INSTITUTE: National Cancer Institute

STUDY NUMBER: 16-C-0121 PRINCIPAL INVESTIGATOR: Andrea Apolo, M.D.

STUDY TITLE: A Pilot Clinical Trial of Genomic Based Assignment of Therapy in Advanced Urothelial Carcinoma

Continuing Review Approved by the IRB on 02/11/19

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Standard

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?

Urothelial cancer that has spread is currently incurable, yet there are only a small number of chemotherapy drugs that have been tested in this disease. Conducting standard trials of already FDA approved drugs in urothelial cancer would take years and be very costly.

In collaboration with the University of Colorado Comprehensive Cancer Center, we have developed an approach, the COXEN (Co-eXpression ExtrapolatioN) model which is the mathematical method that predicts whether cells respond to treatment, and that we think will help us determine, which, if any currently FDA approved anticancer drugs would be effective in your urothelial cancer based on the mutations (changes in genes) that are present in your tumor.

The study is being done in order to test whether it is possible to use the COXEN model to choose the next best therapy for your urothelial cancer (after it has gotten worse on standard therapy) in three weeks, which is about the usual amount of time a doctor would have to make treatment decisions outside of a clinical trial.

We will also look at how well your tumor responds to the next best therapy.

While all of the drugs used in this study are FDA approved, they are not necessarily approved for the treatment of urothelial cancer.

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

You are being asked to participate in this study because you have been urothelial cancer that has spread after you have received at least one line of chemotherapy.

How many people will take part in this study?

Up to 20 subjects will take part in this study.

Description of Research Study

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

Before you begin the study

You will undergo the following tests and/or procedures to find out if you can be in the study:

- Medical history
- Physical examination
- Routine blood and urine tests
- CT scan or MRI of your tumor
- Tests for certain viruses
- Pregnancy test if you are a woman who can have children (you will not be allowed to participate if you are pregnant)

We will also need a sample of your tumor from a previous surgery and a fresh mandatory biopsy to test using the COXEN model so that we may determine which of 75 approved drugs or combinations of these drugs should work best on your tumor. You will be given an information sheet about the drug(s) selected by the model.

During the study

You will undergo additional tests/procedures before you begin any study therapy. Some of the tests are the same as those done at screening and be repeated if they were performed within the appropriate timeframe. Additional tests/procedures include an EKG.

You will begin taking the assigned medication based on the study doctor's instructions and the information sheet specific to the drug(s) assigned to you by the COXEN model. Depending on the dosing schedule of the medication(s) you are assigned, you will be seen every 2 or 3 weeks. At each visit you will undergo routine blood and urine tests. You will continue taking the assigned drug(s) until you have intolerable side effects or until your disease worsens. If your disease worsens after beginning your first COXEN selected therapy, you will be given the option to then be assigned to a second COXEN selected therapy which will continue until intolerable side effect occur or your disease worsens. A second COXEN based regimen may also be selected if you must be removed from the first one due to side effects and the study doctor feels that it would be to your benefit.

If you are being seen every 2 weeks, you will have scans of your tumor every 8 weeks so we can determine whether your cancer is responding. If you are being seen every 3 weeks, you will have your scans every 9 weeks. You will undergo a second tumor biopsy, this one optional, at the time your disease gets worse the first time. The biopsy to be performed is exclusively for research purposes and will not benefit you. It might help other people in the future. You can decide whether or not you'd like to participate in the optional biopsy at the time of the biopsy.

Research Procedures

In addition to the biopsy, you will also be asked for additional blood and undergo scans for research testing.

Sampling

Blood and tumor tissue used for research studies will undergo genetic testing. Please note that the genetic analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your specimens that is performed in our research lab. However, in the unlikely event that we discover a finding that is believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

Scans

There are two additional FDG-PET MRIs scans which are being performed for research. These will be done before you start treatment and after 8 or 9 weeks, depending on the first treatment to which you are assigned. PET is a nuclear medicine medical imaging technique that produces a 3-D image of functional processes in the body. An FDG PET scan uses a small amount of a radioactive drug, ^{18}F-FDG (fluorodeoxyglucose) to show differences between healthy tissue and diseased tissue. Before the PET scan, a small amount of FDG is injected into you. Because cancer grows at a faster rate than healthy tissue, cancer cells absorb more of the ^{18}F-FDG. The PET scanner detects the radiation given off by the ^{18}F-FDG and produces color-coded images of the body that show both normal and cancerous tissue.

The PET scan will be done in combination with a convention MRI scan so that images of both anatomy (MRI) and function (PET) can be taken during the same examination.

On the day of your exam, you will be encouraged to drink water. You will be given an injection of ^{18}F-FDG. Then you will wait ~ 60 minutes for the drug to travel through your body after which you will be asked to urinate and then lie on a partially enclosed scanning table. The table will slide into the machine. You will be asked to remain still during the scan. You will hear buzzing or clicking sounds during the scan. You will need to lie still for about 20-60 minutes before coming off of the scanning table. If you feel any anxiety over being in enclosed spaces, let your study doctor know.

When you are finished taking the drugs

Four to five weeks after you have had your last dose of study drug, you will be asked to return to the NIH for a safety assessment that will include a medical history, a physical examination and routine blood tests. If you are unable to return to NIH, we will contact you by phone for an assessment.

We will remain in contact, generally by telephone, approximately every two months to follow the progress of your disease, to find out about any new cancer drugs you are taking and your survival status.

Treatment

Treatments covered under this study may include a single medication or a combination of medications, surgery or radiation to treat your cancer. These treatments will not be experimental. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. You may be asked to sign a separate consent form for any treatment procedures not outlined in this consent.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because the medicine may affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment and during study treatment. Please refer to your information sheet for how long after your last dose of study therapy you should continue practicing contraception. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Please refer to your information sheet. It is possible that some of the methods listed above may not be recommended for use with your assigned drug(s).

Risks or Discomforts of Participation

Risks of study drugs

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.

- The study doctor may adjust the study drugs to try to reduce side effects.

Please refer to the information sheet for your assigned drug(s) for the specific side effects.

Risks of research blood sampling

Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

Risks of biopsy

As indicated above, you will undergo 2 research biopsies (1 optional and neither of any medical benefit to you) to obtain tumor tissue during your participation in this study. One biopsy will be done before you have taken any study medication and the second biopsy is optional that will be done at the time your disease gets worse. The specific risks will depend upon the location of your tumor and the method by which it is biopsied. The doctor will review these specific risks with you and have you sign a separate consent for the biopsy. In general the potential risks of biopsy include bleeding and infection. A CT scan may also be used to guide the biopsy which brings the additional risk of exposure to radiation as discussed below.

Research radiation risks

In this study, you may be exposed to up to 2 CT scans to guide your biopsies and 2 injections of ^{18}F-FDG of 7 mCi each for imaging studies. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 2.5 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes 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.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material, you will not be

permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

Risks of genetic research

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

Additional risk from genetic testing in the face of a diagnosis of cancer is less likely.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Privacy Risks Associated with Return of Incidental or Secondary Findings

Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. While neither the public nor the controlled-access databases developed for this project will have information such as your name, address, telephone number, or social security number, it may be possible to identify you based on the information in these databases and other public information (including information you tell people or post about yourself). The risk of this happening is currently very low.

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

It is possible also that someone could get unauthorized access or break into the system that stores information about you. Every precaution will be taken to minimize this risk. There also may be other privacy risks that we have not foreseen.

Protections against misuse of genetic information

Since some genetic variations can help to predict future health problems for you and your relatives, this information might be of interest to health care providers, life insurance companies, and others. However, Federal and State laws provide some protections against discrimination based on genetic information. For example, the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, GINA does not prevent companies that sell life insurance, disability insurance, or long-term care insurance from using genetic information as a reason to deny coverage or set premiums. GINA also does not apply to

members of the United States military, individuals covered by the Indian Health Service, or veterans obtaining health care through the Veteran's Administration. Lastly, GINA does not forbid insurance medical underwriting based on your current health status though the Affordable Care Act limits consideration of pre-existing conditions by insurers.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental method of assigning treatment can be done quickly enough (within 3 weeks) to make it an effective tool in clinical practice. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

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

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back after your second COXEN selected treatment
- if you become pregnant
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- 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.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to collaborators or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

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

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- 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.

Will your 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. 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), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- Collaborators at the University of Colorado Comprehensive Cancer Center where the COXEN assay will be performed

Your individual genomic data and health information will be put in a controlled-access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to identify you. Researchers approved to access information in the database have agreed not to attempt to identify you.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand, however, that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

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.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

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, Andrea Apolo, M.D., Building 10, Room 13N240, Telephone: 301-480-0536. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

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 11, 2019 THROUGH FEBRUARY 25, 2020.

Signature of Investigator | Date | Signature of Witness | Date

Print Name | Print Name