INSTITUTE: National Cancer Institute

STUDY NUMBER: 15-C-0040 PRINCIPAL INVESTIGATOR: Naris Nilobul, M.D.

STUDY TITLE: A Phase II Trial of Mutation-Targeted Therapy with Sunitinib or Everolimus in Patients with Advanced Low-or Intermediate Grade Neuroendocrine Tumors of the Gastrointestinal Tract and Pancreas

Continuing Review Approved by the IRB on 07/09/18
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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?

Patients with advanced neuroendocrine tumors (NETs) have several treatment options available. Surgery to reduce the size of the tumor(s) has been somewhat successful in cases where the size of the tumor(s) can be reduced tenfold or more. However, less than half of patients with advanced NETs can meet this potentially curative threshold, and of those that do, the tumors tend to come back after surgery. Patients with NETs that do not undergo surgery have been treated using chemotherapy. Nevertheless, it is not known to what extent surgery that reduces but does not remove all of the disease will result in any benefit to patients. Additionally, it is not known whether this surgery in combination with chemotherapy might improve outcomes.

In this study, we will determine if two drugs, sunitinib and everolimus, in sequence (one after the other) and assigned based on the genetics of your tumor result in a longer time between treatment and the worsening of your cancer.

The study drug, everolimus, is supplied by Novartis Pharmaceuticals Corporation. The study drug, sunitinib, is supplied by Pfizer. Both have been approved by the US FDA for treatment of NETs. Both are considered to be targeted therapy, in that they work by interrupting specific pathways that are necessary to the survival of a tumor. Not everyone's tumor depends on the same pathways, so in this study, your tumor will be tested to determine what type of mutation you have so that we will know which pathway is affected and assign you to the drug that targets the pathway your tumor depends on. You will be switched to the other drug if your tumor worsens or if you experience intolerable side effects related to the first drug.

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

You are being asked to participate in this study because you have been diagnosed with an advanced low or intermediate grade gastrointestinal or pancreatic neuroendocrine tumor.

How many people will take part in this study?

Up to 120 subjects at the National Cancer Institute and Rush University Medical Center will take part in this study.

Description of Research Study

Before you begin the study

Before you begin this study, you will have several exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care and may be done even if you do not join the study. If you recently had some of the tests, they may not need to be repeated. The research team will explain these exams and tests to you. You will have:

- History and physical exam
- Review of histological samples, current medications, and past treatments
- Electrocardiogram
- Routine blood work
- Viral blood tests
- Tumor measurements using special x-rays called computerized tomography (CT or CAT scans), positron emission tomography (PET) scan or magnetic resonance imaging (MRI) of your brain, chest, abdomen, and pelvis areas, bone scan.
- Urine tests

- Pregnancy test.

During the study

You will undergo the following studies to help us monitor your health and tumor size/number at the beginning of and throughout the course of the study. The first time a test is done, it will be before you have taken any study drug, but after you have signed the consent. This is called a baseline study. The baseline study may not have to be repeated if you have already had it done at screening. Your doctor will let you know.

Evaluations during the study:

- Physical Exam^{+}
- Vital Signs^{+}
- Routine blood and urine tests^{+}
- Tests for Hepatitis B and C$^{\#}$
- ~ 6 teaspoons of blood for genetic studies$^{\#}$ (see discussion in Research Studies section below)
- Echocardiogram (if you have a carcinoid tumor)
- CT scan or MRI of chest, abdomen and pelvis to evaluate your disease‡
- 12 lead ECG*
- Tests to determine the types of hormones your tumors are secreting$^{\#}$
- Pregnancy test (in women that can have children only) *
- Evaluation of your heart (in patients at risk for heart and lung disease) $^{\#}$
- We will ask you to provide tumor tissue from prior biopsy or surgery. If this is not available or it is of poor quality for tumor analysis, you will be asked to undergo a mandatory biopsy so that we can determine what type of mutation you have. Patients that are known to have a familial cancer syndrome in which the mutation is known will not have to have a biopsy$^{\#}$

$^{\#}$Baseline only

$^{+}$Baseline, ~day 1 of each 28-day cycle, ~day 15 of cycles 1 and 2

*Approximately every 28 days (every cycle)

‡Baseline and every 3 cycles after you have started treatment

Taking the study drug:

You will begin taking your assigned study medication after baseline studies are complete.

