INSTITUTE:National Cancer Institute

STUDY NUMBER: 12-C-0118 PRINCIPAL INVESTIGATOR: Arun Rajan, MD

STUDY TITLE: A Phase II Study of Sunitinib in Patients with Advanced Relapsed or Refractory Thymoma or Thymic Carcinoma with at Least One Prior Line of Platinum-Based Systemic Chemotherapy

Continuing Review Approved by the IRB on 07/22/19
Amendment Approved by the IRB 05/08/19 (N) Date Posted to Web: 07/26/19
Standard – Group 2

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?

The purpose of this study is to evaluate the safety, tolerability and effectiveness of the drug sunitinib malate (referred to as sunitinib) in cancers of the thymus. Sunitinib is a Food and Drug Administration (FDA) approved drug for use in at least three other types of cancers including cancers of the kidney, but it is not FDA approved for treatment of thymic carcinomas and is experimental in this setting. Sunitinib acts by blocking several proteins involved in control of cell division and growth. In tumor cells such controls are altered and lead to abnormal and uncontrolled cell growth. Some of the proteins which are blocked by sunitinib are known to be

abnormal in a few patients with cancers of the thymus. There have also been isolated reports of effectiveness of sunitinib in cancers of thymus.

This study will evaluate the amount of tumor reduction, if any, and the length of time the tumor growth is controlled, as well as the safety and tolerability of sunitinib in advanced cancers of thymus, which have progressed despite at least one prior chemotherapy regimen containing platinum. Some patients may not have any tumor reduction or control of tumor growth with sunitinib.

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

You are being asked to take part in this study because you have an advanced thymic carcinoma which has progressed despite prior treatment with at least one platinum-based chemotherapy regimen.

How many people will take part in this study?

This study consists of two groups. A total of 41 people participated in Group 1, and enrollment has now been completed for that group. In Group 2, approximately 15 patients with thymic carcinoma will take part in the study, which is being conducted at the National Cancer Institute and affiliated institutions. You are being invited to participate in Group 2.

Description of Research Study

This study is being conducted on an outpatient basis. Sunitinib is taken orally once a day, with or without food. Sunitinib is stored at room temperature. The dose regimen for this study is 50 mg of sunitinib daily for 2 weeks, followed by 1 week of rest with no sunitinib. This 3-week period is called a cycle. The cycles may be repeated as long as you are receiving benefit from the drug and any side effects which you may experience are tolerable.

Clinic visits will take place every three weeks in order to monitor your progress on this trial and manage any side effects which you may be having. Every 2 cycles (every 6 weeks) we will perform a CT scan, MRI and/or chest x-ray to see if you are getting any benefit from the study drug. As long as you are receiving benefits from the treatment and you do not have unacceptable side effects, then we will continue to provide you with the treatment. Once you have completed one year of the study drug, we will perform a CT scan, MRI and/or chest x-ray every 4 cycles (every 12 weeks) to see if you continue to receive benefits from the study drug. Once you stop getting any benefit from the study drug, or the side effects are no longer tolerable, we will stop the treatment.

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

Before you begin the study

Before any study-related procedures are performed, you will be asked to read and sign this informed consent form. If you wish to participate, you agree to return to this clinic for all study-related appointments and tests mentioned below. Additional visits may be required to treat side effects. No overnight hospital or clinic stays are required; however, if serious side effects occur, overnight hospital stays may be required to treat the side effects.

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 your study doctor.

- Routine physical exam (includes an examination of major body systems, height, weight, blood pressure, and pulse rate)
- Documentation of all prescription and over-the-counter medications which you are taking
- Blood tests including blood cell counts, chemistries, tests to see how well your blood clots and thyroid functions
- Computed tomography (CT) or MRI and/or chest x-ray (CT- a series of x-rays will be passed through your body while you lie inside a machine) or other imaging tests to locate and measure your tumors
- Brain MRI
- Tissue block of the cancer to submit to the study doctor or a member of the research team
- An electrocardiogram (ECG), a recording of the electrical activity of your heart
- An echocardiogram or MUGA scan, an ultrasound study which shows the structure and function of your heart
- Serum pregnancy test for women of childbearing age

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 that are part of regular cancer care:

- Clinic visits once every three weeks, on Week 1 of each cycle, to discuss any symptoms you may have and to undergo a physical examination.

- Blood tests
- Computed tomography or other imaging test approximately every 6 weeks for the first year you receive the study medication, and approximately every 12 weeks thereafter, as long as you continue to receive the study medication.
- Tests to monitor your heart function, as needed

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 and your cancer:

- Blood test to study different biological markers that we anticipate may be affected after treatment with sunitinib
- Blood test to evaluate the effect of the study drug on cells involved in specialized functions such as blood vessel formation.

You will be asked to maintain a medication diary and a blood pressure (BP) chart.

When you are finished taking the study drug (sunitinib malate)

As explained in the paragraphs above, if you do not experience benefit from the sunitinib, or the side effects are no longer tolerable, then we will stop giving you the sunitinib. We will continue to monitor you, either by clinic visit or telephone interview, until all of the side effects have been resolved or stabilized, and then annually until death.

Study Chart

Day	What you do
Before starting study	• Check-in to the *Outpatient* Clinic • Physical examination by a Health Care Provider • Blood Pressure (BP) measurement • Routine blood tests • Research blood tests • Tissue block of the cancer to confirm the diagnosis • CT or other imaging studies • Brain MRI • ECG • Echocardiogram • Serum pregnancy test for women of childbearing age
During treatment	• Sunitinib 50 mg daily for 2 weeks, then 1 week of rest with no sunitinib • Clinic visits on Week 1 of each cycle, including physical examination by a Health Care Provider, and other tests as determined by your study doctor.

	• Research blood tests on Week 1 of Cycles 2, 3, and 5 • CT or other imaging studies every 6 weeks for the first year you receive the study medication, and every 12 weeks thereafter, as long as you continue to receive the study medication. • Routine blood tests on Week 1 of each cycle • Maintain a medication diary • Maintain a BP diary with weekly BP recordings.
After treatment	• Follow-up clinic visits or telephone interviews until side effects are resolved or stabilized, and then annually until death.

Study Drug Administration

Sunitinib is taken orally once a day, with or without food. Sunitinib is stored at room temperature. The dose regimen for this study is 50 mg of sunitinib daily for 2 weeks, followed by 1 week of no sunitinib. This 3-week period is called a cycle. After 12 weeks of treatment, we will perform a CT scan to see if you are getting any benefit from the treatment. If you do not experience benefit from sunitinib, we will stop it. If you experience benefit from sunitinib, we will continue it until you stop benefiting from it and do not have unacceptable side effects. We would like to follow up with you even after you stop taking sunitinib; for your entire life with the intention of knowing more about how the genetic characteristics of your cancer have an impact on how your cancer behaves.

Study Restrictions/Subject Responsibilities

- Store sunitinib at controlled room temperature (15to 30^{o} C), and protect from light.
- Sunitinib may be taken without regard to meals.
- A yellow discoloration of the skin area may result following direct contact with the capsules. Wash the exposed area with soap and water immediately.
- Blood pressure (BP) should be monitored before you begin the study, and then weekly for the duration of treatment. Blood pressure may be monitored either at the doctor's office or using any calibrated electronic device (such as those found at a local drug store or pharmacy).
- Sunitinib may interact with many other medications and remedies. We would like to know all the medications that you take before starting sunitinib as well as any new medications and over the counter drugs. We will provide you information sheet describing drugs, remedies, and medications with potential interactions with sunitinib.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how these medicines used in this study would 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 while receiving study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once. It is also important to note that some of the drugs used in the study may make you unable to have children in the future.

