INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0014 PRINCIPAL INVESTIGATOR: Karen A. Kurdziel, M.D.

STUDY TITLE: Phase 0 Trial of [F-18]-5-Fluoro-2'-Deoxycytidine with Tetrahydrouridine

Continuing Review Approved by the IRB on 02/27/17
Amendment Approved by the IRB on 03/18/15 (G) Date Sent to Web: 03/18/17
IV FdCyd + THU

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

There is a treatment research study being done in patients with advanced cancer in which two experimental drugs are being given, FdCyd (also called 5-fluoro-2'-deoxcytidine), and THU (also called tetrahydrouridine). You have agreed to participate in that treatment study. There is not a lot of information known about how FdCyd works in the body. Therefore, this study is being done to test if PET (Positron Emission Tomography) imaging with F-18 FdCyd (a radiolabeled version of the experimental treatment drug FdCyd) will give us information about how much of the treatment drug your tumor is taking up. This will help us understand how

FdCyd works in the body to fight cancer. This is not a treatment study; participating in this study will not help in the treatment of your cancer.

Why are you being asked to take part in this study?

You are being asked to participate because you are enrolled in the treatment protocol entitled: A Multi-Histology Phase II Study of 5-Fluoro-2'-Deoxycytidine with Tetrahydrouridine (FdCyd + THU) NCI # 09-C-0214/CTEP # 8351 being performed in the Medical Oncology Branch, NCI/NIH. Throughout this consent document, the treatment protocol will be referred to as 09-C-0214/8351.

How many people will take part in this Study?

We expect to enroll 10-20 patients in this experimental imaging study.

Description of Research Study

Participation in this study involves undergoing 2 PET/CT imaging sessions, one before starting your treatment on 09-C-0214/8351, and one after you start treatment on 09-C-0214/8351. The reason 2 imaging sessions are being done is to see if the quality of the images gets better after you have some of the treatment FdCyd in your body.

What will happen if you take part in this research study?

Before you begin the imaging study

This study is being performed in conjunction with protocol 09-C-0214/8351 that you have enrolled in. If you chose to participate in this imaging study, we will first make sure you are eligible. To make sure it is safe to undergo the scans we will ask you some questions about your medical history and any allergies, if you are a woman able to get pregnant, we will also perform a pregnancy test (blood or urine) to make sure you are not pregnant, and ask you to sign this informed consent.

During this imaging study

Before beginning your first therapy dose of FdCyd on protocol 09-C-0214/8351, we will start giving you Tetrahydrouridine (THU), a compound that blocks the enzyme which breaks down FdCyd, through an IV (intravenous-small plastic tube placed in a vein in your arm). There are no known side effects to THU at the dose levels you will be given, and this additional dose will NOT affect your future treatment with FdCyd + THU. While the THU is being given to you, you will also receive a small amount of F-18 FdCyd. This is a radiolabeled version of the therapy drug you will receive on 09-C-0214/8351. The F-18 radiolabel acts as a tag, and lets us see on the PET/CT scan where the FdCyd goes in your body.

The F-18 FdCyd is given into your IV over about 1-3 minutes. You should not feel anything during this time. After you are given the F-18 FdCyd you will have a PET/CT scan. You will need to lie still on your back on the scanning table for up to 75 minutes for the first scan and ~35 minutes for an additional scan. The PET/CT scan consists of a "low dose transmission" CT (sometimes called a CAT scan), followed by PET imaging. The IV of THU will be continued throughout the scanning period and we will watch you closely for any side effects.

This imaging procedure will be repeated on a separate day, while you are receiving your therapeutic infusion of FdCyd + THU on protocol 09-C-0214/8351. Repeat imaging will be performed 2-5 days after the initiation of FdCyd + THU therapy and at least 2 hours after dosing.

When you are finished the Imaging Sessions

When you are finished with each PET/CT imaging session, there are no restrictions on your diet or activity as a result of this protocol. After you have completed the second imaging session you will be taken off this imaging study and will continue your participation on protocol 09-C-0214/8351. We may use the information from the protocol 09-C-0214/8351; we will compare how well the F-18 FdCyd went into the tumor with your tumor response after receiving the experimental treatment agents.

What does this study involve?

This study involves two F-18 FdCyd PET/CT imaging sessions, one performed during infusion of THU, and a second performed while receiving a treatment dose of FdCyd + THU as prescribed by the Phase 2 protocol. You will be required to have an IV catheter put into a vein in your arm for each PET/CT imaging study. You will need to lie still on the PET scan table for up to 2 hours during the imaging session.

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child.