During the study, you must talk to the study doctor before you take any drug other than the study drugs. This includes alternative or herbal medicines, and vitamins. **Please avoid eating**

grapefruit, star fruit, and Seville oranges or drinking their juices while in the study. The juices in these fruits can change the way your body treats or breaks down the study drugs.

The amount of study drug you take and the time when you take it may be changed during the study. This may be because of test results or side effects that you experience. Your study doctor may also ask you to stop taking your study drug for a brief time. If this happens, you will always be told when it is safe to start taking the study drug again. If study drug is stopped for a while, you may have to go to extra visits at the clinic for your safety.

While you are taking assigned study drug, you will be asked to keep track of this drug and of any side effects you experience while taking it. A patient diary will be provided for this purpose. Please bring the diary will you at each study visit along with any unused capsules/tablets or empty containers.

You will continue to take assigned study drug (sunitinib or everolimus) until you experience any intolerable side effects or until your disease worsens. In this case you will then switch to taking the other study drug (sunitinib or everolimus). You will be removed from study therapy for worsening disease or intolerable side effects only if your disease has worsened or you have intolerable side effects to both drugs in the study.

Before switching to another drug, some eligibility evaluations might be repeated.

Sunitinib

Those patients assigned to sunitinib will take the drug by mouth once per day with or without food. Please note that a yellow discoloration of the skin area may result following direct contact with the capsules. Wash the exposed area with soap and water immediately.

You will also be asked to keep track of your blood pressure at least once per week. Please, record the results in the patient diary provided for this purpose.

Everolimus

Those patients assigned to everolimus will take the drug by mouth once per day (or once every other day if your dose has been reduced). It is very important for you to take the study drug just as the study doctor tells you. Do not skip any doses unless your study doctor tells you to skip doses. If you throw up after taking the study drug, you should NOT take another tablet that day. Let your study doctor know that you got sick. If you do forget to take the study drug one day, do not take any extra doses the next day. Call your study doctor and ask for advice.

You should not receive live vaccines and have close contact with people who have received live vaccines within 7 days of starting everolimus and while on this study drug without consultation with your study doctor. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella (Chicken Pox), and typhoid vaccines.

Research studies

We will conduct genetic studies on the blood, saliva and tumor samples that you have provided in order to test for genes that are known to be associated with cancer. You will be informed of the results of these specific studies as they will determine your initial treatment.

Your blood may be further tested in the future for additional genes that may cause NETs or other cancer. When we are conducting these tests, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

However, the 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 tissue and blood 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 that 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.

Please also review the privacy risks associated with genetic testing in Privacy Risks section of the consent.

When you are finished taking the drugs (treatment)

Approximately 30 days after the last day you will take any study drug, you will be seen for a follow up safety visit. At this visit, you have the following tests:

- Physical Exam
- Vital Signs
- Routine blood and urine tests
- CT scan or MRI of chest, abdomen and pelvis to evaluate your disease. If you are being removed from the study due to worsening of your disease, this will not be done.
- Tests to determine the types of hormones your tumors are secreting
- Pregnancy test (in women that can have children only)

After this safety follow up visit, we will contact you by telephone or e-mail every 3 months to determine your health status and any new cancer treatments that you have begun.

Birth Control

Women who are pregnant or nursing a child cannot participate in this trial. You must confirm, to the best of your knowledge, that you are not now pregnant, and that you do not intend to become pregnant during the trial.

The risks to an unborn human fetus or a nursing child from everolimus or sunitinib are not known. If you are a woman who can become pregnant, you must use a highly effective method of contraception while receiving any study drug, and for up to 8 weeks after ending treatment. Highly effective contraceptive methods are also required for female partners of male patients who are sexually active and may become pregnant.

Please discuss with your Study Doctor the most appropriate birth control method for you that also respect your cultural and religious situation.

Examples of highly effective birth control methods are:

- Total abstinence, when this is in line with your preferred and usual lifestyle.
- Female sterilization, when you have been already surgically sterilized prior to the study by surgical removal of both ovaries (woman's reproductive system that stores and releases eggs for fertilization and produces female sex hormones), or tubal ligation (getting your "tubes tied") at least six weeks ago.
- Your male partner has already been sterilized (with the appropriate documentation). The sterilized male partner should be your sole partner.
- Use of a combination of any two of the following (a+b or a+c or b+c):

a. Use of oral, injected or implanted hormonal methods of contraception. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception (in case of oral contraception you should have been using the same pill on a stable dose before taking study treatment),

b. Placement of an intrauterine device (IUD) or intrauterine system (IUS),

c. Use of an occlusive cap (diaphragm or cervical/vault cap) by you, or a condom by your male partner combined with a spermicidal foam/gel/film/cream/vaginal suppository.

