Official Title: A Pilot Study of 18Fluorine-Fluciclovine Positron Emission Tomography/Computed Tomography for Staging Muscle Invasive Bladder Cancer Preceding Radical Cystectomy.

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Protocol Title:

A Pilot Study of 18Fluorine-Fluciclovine Positron Emission Tomography/Computed Tomography for Staging Muscle Invasive Bladder Cancer Preceding Radical Cystectomy.

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DF/HCC Site-Responsible Research Doctor(s) / Institution(s):
Heather Jacene, MD., Dana-Farber Cancer Institute

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have muscle invasive bladder cancer, for which a radical cystectomy is planned.

This research study is studying a positron emission tomography (PET) agent called ^{18}F-fluciclovine. The purpose of the study is to evaluate how well ^{18}F-fluciclovine-PET scans determine the extent of muscle invasive bladder cancer (as compared to regular CT and MRI imaging) and whether ^{18}F-fluciclovine-PET scans can provide information about the pathologic grade of the tumor (which is traditionally only available from surgical samples).

^{18}F-fluciclovine does not treat cancer; it only allows physicians to take images (pictures) of it. While you are on this study, you will receive treatment for your cancer based on the recommendations of your primary oncologist/urologist. This research does not specify which type of treatment you will get.

The study will involve you undergoing one ^{18}F-fluciclovine-PET/CT scan within 6 weeks of your regular CT and MRI imaging, and before your scheduled surgery. This scan will take 1 hour to complete.

For purposes of this research, you will be referred to as a “participant”.

Blue Earth Diagnostics Inc. is supporting this research study by providing funding for the research study and the ^{18}F-fluciclovine.

This research consent form explains why this research study is being done, what

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is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

Because information about you and your health is personal and private, it generally cannot be obtained without your written permission. By signing this form, you are providing that permission and your information may be obtained and used in accordance with this informed consent and as required or allowed by law. This means that researchers may obtain information regarding your past medical history, as well as specimens and samples from previous health care providers such as hospitals and labs.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a pilot study, which is the first-time investigators are examining this study imaging agent, ^{18}F-fluciclovine, for use in imaging bladder cancer.

Staging of muscle invasive bladder cancer is currently done using computed tomography (CT) and/or magnetic resonance imaging (MRI). Both CT and MRI are useful to determine the extent of bladder cancer, but some studies show that up to 40% of patients with negative CT or MRI scans for disease outside the bladder are found to have disease outside the bladder (in lymph nodes near the bladder) at the time of surgery.

Given the limitations of the imaging exams currently used for staging bladder cancer, new techniques and imaging agents that can better identify metastatic lesions, especially within the pelvis, are desired and would be very useful.

^{18}F-fluciclovine is a new radiotracer that was recently approved to evaluate lesions in recurrent prostate cancer (but not for bladder cancer). This radiotracer targets amino-acid receptors, which are overexpressed in multiple cancers.

Studies have shown that ^{18}F-fluciclovine PET/CT can visualize other types of cancers, such as breast cancer. A major advantage of ^{8}F-fluciclovine is that it does not get into the bladder during the time of imaging. This may make it easier to see disease in the pelvis that is outside the bladder.

The purpose of this study to determine whether ^{18}F-fluciclovine PET/CT can better stage muscle invasive bladder cancer compared to conventional CT or MRI. A secondary aim of this study is to determine whether ^{18}F-fluciclovine PET/CT can reveal the pathologic grade of the bladder cancer, which is only determined from pathology specimens obtained at surgery.

While you are on this study, you will be receiving treatment for your cancer based on the recommendations of your primary oncologist/urologist. The treatment for your cancer is not specified by this study. The results of the ^{18}F-fluciclovine PET/CT scan will be given to your oncologist/urologist.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following

- Have CT and/or MRI imaging only
- Receive standard treatment including radical cystectomy.
- Take part in another research study.
- Receive no therapy specific to your cancer.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Performance status**, which evaluates how you can carry on with your usual activities.
- **An assessment of your tumor** by one or more of the following standard assessment tools: X-ray, CT (Computerized Tomography) scan, MRI (Magnetic Resonance Imaging) or PET (Positron Emission Tomography) scans
- **Blood tests.**
- **Urine test**.

If these tests show that you are eligible to participate in the research study, you may begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Study Treatment Overview:

If you take part in this research study, you will be scheduled for a ^{18}F-fluciclovine PET/CT scan within 4 weeks of your staging CT or MRI study.

Study Visit:

This visit will involve the following:

- ***Scans (or Imaging tests):*** *We will assess your tumor by* ^{18}F-fluciclovine PET/CT

You will be asked to stop any strenuous exercise for 24 hours immediately *before* the PET/CT scan, since this may cause the imaging agent to preferentially accumulate in muscles rather than in cancer cells.

Pictures of your organs will be taken using a PET (Positron Emission Tomography) scanner. At the same time, a CT (computed tomography) scan will be performed. You will be asked to lie flat on your back for up to 60 minutes while research PET and research CT images are being taken. ^{18}F-fluciclovine, a radioactive substance that can look at amino acid receptors present in cancer cells, will be injected into your vein using a needle while the PET/CT scan is performed. the PET/CT scan.

