due to any newly identified significant information.

5. Description of adverse events and reporting procedures:

ADVERSE EVENTS: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Any and all adverse events will be recorded on the UACC adverse events record form and reviewed by the Principal Investigator.

All adverse events will be classified using either the MedDRA term or NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and will address:

- Grade
- Relationship to study drug (not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

SERIOUS ADVERSE EVENTS: A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

a) Results in death;
b) Is life-threatening;
c) Requires in-patient hospitalization or prolongation of an existing hospital stay;
d) Results in disability persistent or significant disability/incapacity, or:
e) Is a congenital anomaly/birth defect.

Note: A SAE may also be an important medical event, in the view of the investigator that requires medical or surgical intervention to prevent one of the outcomes listed above.

All serious adverse events, regardless of attribution, and any deaths will be reported within 24 hours of notification of the event to the sponsor and, if applicable, any collaborating entity. All serious adverse events and any deaths will be reported to the DSMB and to the University of Arizona Human Subjects Protection Program per the guidelines set forth in University of Arizona Cancer Center Data and Safety Monitoring Board Charter, Table 5: Adverse Event Reporting.

All submitted serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and then reviewed by the DSMB Chair. The assigned QA/QC Monitor will review the SAE reporting process to confirm reporting requirements are met.

6. Plan for assuring data accuracy and protocol compliance:

Routine study activity and safety information will be reported to the DSMB on a quarterly basis, or more frequently if requested. These reports will include:

- Study activity, cumulative and for the period under review;
- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies)

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least annually.

7. Identification of the sponsor or funding agency, as applicable:

The PI will immediately notify; in writing, the funding agency, if applicable, any action resulting in a temporary or permanent suspension of the study. A copy of this correspondence will also be forwarded to the DSMB and the SRC.

References:

1) Christopher Sweeney NEJM 2015, N.D. James NEJM 2017, and Karim Fizazi NEJM 2017

2) J Mateo NEJM 2015

3) Luis A Diaz JCO 35, no. 15 suppl. May 2017 3071-3071