If you become pregnant or suspect being pregnant during study treatment or within 8 weeks after completing study treatment, you must inform the Study Doctor immediately, and you have to stop ongoing study treatment immediately. You will not be allowed to continue study treatment if you are pregnant. Your Study Doctor will medically follow your pregnancy until delivery to monitor you and your child`s safety.

As a male participant in the study you must agree to use a condom during intercourse and not father a child during the study and for the period of 8 weeks following stopping of study treatment. In addition, it is advised that your female partner uses a highly effective form of birth control method (contraception) if she is sexually active and may become pregnant.

In case you father a child while in this study you will be asked to report the pregnancy to the Study Doctor. Consent from your partner will be needed to allow your Study Doctor to medically follow this pregnancy until delivery to monitor the mother`s and child`s safety.

Risks or Discomforts of Participation

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The study drugs 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.

Listed below are the most common and serious side effects of the study drugs that the researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Sunitinib:

COMMON, SOME MAY BE SERIOUS In 100 people receiving sunitinib malate, more than 20 and up to 100 may have:
• Pain • Diarrhea, nausea, vomiting • Sores in mouth (which may cause difficulty swallowing) • Tiredness • Loss of appetite • Changes in taste • Sore throat

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving sunitinib malate, from 4 to 20 may have:
• Anemia which may require blood transfusion • Blurred vision with chance of blindness • Bloating, constipation, heartburn, passing gas • Dry mouth, skin • Chills, fever • Swelling of arms, legs • Bruising, bleeding, weight loss • Infection, especially when white blood cell count is low • Dehydration • Dizziness, headache • Difficulty sleeping • Cough, shortness of breath • Nose bleed • Hair loss, rash, skin changes • Redness, pain or peeling of palms and soles • Change in hair color • High blood pressure

RARE, AND SERIOUS In 100 people receiving sunitinib malate, 3 or fewer may have:
• Blood clot which may cause confusion, paralysis, swelling, pain, or shortness of breath • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or hole in the stomach that may require surgery • Liver damage which may cause yellowing of eyes and skin, swelling • Change in the heart rhythm • Kidney damage which may require dialysis • Damage to organs which may cause loss of teeth or change in thinking • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Severe skin rash with blisters and can involve inside of mouth and other parts of the body

Everolimus

COMMON, SOME MAY BE SERIOUS In 100 people receiving everolimus, more than 10 and up to 100 may have:
• Sores in mouth which may cause difficulty swallowing (up to ½ of subjects experience this) • Fatigue • Weakness • Chills • Nausea and vomiting • Loss of appetite • Weight loss • Skin problems such as rash or itching • Diarrhea • Pain or swelling of the arms or legs • Nosebleeds • Cough • Shortness of breath • Headache • High levels of blood sugar – which could lead to diabetes • High levels of lipids (cholesterol) • Change in taste • Low levels of red blood cells • Infections

- Spontaneous bleeding or bruising
- Inflammation in the lungs (generally mild)

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving everolimus, from 1 to 10 may have:

- Dry mouth
- Dehydration
- Skin changes (acne, rash, redness, dryness or irritation, itching and skin inflammation)
- Abdominal pain
- Stomach virus
- Constipation and passing gas
- Irritability
- Nail disorders
- Increased blood pressure
- Joint stiffness or pain
- Mouth pain
- Difficulty swallowing, (heartburn)
- Fever
- Insomnia
- Inflammation of the lining of the digestive system and other mucous membranes such as the sinus
- Stomach pain
- Bleeding
- Low white blood cells which may lead to infection
- Liver damage
- Lowering of the blood cells that help the blood to clot (which could cause you to bleed more easily
- lowering of the protein in your blood (hemoglobin) that helps carry oxygen; this could lead to anemia.