This ^{18}F-fluciclovine-PET/CT scan is part of research (in addition to the regular CT or MRI scans) and is not part of regular cancer care.

Surgery:

Your participation in this research study will be complete at the time of your radical cystectomy surgery. At that time, surgical samples obtained during the operation will be compared to the findings made during the PET/CT scan.

Research Study Plan:

	Visit 1 Screening (Standard of care)	Visit 2 Research study	Visit 3 Surgery (Standard of care)
Medical History & Physical Exam	X		
Blood Test	X		
CT or MRI Scan	X		
^{18}F-fluciclovine PET/CT		X	
Radical cystectomy			X
Pathology analysis of surgical specimens			X

Planned Follow-up:

We will plan to keep track of your medical condition within 30 days of the research PET/CT scan. During and after this time period, you will continue to be managed by your urologist, as per the standard of care for your condition.

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this research study up to the time of your radical cystectomy surgery.

You may be taken off the research study to evaluate ^{18}F-fluciclovine PET/CT for many reasons including if:

- It is in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens
- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed. You will continue to receive care from your urologist to manage your bladder cancer.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a study imaging agent that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study imaging agent for any reactions to the agent. If you experience side effects, they may go away after a short period of time. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study imaging agent taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with ^{18}F-fluciclovine PET/CT:

Rare (Less than a 1% chance that this will happen)

- Pain at the injection site.
- *Skin redness and swelling at the injection site*
- *Changes in taste sensation after the imaging agent injection*
- *Bleeding at the injection site.*
- *Infection at the injection site.*
- *Claustrophobia while acquiring the PET/CT scan*

Cancer research often includes biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures done only for the purposes of research.

Radiation Risks Associated with Scans:
While you are in this research study, one ^{18}F-fluciclovine PET/CT scan utilizing radioactivity will be used to evaluate your disease. This radiation exposure is not necessary for your medical care but is required to obtain the desired research information. From participating in this study, the maximum amount of additional radiation your body will be exposed to in one year is less than what a radiation worker is legally allowed to receive in one year. In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

Very rarely, some people have allergic reactions (such as hives and itching) to the radiotracers that are injected into the vein for the PET/CT scans. Any adverse events are very rare for radiotracers (<0.003%) and serious reactions

(for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are even more rare.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

We do not know if taking part in this study will help you. Your oncologist/urologist will be given the results of the ^{8}F-fluciclovine PET/CT scan and they may decide to use the results to guide their treatment plan. We hope the information learned from this research study will help doctors learn more about ^{18}F-fluciclovine PET/CT as a diagnostic imaging test in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

If you decide to withdraw from a study that involves de-identified imaging data, it will not be possible to remove the imaging dat that have already been submitted to a imaging data archive.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for participating in this study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

J. WHAT ARE THE COSTS?

You will not be charged for the costs of the imaging agent or the PET/CT scan.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. Standard of care is the care that you would receive regardless of whether you were enrolled in the study or not. You may be responsible for co-payments, co-insurance, premiums and deductibles that are typical for your insurance coverage.

Taking part in this research study will not lead to added costs to you or your insurance company.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

[redacted]

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

K. WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to your insurance company. You will be responsible for deductibles, co-insurance and co-payments. There are no plans to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for

Medicare & Medicaid Services. We will not use this information for any other purpose.

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The study team plans to publish the results of this research study and when we do, we may be asked to make the data we collect available to other researchers. We will not include information that identifies you in any publications or to the researchers who request the data to do additional research.

"As participation in this study involves providing a specimen of your tissue, please know that if the research doctor leaves the institution, the research and the tissue might remain at the DF/HCC or might be transferred to another institution."

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

[redacted]

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at Dana-Farber Cancer

Institute (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

N. FUTURE USE OF DATA AND SPECIMENS

Your personal information and/or biospecimens collected during this study may be stored and used for future research. If so, any personal identifiers will be removed so that the information or samples cannot be linked back to you. As a result, we will no longer be able to identify and destroy them.

Investigators, including investigators from collaborating institutions, can request this data and samples for new research. Samples and data may also be shared with outside non-profit academic investigators as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate.

You will not be asked to provide additional informed consent for the use of your de-identified information or samples in future research.
Future research studies may include genetic research. Your genes are unique to you. At this time, you cannot be identified through this research. There is a risk that you might be reidentified in the future as genetic research progresses

O. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug(s) used in the study and for the purpose of this or other research relating the study drug(s) and their use in cancer;
- To better understand the diseases being studied and to improve the design of future studies; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, representatives, business partners, and its agent(s): Blue Earth Diagnostics Inc.

- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"

P. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary, and I can withdraw at any time

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

☐ *As someone who understands both English and the language used by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.*

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

- ☐ 2a) gave permission for the adult participant to participate
- ☐ 2b) did not give permission for the adult participant to participate

To be completed by person obtaining consent: