INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0205 PRINCIPAL INVESTIGATOR: Andrea Apolo, M.D.

STUDY TITLE: A Phase II Study of Cabozantinib (XL184) in Patients with Advanced/Metastatic Urothelial Carcinoma

Continuing Review Approved by the IRB on 12/10/19
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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?

Cabozantinib is an agent that slows down the growth of blood vessels that feed tumors. Although it has been approved by the Food and Drug Administration to treat medullary thyroid cancer, it has not been approved for urothelial cancer and its use in this study is experimental. Early studies have also shown that prostate and ovarian tumors respond to cabozantinib. This study is being done to determine whether and measure how much tumors in patients with progressive urothelial carcinoma that have received prior chemotherapy respond to cabozantinib. In addition, we will measure how long it takes for disease to progress and whether cabozantinib improves overall survival and what the side effects of cabozantinib are.

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

You are being asked to take part in this study because you have been diagnosed with metastatic urothelial carcinoma or another form of bladder cancer that has been treated with chemotherapy in the past but continues to worsen.

How many people will take part in this study?

About 71 people will take part in this study.

How long will you be in the study?

You will be in the study for as long you are receiving benefit from cabozantinib without experiencing any intolerable side effects.

Description of Research Study

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

This study will be conducted primarily on an outpatient basis. You will take 60 mg of cabozantinib by mouth once per day on each day of a 28 day cycle. Cabozantinib should be taken on an empty stomach (no food should be eaten 2 hours before and 1 hour after taking cabozantinib). If you miss a dose, do not make it up the next day. Avoid eating or drinking grapefruit/juice or Seville orange while on this study.

You will be given a pill diary and a blood pressure monitoring form as part of the study. We ask that you record the times that you take cabozantinib each day in the pill diary.

If you have a history of high blood pressure, you will also be asked to take your blood pressure at home once a week and record it on a blood pressure monitoring form.

Please bring this (these) forms as well as all of your remaining study pills at each study visit.

In addition, if you are taking a type of drug called a bisphosphonate (eg. alendronate, risedronate, pamidronate, etc.), we ask that you tell your doctor about any dental procedures that you have planned before you see the dentist.

Before you begin the study:

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to the study team. These tests include:

- A complete physical examination including your medical history
- A 12-lead ECG (electrocardiogram)
- Blood and urine tests

- MRI or CT scan of your chest, abdomen and pelvis (This scan will be repeated if you have stopped taking the study drug and start again after more than 6 weeks)
- Sodium fluoride-18 PET CT scan in the event that you have bone disease. This is a special CT that uses a radioactive tracer (fluoride 18) to help us better see disease in your bones. (This scan will be repeated if you have stopped taking the study drug and start again after more than 6 weeks)

A pregnancy test if you are female. You will need to supply a complete list of your current medications to the study doctor. This includes over-the-counter medications and herbal supplements. Some medications may interact adversely with cabozantinib and it is important that your study doctor and prescribing physician be aware of any potential risks so that they can prescribe alternative medications as necessary. If you do not already do so, please consider carrying a list of your medications at all times.

During the study:

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures:

- Dental examination (if you have used or are using a type of medication called a bisphosphonate) – before you receive study drug

You will need the following tests and procedures that are part of regular cancer care.

- Blood tests
- Pregnancy test if you are female – every 4 weeks

You will also need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- MRI or CT scan of the chest, abdomen, and pelvis - every 8 weeks
- Sodium fluoride-18 PET CT scan in the event that you have or are suspected of having bone disease – every 8 weeks
- Physical examination - every two weeks for the first 12 weeks, then every 4 weeks
- Blood tests to evaluate toxicities- every two weeks for the first 12 weeks, then every 4 weeks
- Urinalysis – every two weeks for the first 12 weeks, then every 4 weeks