RARE, AND SERIOUS
In 100 people receiving everolimus, fewer than 1 may have:

- Blood clot or blockage in your lungs or extremities.
  (Tell your doctor right away if you experience new or worsening lung or breathing symptoms like cough or shortness of breath, even when symptoms are mild, as this might have life-threatening consequences.)
- Severe decrease in red blood cells or all blood cells

- Loss of taste, rash of small blisters, bronchitis
- Coughing up of blood
- Swelling of the tissue just beneath the top layer of skin
- Congestive heart failure (fluid build-up and shortness of breath)
- Non-cardiac chest pain
- Impaired wound healing
- Increased daytime urination
- Changes in menstrual period (female patients only)
- Changes in fertility

Drugs like everolimus can cause the patient's immune system not to work as well as usual. A patient with hepatitis B or hepatitis C who takes everolimus could be susceptible to the virus becoming more active. If you had or have active hepatitis B or C, you will not be allowed into the study. Changes to the levels of blood sugar (glucose), which could lead to diabetes, could occur while taking everolimus, so your blood sugar levels will be checked often during the study. If you are taking another medicine which may increase blood sugar levels, more frequent monitoring may also be required. Another diabetes test (Hemoglobin A1c) will be checked at the beginning of the study. Everolimus may also contribute to increased levels of an enzyme called blood lactate dehydrogenase which gives information about the health of certain organs.

If you experience any hypersensitivity or signs of serious allergic reaction such as rash, itching, hives, difficulty breathing or swallowing, dizziness, please contact your doctor.

Research Procedure Risks

Blood Draw

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.

Saliva collection

There are no physical risks or discomforts associated with saliva collection.

Tumor biopsy

If you do not have a tissue sample available, and do not have a hereditary cancer syndrome of known mutation, we will collect a small piece of tumor tissue from you. A hollow needle is used to withdraw small cylinders (or cores) of tissue from your tumor using a CT scan or ultrasound for guidance. The needle is put in 3 to 6 times to get the samples, or cores. This procedure usually causes only brief discomfort at the site from which the biopsy is taken and you will be offered medication to help numb the pain. Biopsy collection may cause bruising and bleeding, but usually does not leave scars. Rarely infection may occur at the needle site.

Radiation Risks from CT guided biopsy

This research study involves exposure to radiation from one CT guided tumor biopsy. 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 0.80 rem which is below the guideline of 5 rem (or 0.5 rem in children) 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.

Privacy Risks

The following general points are indirectly related to your participation in the research study.

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 medical records. In the course of applying for certain types of insurance (e.g., medical insurance, life insurance, or disability insurance), people are often asked to sign forms that authorize insurance companies to obtain their medical records. If you sign such a release form at some point in the future, it is possible that the insurance company would present this signed release form to the Clinical Center of the National Institutes of Health. In that event, the National Institutes of Health would comply with your request to provide the insurance company with your medical record. It is possible that information contained in your medical record might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance. Your employability may also be affected.

3. Release of genetic information:

- 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. 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.
- 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) carry a genetic disease.
- 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.

Potential Benefits of Participation

The aim of this study is to see if this experimental treatment will have any effect on the length of time that it takes your disease to worsen. 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

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

- Expectant management without particular care or treatment for your cancer
- 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 during treatment with the second of the two study drugs assigned
- 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 become pregnant
- if he/she decides to close the study

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 Pfizer and to Novartis 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. Unless and until you do withdraw your consent to participate in this study, it will remain valid and effective.

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?

For purposes of this study, NCI and Dr. Nilobul will use medical information collected or created as part of the study, such as medical records and test results, which identifies you by name or in another way. Your consent to participate in the study means you agree that NCI and Dr. Nilobul may obtain your medical information that they request for study purposes from your physicians and your other health care providers. You are also agreeing that NCI and Dr. Nilobul may use and share this information with the parties described below. In addition, you agree that, during the study, you may not have access to some of your medical information obtained or created as part of this study. You will be allowed to access this information once the study is finished.

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.
- Governmental agencies in other countries where the study drug may be considered for approval
- National Institutes of Health Intramural Institutional Review Board
- Qualified representatives from Pfizer and Novartis, the pharmaceutical companies who supply sunitinib and everolimus respectively, or its authorized representatives

Portions of your samples, genomic data, and health information will be stored for an unlimited period of time to be used in future research. 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.

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.

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.

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 everolimus developed by Novartis through a joint study with your researchers and the company. Novartis also provides financial support for this study.

Pfizer is providing sunitinib for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Pfizer.

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 they 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, Naris Nilubol, M.D., Building 10, Room 4-5932, Telephone: 240-760-6154. 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 JULY 09, 2018 THROUGH JULY 08, 2019. Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____ Print Name _____ Print Name _____	