Testing the Addition of Everolimus (Chemotherapy) After Surgery to Remove Metastatic Pancreatic Neuroendocrine Tumors from the Liver

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A Randomized, Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver

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WHAT IS THE USUAL APPROACH TO MY METASTATIC PANCREATIC NEUROENDOCRINE CANCER?

You are being asked to take part in this research study because you have pancreatic neuroendocrine cancer which spread to your liver and was surgically removed. People who are not in a research study are usually monitored after their surgery in case their cancer returns.

WHAT ARE MY OTHER CHOICES IF I DO NOT TAKE PART IN THIS STUDY?

If you decide not to take part in this study, you have other choices for your care. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different research study, if one is available
- or you may choose not to be treated or monitored for cancer but you may want to receive comfort care to relieve symptoms if your cancer returns.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to compare any good and bad effects of using the study drug, everolimus (also known as Afinitor), along with the usual monitoring after surgical removal of pancreatic neuroendocrine cancer tumor that has spread to the liver, to using the usual monitoring alone after surgery. The addition of everolimus to the usual monitoring could decrease the chance that your tumor(s) will come back but it could also cause side effects. This research study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. To be better, the study drug should improve how long patients with your type of cancer are able to live without their cancer returning by 12 months (1 year) or more compared to the usual approach. The chemotherapy drug, everolimus, is already FDA-approved to treat progressive neuroendrocrine tumors of pancreatic origin (PNET) that is unresectable, locally advanced, or metastatic, but

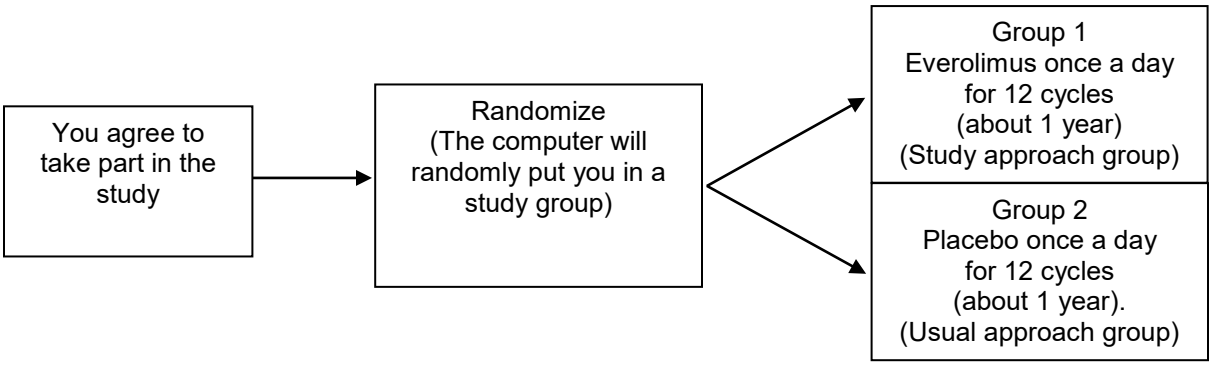
has not been FDA-approved for treating patients who have had surgical resection of pancreatic neuroendocrine tumor metastases to the liver. Experiments have shown that everolimus can prevent cells such as cancer from growing in number.. For this study, everolimus is supplied by Novartis Pharmaceuticals Corporation.

There will be about 150 people taking part in this research study.

WHAT ARE THE STUDY GROUPS?

This research study has two study groups. Group 1 will receive the study drug everolimus and Group 2 will receive a placebo, a tablet that looks like the study drug but contains no medication.

A computer will by chance assign you to treatment groups in the research study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others. You will have an equal (50%) chance of being placed in either group. You and your doctor will not know which group you are assigned until you have completed treatment, unless needed for a medical emergency. Another way to find out what will happen to you during this research study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



HOW LONG WILL I BE IN THIS STUDY?