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- 12-lead ECG
- Research blood tests to study the effects of cabozantinib on markers in your blood. The research blood samples collected as part of this study are not expected to produce a significant decrease in the total amount of blood in your body. These tests will be done:
  - After you have enrolled but before you receive any study drug
  - Before you receive the study drug at each study visit and at the time of tumor biopsy. (May be collected up to 5 days before.)
  - At the time your disease worsens
  - Some samples collected may be sent outside NIH for analysis
- Research urine sample will be collected, at each clinic visit to study the effects of cabozantinib on markers in your urine.
- Quality of life survey. We will ask you to complete a survey before you take any study drug and at the beginning of cycle 3 of your treatment to help us determine the severity of any symptoms you might be experiencing. The survey will take about 5 – 10 minutes to complete.
- Biopsy (required for study participation)
  - We will also require a sample of your tumor to study how cabozantinib might affect the immune cells within the tumor and the effects of this treatment on the blood vessels of your tumor. If you have any tissue from a previous surgery or biopsy, we will ask you to provide it to us. If adequate tumor tissue is not available, we will ask you to undergo a biopsy.
- FDG PET/CT and optional FDG PET/MRI for research
  - PET stands for Positron Emission Tomography. It is a technique that produces a 3-D image of functional processes in the body. PET/CT is an imaging technology that fuses PET images and CT images into one image. FDG or Fluorine-18 2-fluoro-2-deoxy-D-glucose is a radioactive tracer similar to sugar that is used to allow us to see images of how your cells take up the tracer. You will be asked to undergo PET/CT at the following times: before you have started taking the study drug, week 4 and week 8. We will not be using the results of the PET/CT to make clinical decisions. We will use these results only to determine how well they can track the progress of your disease.

- On the day of your FDG-PET/CT scan, you will be first given an injection of a small amount of FDG into a vein in your arm or hand. The amount of radiation is very small, no more than what you would have during a normal x-ray. It only stays in your body for few hours. The FDG will travel to particular parts of your body. It travels to places where glucose is used for energy. It shows up cancer because the cancer cells use glucose in a different way from normal tissue.
- The PET/CT scanner is a large machine with an opening of 27 to 30 inches in the middle. It looks like a donut with a table in the middle. Approximately 30-90 minutes after the injection of FDG, you will be asked to go to the bathroom (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.
- The entire FDG-PET/CT scan procedure is expected to take about 2 hours.
- After the FDG-PET/CT scan is completed, you will be given the option of undergoing an additional scan called FDG-PET/MRI. You will not receive any additional injections of radioactivity and, because the MRI does not use ionizing radiation, there will be no additional radiation exposure. An additional hour of scanning will be required to complete this optional study.

  You will be given the opportunity to undergo the optional FDG PET/MRI after your FDG-PET/CT.

You will be provided with a wallet-sized information card ("Information on Possible Drug Interactions") that names your study agent and outlines the specific risk of adverse interactions with other drugs or substances. Should you require any new medications while on study, please consult with your study doctor if possible, and present the card to the prescriber (doctor, pharmacist, physician's assistant, or nurse practitioner). Please check with your doctor/prescriber or pharmacist before using any new over-the-counter medications or herbal supplements.

Stopping Therapy

Your participation in this study will continue until either you or your study team decides that this medication is not beneficial to you. If your disease completely disappears, the medication will be stopped (drug holiday). You will be monitored by scans every 12 weeks. If your disease comes back, you will have the option to resume treatment. Your participation is voluntary; so you may stop receiving the study drugs at any time, but we ask that you speak to your study team before stopping. Your doctor may decide to permanently stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease progresses during treatment
- 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
- if you are unable to comply with the protocol requirements
- if you are unable to tolerate the lowest dose of cabozantinib (20 mg once per day)
- if your treatment has been delayed for more than 6 weeks and it is not clear that you have been benefiting from cabozantinib
- if you are a woman and you become pregnant

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 Exelixis, the manufacturer of the study drug, or their 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.

When you are finished taking cabozantinib:

30 – 37 days after you have stopped taking the study treatment (except when you stop treatment in order to take a drug holiday), we will telephone you to determine whether you have experienced any side effects. You will receive instructions on how to mail back any drug you have remaining at this time.

If you have experienced any side effects that are still ongoing at the time of this call, the study team may request that you continue follow-up and/or testing for this until it has resolved.

After this phone call, someone on the study team will try to contact you or a member of your family every 2 months, give or take a week to see how you are doing and to find out if you have started any other anti-cancer therapy.

Birth Control

You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. It is important you understand that you need to use birth control before starting study treatment, during study treatment, and for 4 months after you finish study treatment. 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

You should recognize that no method of birth control besides abstinence provides 100% protection from pregnancy.

Women should not breastfeed a baby while on this study.

Risks or Discomforts of Participation

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

If you choose to take part in this study, there is a risk that the XL184 (cabozantinib) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The XL184 (cabozantinib) 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 test 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 things to know 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, and some may never go away.

- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Risks and side effects related to cabozantinib:

COMMON, SOME MAY BE SERIOUS In 100 people receiving XL184 (cabozantinib), more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Weight loss, loss of appetite • Changes in taste • Redness, pain or peeling of palms and soles • High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving XL184 (cabozantinib), from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Constipation, heartburn • Dry mouth, skin • Sores in the mouth which may cause difficulty swallowing • Swelling of arms, legs • Infection • Bruising, bleeding • Dehydration

- Muscle weakness
- Dizziness, headache
- Cough, shortness of breath
- Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine
- Bleeding from multiple sites including the nose
- Changes in voice
- Hair loss, rash
- Change in hair color
- Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS

In 100 people receiving XL184 (cabozantinib), 3 or fewer may have:

- A tear or hole in internal organs that may require surgery
- Non-healing surgical site
- Damage to the jawbone which may cause loss of teeth
- Bleeding in the brain which may cause confusion
- Stroke which may cause paralysis, weakness
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Lung collapse

Procedure Risks

In addition to risks posed by the cabozantinib, you may be exposed to the following risks/discomforts:

Blood drawing: Local pain, bruising, bleeding, blood clot formation, and, in rare instances, an infection might occur at the site where blood is drawn. There is also the possibility of dizziness or fainting while your blood is being drawn.

ECG: The ECG (electrocardiogram) is a procedure that requires you to lie still for a few minutes while adhesive pads are attached to your chest to record the activity of your heart. The ECG leads may cause slight discomfort during their placement on and removal from your skin.

Biopsy: Your tumor tissue will be analyzed for the presence of a protein called c-met. Tissue may be analyzed from a previous biopsy or a new tissue biopsy will be obtained prior to starting therapy. If we have enough tissue, we may also test this sample for white blood cells, blood vessels along other factors that affect tumor growth or factors that are expected to respond to the study drug. Furthermore, we may test any remaining sample for gene changes (see

Optional Biopsy for a description). This procedure usually causes only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site.

Radiation Risks:

This research study involves exposure to radiation from 3 whole body PET/CT scans of 10mCi F-18 FDG. 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 3.2 rem which is below the guideline of 5 rem per year allowed for adult 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.

Potential Benefits of Participation

Are there benefits to taking part in this study?

Taking part in this study may or may not make your health better. While doctors hope cabozantinib will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about drugs as a treatment for cancer. This information could help future cancer patients.

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.

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:

- The study agent, cabozantinib, will be provided by the NCI. 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.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the cabozantinib to the NCI for some reason. If this would occur, other possible options are:

- You might be able to get cabozantinib from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no cabozantinib available at all, no one will be able to get more and the study would close.

If a problem with getting cabozantinib occurs, your study doctor will talk to you about these options.

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

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 study results. You can search this Web site at any time.

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.

The National Institutes of Health and the research team for this study are using a drug developed by Exelixis through a joint study with your researchers and the company. The company also provides financial support for this study.

Optional Biopsy

We would like to collect samples of your tumor after you have been using cabozantinib for 8 to 18 weeks. We will take no more than 4 – 6 pieces of tissue from each tumor site. The samples will be used to study blood vessel development and the types of white blood cells in your tumor along with other factors that affect tumor growth or factors that are expected to respond to the study drug. Leftover tissue will be used to study gene changes in your tumor that could be used to develop new ways of diagnosing and treating cancer. Genes are segment of DNA (also called deoxyribonucleic acid) that provide instructions for making a particular protein. DNA are the molecules inside cells that carry genetic information and pass it from one generation of cells to the next – like an instruction manual. The manual used only an alphabet consisting of four letters, called bases. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow. DNA changes in your tumor tissue are not passed on from generation to generation and have usually been acquired over the course of your lifetime.

The biopsy procedure usually causes only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site.

Optional Saliva Sample

We would like to collect a saliva sample from you after you have enrolled on the study. The sample (~ ½ tsp) of saliva may be taken at any after you have enrolled, but we will most likely collect it before you have taken any study drug. This sample will be used to compare the genetic material in your tumor tissue with genetic material in normal tissue (saliva) to determine if there have been any changes in the molecules that make up your DNA or if the order of the molecules is different. This will be done by determining which bases or "letters" appear in your DNA and the order in which they appear. This technique is called sequencing.

Once we obtain the saliva sample, the investigators take all your personal information off those samples and label them with a study code number. Only the investigators on this study know who the sample came from. The key linking your personal information with the code number is kept in a secure computer data base, with access only to the 2-3 research staff who will be discussing this study with you. Once the sample has been labeled with a code, it is sent to an NIH laboratory for storage and testing. No one testing your samples will be able to link the results to you personally. Specimens obtained during your participation in this study may be sent for testing to investigators outside of NCI or the NIH. All samples will be coded to protect your privacy and no personal information will be included. Other investigators on this study will have access to limited clinical and biologic information such as age, gender and disease status.