Effective forms of birth control include:

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

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 sunitinib malate (SU011248 L-malate) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

- 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 sunitinib malate (SU011248 L-malate) 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 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 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 table below shows the most common and the most serious side effects that doctors know about. Keep in mind that there might be other side effects that doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Sunitinib Risks

COMMON, SOME MAY BE SERIOUS In 100 people receiving sunitinib malate (SU011248 L-malate), more than 20 and up to 100 may have:
• Pain • Constipation, diarrhea, heartburn, nausea, vomiting • Sores in the mouth • Tiredness • Loss of appetite • Changes in taste • Sore throat • Redness, pain or peeling of palms and soles

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving sunitinib malate (SU011248 L-malate), from 4 to 20 may have:
• Anemia which may require blood transfusion • Blurred vision with chance of blindness • Bloating, passing gas • Dry mouth, skin • Chills, fever • Swelling of arms, legs • Flu-like symptoms including body aches • Bruising, bleeding • Weight loss • Infection, especially when white blood cell count is low • Dehydration • Dizziness, headache • Feeling of "pins and needles" in arms and legs • Depression • Difficulty sleeping • Cough, shortness of breath • Nose bleed • Hair loss, rash, itching, skin changes • Change in hair color • High blood pressure which may cause headaches, dizziness, blurred vision

RARE, AND SERIOUS In 100 people receiving sunitinib malate (SU011248 L-malate), 3 or fewer may have:
• Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis • Blood clot which may cause confusion, paralysis, seizures or swelling, pain, shortness of breath • Damage to organs (heart, brain, others) which may cause shortness of breath, swelling of ankles, and tiredness, changes in thinking • Heart failure, heart attack which may cause shortness of breath, swelling of ankles, and tiredness • Pain and swelling of thyroid • Visual loss • Difficulty swallowing • A tear or hole in or between internal organs which may cause drainage and may require surgery • Swelling of the gallbladder • Liver damage which may cause yellowing of eyes and skin, swelling • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Flesh-eating bacteria syndrome • Non-healing surgical site • Change in the heart rhythm • Kidney damage which may require dialysis • Damage to the jawbone which may cause loss of teeth • Damage to muscle which may cause muscle pain, dark red urine • Cancer of bone marrow caused by chemotherapy • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Stroke • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Sores on the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Test and Procedure Risks

In addition to the side effects for the drugs in this protocol there may be side effects associated with the tests and procedures that occur during this study. These include:

- Drawing blood: Risks associated include pain at the needle site, bruising, possible dizziness if you stand up quickly and possible inflammation of the vein or infection at the needle site. Care will be taken to avoid these complications.

- Scans, x-rays, and heart tests: There is a small risk of developing a reaction to the agents used during the test. Otherwise risk factors are similar to those associated with taking a blood sample which includes pain at the needle site, bruising, possible dizziness if you stand up quickly and possible inflammation of the vein or infection at the needle site. Care will be taken to avoid these complications.
- An intravenous line will be used in some cases. There may be a risk of infection, blood clot or bleeding at the site of the line. There is also a risk of some of the drug leaking out, referred to as extravasation. If that occurs there may be some damage to skin tissue in a limited area. Patients are urged to alert the study physicians at the first sign of any skin changes, for example redness or tenderness around the infusion site or any discomfort near that area as well. If there is any evidence of toxicity from leaking, the infusion will be held until a central line can be placed for the infusion of drug. In addition, any toxic effects to the skin will be treated to the fullest extent possible. Development of air in the chest is a risk of a central line catheter. However, this complication is rare. Air in the chest outside the lung would require temporary placement of a chest tube by the surgeon.

For more information about risks and side effects, ask your study doctor.

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. The aim of this study is to see if the drug sunitinib malate will cause your tumor to shrink. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the tumor. We do know that the information gained from this study will help doctors learn more about sunitinib 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, with standard of care chemotherapy regimens

- 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 gets worse 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

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 until that point may still be provided to the NCI or Pfizer, or designated representatives.

If you withdraw from the study early, you may be asked if you will allow further medical information to be collected for study purposes. In that case, we would ask you to enroll on a separate protocol.

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
- The study Sponsor or their agent(s)
- Qualified representatives from Pfizer, the pharmaceutical company who produces sunitinib.

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.

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, Arun Rajan, M.D., Building 10, Room 12N226, Telephone: 240 760-6236. 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 22, 2019 THROUGH AUGUST 20, 2020.

_____ _____ _____ _____
Signature of Investigator Date Signature of Witness Date

_____ _____
Print Name Print Name