You will receive the everolimus/placebo once a day for up to 12 cycles (about 1 year.) Each cycle is 4 weeks long. After each 4-week cycle, you will visit your doctor for an evaluation. Further treatment will depend on whether your doctor thinks the treatment is helping you and you are tolerating the drug well. After you finish everolimus/placebo treatment, your doctor will continue to watch you for side effects and follow your condition for up to 5 years from when you first join the study.

WHAT EXTRA TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?

Most of the exams, tests, and procedures you will have are part of the usual care for your cancer. However, there are some extra exams, tests, and/or procedures that you will need to have if you take part in this research study.

Before you begin the study:

You will need to have the following extra exams, tests, and/or procedures to find out if you can be in the research study:

- Blood tests to make sure your internal organs are functioning normally and your red and white cell counts are adequate. About 1 tablespoon of blood will be drawn.
- CT scan of chest, abdomen and pelvis or MRI of abdomen and pelvis and CT scan of chest
- Blood tests to measure Chromogranin (CgA), neuron-specific enolase (NSE) level and hemoglobin A1c will be performed at the same time when scans are performed. About 1 tablespoon of blood will be drawn.
- Blood test to check for hepatitis antibodies, pregnancy, and/or blood sugar levels, if your doctor thinks it is necessary. If you need to be tested for hepatitis, pregnancy, or blood sugar, about 1 tablespoon of blood will be drawn.

Small pieces of cancer tissue removed during your previous surgery and/or biopsies will be taken for the research study before you begin study drug. This sample is required in order for you to take part in this research study because the research on the sample is an important part of the research study.

No additional surgeries or biopsies are required to collect the tumor tissue for this research study.

If the exams, tests, and procedures show that you can take part in the research study, and you choose to take part, then you will need the following extra tests and procedures. They are not part of the usual care for your type of cancer.

During the study:

- Blood tests every month for as long as you are receiving everolimus/placebo (about 1 year). About 1 tablespoon of blood will be drawn each month.
- Urine pregnancy test, if a woman is capable of getting pregnant, every month for as long as you are receiving everolimus/placebo (about 1 year), if your doctor thinks it is necessary.
- CT scan of chest, abdomen and pelvis or MRI of abdomen and pelvis and CT scan of chest every 3 months for 2 years, then every 6 months until 5 years from when you entered the study.
- Blood tests to measure Chromogranin (CgA), neuron-specific enolase (NSE) level and hemoglobin A1c will be performed at the same time when scans are performed. About 1 tablespoon of blood will be drawn.

- Blood tests, including a serum pregnancy test, if a woman is capable of getting pregnant, will be performed when you finish taking everolimus/placebo.
- Samples of your tissue from a previous biopsy or from your surgery will be sent to a central laboratory to be examined by central reviewers. No additional procedures will be performed to collect this tissue for these reviews. This central review will be used to confirm the results of the local institutional review, but will not affect your participation in this trial. The results of the review will be returned to your doctor and may be placed in your medical record.

WHAT POSSIBLE RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

If you choose to take part in this research 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 drug may not be better, and could possibly be worse, than the usual approach for your cancer.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

The drug used in this research study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. These risks are described in more detail below.

There is also a risk that you could have other side effects from the study drug.

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.
- There may be some side effects or risks that are not known.

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.

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 doctor tells you to skip doses. You should take everolimus/placebo about the same time each day, either consistently with or without food.

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 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.

Tell your study doctor before you any take any other drug besides everolimus/placebo. This includes homeopathic, alternative or herbal medicines, and vitamins. Please avoid eating grapefruit and citrus fruits or drinking their juices for as long as you are on the study. The juices in these fruits can change the way your body treats or breaks down everolimus/placebo. Other drugs or citrus juices may change how the study drug works or make your side effects worse.

Everolimus/placebo may cause your immune system not to work as well as usual.You should not receive live vaccines or have close contact with people who have received live vaccines for as long as you are taking everolimus/placebo. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella (Chicken Pox), and typhoid vaccines.

The tables below show the most common and the most serious side effects that 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.

Possible Side Effects of Everolimus/Placebo:

COMMON, SOME MAY BE SERIOUS **In 100 people receiving everolimus/placebo, more than 20 and up to 100 may have:**
• Mouth lining changes (stomatitis) ranging from redness, irritation, swelling in the mouth to mouth ulcers • Fatigue • Weakness • Nausea • Vomiting • Dry mouth • Skin or nail changes (including acne, rash, redness, itching, dryness or irritation) • Diarrhea • Abdominal pain (belly pain) • Loss of appetite • Weight loss • Increased blood pressure • Pain or swelling of the arms or legs • Fever • Abnormal or loss of taste • Loss of red blood cells, also called anemia • Inflammation of the throat • Bleeding of the nose • Inflammation of the lining of the digestive system and other mucous membranes • Shortness of breath • Headache • Migraine

OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving everolimus/placebo, from 4 to 20 may have:**
• Change of sleep patterns • Sleeplessness • Difficulty breathing • Back pain • Pain in arms and legs • Joint pain • Dizziness • Dry mouth

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving everolimus/placebo, from 4 to 20 may have:
• Muscle spasms • Lowering of the number of your blood cells that help fight infection • Lowering of the blood cells that help the blood to clot and a lowering of the protein in your blood (hemoglobin) that helps carry oxygen • Changes to the levels of blood sugar (glucose) which could lead to diabetes • The levels of cholesterol and triglycerides or liver enzymes (transaminases) in your blood could increase (increased levels of cholesterol are an important factor of risk of heart disease) • The level of waste products from the liver (bilirubin) could increase, which could mean your liver is not working as well • Secondary amenorrhea (delayed menstruation) • Inflammation in the lungs (pneumonitis)

RARE, AND SERIOUS In 100 people receiving everolimus/placebo, 3 or fewer may have:
• Embolism or blockage in your lungs • Toxicity to your kidneys that causes the level of creatinine in your blood and protein in your urine to increase. In very rare cases, this toxicity could lead to kidney failure.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks:

You should not become pregnant or father a baby while on this research study because the drugs in this study can affect a fetus.

If a woman becomes pregnant while on this research study or within 28 days after the last dose of study drug, she will be asked information concerning the outcome of her pregnancy. If a female partner of a male patient becomes pregnant while the male patient is on the study or within 28 days after the last dose of study drug, the pregnant female partner should be advised to call her healthcare provider immediately and be aware that the investigator will ask to follow her pregnancy.

Women should not breastfeed a baby while on this research study.

It is important that you understand that you need to either practice “abstinence” (that is avoiding sexual activity) or use birth control while on this research study. Check with your doctor about what kind of birth control methods to use and how long to use them.

Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you must agree to use an appropriate double

barrier method of birth control (such as female use of a diaphragm, intrauterine device (IUD), sponge and spermicide, in addition to the male use of a condom) or involve female use of prescribed "birth control pills" or a prescribed birth control implant. Both double barrier contraception and birth control pills or implants must be used for at least one week prior to the start of the research study and continuing for up to 8 weeks after the last dose of the study drugs. If you choose to be sexually active during the study, you must accept that pregnancy could still result, exposing you or your sexual partner to potential loss of pregnancy as well as other unknown effects on the developing fetus.

WHAT POSSIBLE BENEFITS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

It is not possible to know at this time if the study drug is better than the usual care for this cancer so this research study may or may not help you. But, this research study will help researchers learn things that will help people in the future.

CAN I STOP TAKING PART IN THIS STUDY?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If you need medicine or treatment not allowed in on the study
- If new information becomes available
- If you do not follow the study rules
- If you become pregnant
- If the study is stopped by the sponsor, IRB or FDA.

WHAT ARE MY RIGHTS IN THIS STUDY?

Taking part in this research study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number)*. *(Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical*

trial questions can also be listed here.)

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

The everolimus/placebo will be supplied at no charge while you take part in this research study. It is possible that the everolimus/placebo may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of preventing or treating your cancer while in this research study, including the cost of study drug preparation and administration, tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are being done at no charge. Before you decide to be in the research study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this research study.

WHAT HAPPENS IF I AM INJURED OR HURT BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or hurt as a result of taking part in this research study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Novartis, the drug supplier, will not pay any money to you or your medical bills. Your insurance company may not be willing to pay for research study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a research study.

WHO WILL SEE MY MEDICAL INFORMATION?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

The ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) is conducting this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS). With this Certificate, ECOG-ACRIN cannot be forced (for example, by court subpoena) to disclose information that may identify you in any

federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- ECOG-ACRIN, the study sponsor, and Novartis, the drug company supporting the study and/or their authorized representatives.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

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- The Cancer Trials Support Unit (CTSU), a service provided by the National Cancer Institute (NCI) to provide greater access to cancer trials.

OPTIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in.

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using samples of tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

At this time, we are requesting that you allow the collection, submission and storage of blood and tumor tissue samples for research projects that may be done at a later date. The tumor tissue will be from previous procedures (biopsies or surgeries). No additional procedures will be performed to collect the tumor tissue for future projects. These specimens will be stored in a "Biobank". The Biobanks are run by ECOG-ACRIN staff and researchers and they are financially supported by the National Cancer Institute.

What is involved if you provide your samples for research?

If you agree to take part, here is what will happen next:

1. Blood and tissue samples will be sent and stored for future research:
    a. Tissue samples left over after the central reviews will be stored for future research.
    b. About 2 tablespoons of blood will be collected from a vein in your arm before you begin protocol therapy and when you discontinue or finish the protocol treatment. These draws will most likely be done at the same time as the blood draws performed to monitor your health. Another stick should not be necessary.

c. If available, additional samples of the tissue that was collected at the time of your biopsies and/or surgeries, including frozen tumor, will be sent to the Biobank.

2. Your samples and some related health information will be stored in the Biobank, along with samples and information from people who took part in this or other research studies. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
3. Only qualified researchers can submit a request to use the materials stored in the Biobanks. A committee of experts at ECOG-ACRIN, and/or the National Cancer Institute, will review each request to use the samples for research. All research projects using these samples will also be reviewed by an ethics or institutional review board to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5. Results from the research may be placed in centralized storage systems call databases. It is possible that some of your genetic information and your health information may be placed in these databases. It is also possible that some of these databases may be public.

What are the possible risks in providing your samples for research?

1. The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2. There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3. There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4. In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

When my samples are used for research, how will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1. When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2. The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and ECOG-ACRIN staff with access to the list must sign an agreement to keep your identity confidential.
3. Researchers to whom ECOG-ACRIN sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4. Information that identifies you will not be given to anyone, unless required by law.
5. If research results are published, your name and other personal information will not be used.

What are the Possible Benefits of allowing my samples to be used for research?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future. Your samples may be helpful to research whether or not your cancer returns.

Are there any costs or payments associated with providing my samples for research?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind about allowing my samples to be used for research?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

What if I have more questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

SAMPLES FOR FUTURE RESEARCH STUDIES:

May we have some samples of your blood and additional tissue samples, if available, for future health research?

I agree to provide additional samples for research.

YES **NO**

May we keep any tissue samples left over from the central reviews for future health research?

My samples and related information may be kept in a Biobank for use in future health research.

YES **NO**

This is the end of the section about optional studies.

WHERE CAN I GET MORE INFORMATION?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ (insert name of study doctor[s]) at _____ (insert telephone number).

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ [*telephone number].*

MY SIGNATURE AGREEING TO TAKE PART IN THE MAIN STUDY

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes'.*

Participant's signature _____

Date of signature _____

Signature of person(s) conducting the informed consent discussion

_____

Date of signature _____