Any genomic data generated from your samples will be uploaded to a controlled-access shared database such as dbGaP. 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.

Your summary genomic data is being placed in an unrestricted database, so researchers will be able to access summary information about all the participants included in the study (including you), or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

Such databases may be useful beyond the aims of this particular study, especially as various diseases turn out to have mechanisms in common. The value of these data can increase when they are shared with the broader research community. While no traditionally identifying information will be shared, it is possible that you or a family member may be identified as outlined below in the section on the release of genetic information.

The saliva is collected exclusively for research purposes and will not benefit you. It might help other people in the future. You will be given the opportunity to decide whether you want to participate at the time of the procedure.

Though there is no risk associated with the collection of the saliva sample, there are privacy risks involved in genetic studies on normal tissues due to the fact that you may be identified by your DNA sequences. There is also the possibility that we may discover something about your health that causes you distress. You will be given the option to learn about certain types of findings later on in this consent. The risks are discussed below:

1. Unanticipated medical information: During the course of this investigation, it is possible (although not likely) that we will obtain unanticipated information about your health or genetic background.
2. Release of genetic information:
   - While the controlled-access databases developed for this project will not contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.
   - Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. Therefore, your genetic information potentially could be used in ways that could cause you or your family distress, such as by revealing that you (or a blood relative) may carry a genetic disease or be at risk for other health problems.
   - There also may be other privacy risks that we have not foreseen.

   There are state and federal laws that protect against genetic discrimination. There is also a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not apply to members of the United States military, to veterans obtaining health care through the Veteran's Administration or the Indian Health Service. Lastly, GINA does not forbid insurance medical underwriting based on your current health status.

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 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. We will also share information as described in item 1 on page 18.

Returning of Genetic Results

The sample you provide for genome sequencing will be analyzed at our laboratories. Our plan is to sequence most of your genetic material. This analysis will take months or years to complete. This is because genome sequencing is difficult to do. It is also because we have much to learn about the DNA we will be sequencing and the genetic variants we find.

Gene changes will be identified that are not related to this research study. These are known as "incidental medical findings".

These include

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

Most of the results that are important to your health and/or the health of your relatives fall in the first category – genetic variants that are known to cause or contribute to disease. If we find one or more of these genetic variants in your sample, it could be that:

- The genetic variant has already caused you to have signs and symptoms of a disorder;
- The genetic variant may cause you to have signs and symptoms of a disorder in the future;
- The genetic variant may be important to the health of your offspring and/or other family members.

If you decide below that you would like to know about incidental findings, we will **only** give you results about specific abnormal genetic variants that we think are important to your health and/or the health of your relatives. As we expect to have the genetic analyses done within 5 years, in general we will only contact you within the first five years after you have signed this consent. If we find a genetic variant that has health implications for you or members of your family, we will contact you so that we can obtain an additional blood sample and repeat the test for that specific genetic variant in a clinical laboratory. In general, would only tell you about the results of tests that have been confirmed in a clinical laboratory. However, if you are deceased at the time that a result that is important to the health of your relatives is discovered, we would like to contact your legal next of kin about the result even though it has not been confirmed in a clinical laboratory. This will allow others in your family the chance to undergo testing for important results in a clinical lab.

Once the results are available, if you or your next of kin would like to receive your results we will offer to have you (or your next of kin) come to NIH (at our expense) to have genetic education and counseling to explain this result.

If you do not want to come to NIH, we will help you (or your next of kin) find a local genetic healthcare provider who can explain the result (at your or your next of kin's expense).

If we find gene changes that are not known to be important at this time, we will not share that information with you or your next of kin. As this is a rapidly changing field, it is possible that genetic variants that are not known to be important at this time may be shown to be important at a later date. If you are receiving care from another physician who thinks that this testing may be of use in your care and treatment, you may contact us at any time and we will share the results with your physician.

Please let us know your preference by circling and initialing your choices in the following statements:

I agree to be recontacted if genetic changes with potential health implications are discovered. (You will be given a choice to learn or not to learn about genetic changes that we find.)

Yes No Initials_____

I agree that my next of kin should be recontacted if genetic changes with potential health implications for my family members are discovered after I am deceased. (Your next of kin will be given a choice to learn or not to learn about genetic changes that we find.)

Yes No Initials_____

Please note that for us to recontact you, you will have to keep us up to date with a current address and phone number.

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 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 12N226, 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 and 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 DECEMBER 10, 2019 THROUGH JANUARY 7, 2021. _____ _____ _____ _____ Signature of Investigator Date Signature of Witness Date _____ _____ Print Name Print Name	