Alternative Approaches or Treatments

This is not a treatment study. This study can only be performed in conjunction with your participation on protocol 09-C-0214/8351. The alternative is to not participate. If you choose not to participate in this imaging study, it will not affect your ability to participate in protocol 09-C-0214/8351.

What other choices do I have if I do not take part in this study?

As this is not a treatment study, you can choose not to participate.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

Risks of FdCyd/THU

COMMON, SOME MAY BE SERIOUS In 100 people receiving FdCyd/THU, more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Tiredness • Bruising, bleeding • Infection, especially when white blood cell count is low • Loss of appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving FdCyd/THU, from 4 to 20 may have:
• Abnormal heartbeat • Bloating, constipation, heartburn, passing gas • Pain • Dry mouth, skin • Sores in mouth which may cause difficulty swallowing • Chills, fever • Swelling of arms, legs • Weight loss • Dehydration • Muscle weakness • Dizziness, headache • Changes in taste

- Numbness, tingling or pain of the arms and legs
- Cough, shortness of breath
- Nose bleed
- Hair loss, itching, rash
- Increased sweating
- Redness, pain or peeling of the palms and soles
- Low blood pressure which may cause feeling faint

Risks of FdCyd

No adverse effects are expected from the small amount of F-18 FdCyd that will be administered under this protocol (for PET/CT imaging). THU has no expected side effects at the dose used in this study and may increase the risk of experiencing FdCyd side effects. Even though we do not anticipate adverse side effects, you should tell the doctors or nurses supervising the scan of any discomfort.

Potential discomforts from the IV and injection of the radiotracer include

- Mild pain and possible bruising at the injection site
- Discomfort from lying on a hard surface for about 75 minutes
- Infection at the IV site or infection in the blood
- Leaking of the dose of F-18 FdCyd into the skin and tissue around the IV
- Allergic reaction
- Vasovagal reaction, a lowered blood pressure and heart rate during the IV insertion

Risks of Radiation

F-18 FdCyd is a radioactive tracer and you will receive a small amount radiation exposure that you would not otherwise receive. Please note that this radiation exposure is **not** necessary for your medical care and is for research purposes only.

Using the standard way of describing radiation dose, from participating in this study and undergoing a total of two F-18 FdCyd PET/CT imaging sessions (including radiation from the F-18 FdCyd injection and low dose transmission scans), the amount of radiation exposure you will receive is equal to a uniform whole-body exposure of 3.5 rem, although each organ will receive a different dose. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil. The dose that you will receive from this research study is about the same amount you would normally receive in 11.7 years from these natural sources. The organs receiving the

highest doses are the urinary bladder wall (15.3 rad), the surfaces of the bones (4.15 rads), and the liver (4.15 rads).

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effects were ever observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose - even low doses such as those received during this research.

If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects. Please tell your doctor if you have taken part in other research studies or received any medical care at the NIH or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

When the medication is put through a vein in your arm, you may experience a moment of pain. In addition, there is the discomfort of having the catheter taped to your arm. Other risks include bleeding, bruising, temporary clotting of the vein, and infection.

Potential Benefits of Participation

Are there benefits to taking part in this study?

As this is NOT a treatment protocol, you will not to have any direct benefits; however, the result of this study may help doctor's better understand how and how much FdCyd enters tumors, which may benefit other patients in the future who have cancer.

Research Subject's Rights

What are the costs of taking part in this study?

Participation in this research study is voluntary and you can withdraw at any time. We encourage you to ask questions so you can make the most informed decisions during your participation in this study. Refusal to participate will not result in penalty or less benefits to which you are otherwise entitled.

It is important to stress that being in this protocol does not promise long-term medical care at the NIH Clinical Center. If there is no further research study that is suitable for you and your state of disease, or if you are not currently on another research study, you will be returned to the care of your referring doctor or institution, or alternative sources of care closer to your home. If you

have any questions about your treatment in this protocol at NIH, you can contact the Principal Investigator, Dr. Karen A. Kurdziel (301-443-0622) or the patient care representative (301-496-2626).

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

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.

Stopping This Study

Your doctor may decide to stop your participation in this study for the following reasons:

- if he/she believes that it is in your best interest
- if you are no longer participating in protocol 09-C-0214/8351
- if you have side effects from the imaging sessions that your doctor thinks are too severe
- if the imaging study is stopped for any reason.

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Karen A. Kurdziel, M.D., Building 10, Room B3B403, Telephone: 301-443-0622. You may also call the Clinical Center Patient Representative at (301) 496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM FEBRUARY 27, 2017 THROUGH FEBRUARY 26, 2018.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____