Testing the Addition of the Drug Crizotinib After Surgery to Remove ALK-Positive Non-Small Cell Lung Cancer

A Randomized Phase III Trial for Surgically Resected Early Stage Non-Small Cell Lung Cancer: Crizotinib versus Observation for Patients with Tumors Harboring the Anaplastic Lymphoma Kinase (ALK) Fusion Protein

WHAT IS THE USUAL APPROACH TO MY LUNG CANCER?

You are being asked to take part in this research study because you have ALK-positive non-small cell lung cancer, which has been removed by a surgeon. In ALK-positive non-small cell lung cancer, molecular changes make the ALK molecule very active and important for cancer growth and progression. Thus, these cancers may respond to treatment with ALK inhibitors. People who are not in a research study are usually monitored after their initial treatment (which may also include chemotherapy and/or radiation therapy) 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 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, crizotinib (also known as XALKORI®), after completion of surgery and, in some cases, after chemotherapy and/or radiation therapy for ALK-positive non-small cell lung cancer. The addition of crizotinib may help prevent your cancer from returning, 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 you are able to live by 2 years and 9 months (33 months total) or more compared to the usual approach. The study drug, crizotinib, is already FDA-approved for use in ALK-positive locally advanced or metastatic (spread to other areas of the body) non-small

lung cancer. The use of crizotinib in this study is investigational (not approved by the FDA) because crizotinib will be prescribed for earlier stage disease after the cancer has been surgically removed.

Patients taking low dose Methotrexate for non-malignant conditions and other cytotoxic agents for non-malignant conditions are allowed to continue treatment while on study.

There will be about 168 people taking part in this research study.

WHAT ARE THE STUDY GROUPS?

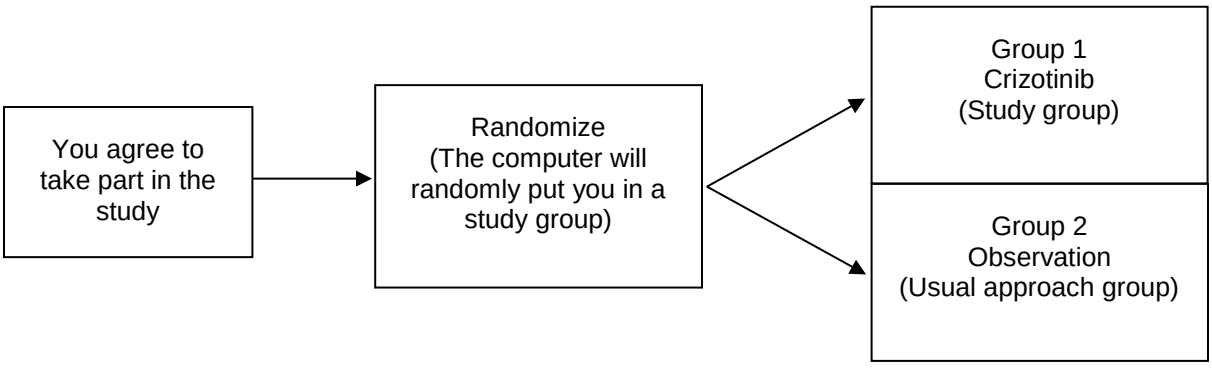
This research study has two study groups.

- Group 1 will get the study drug, crizotinib.
- Group 2 will be monitored with standard post-operative follow up treatment

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.

The original design of this study had patients randomized to receive the study drug, crizotinib, or a placebo. A placebo is a capsule that looks like the study drug but contains no medication. The study investigators felt a placebo was no longer necessary for this study, therefore you will be randomized to receive the study drug, or be followed for observation.

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?

If you are in Group 1, you will receive the crizotinib twice a day for up to two (2) years. After you finish taking crizotinib, your doctor will continue to watch you for side effects and follow your condition for up to 10 years.

If you are in Group 2, your doctor will follow your condition for up to 10 years.

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 exams, tests and 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 and tests to find out if you can be in the research study:

- Electrocardiogram (EKG) to check your heart rhythm
- Blood or urine pregnancy test, if you are a woman of child-bearing potential
- Smoking status survey
- ALK Fusion Status test using tissue from your previous surgery and/or biopsies

Small pieces of cancer tissue removed during your previous surgery and/or biopsies will be taken for the research study before you begin taking 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.

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

During the study:

- Toxicity assessments to see if you are experiencing any side effects every 3 weeks for the first 12 weeks, then every 6 weeks until 30 days after you stop taking study drug.

If your cancer returns:

- Your doctor may take a biopsy to confirm that your cancer has returned and compare the tissue to the samples collected before you started study drug. If you agree, small pieces of the cancer tissue will be taken for the research study.

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.

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 dose or schedule of the study drug to try to reduce side effects.

- You will not be allowed to consume grapefruit or grapefruit juice because of the drugs used in this study. Your doctor will have more information for you.

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 Crizotinib:

COMMON, SOME MAY BE SERIOUS **In 100 people receiving crizotinib, more than 20 and up to 100 may have:**
• Visual disturbances • Swelling of the eye • Constipation, diarrhea, nausea, vomiting • Swelling of the body • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving crizotinib, from 4 to 20 may have:**
• Anemia which may require blood transfusion • Abnormal heartbeat • Pain • Heartburn • Sores in the mouth • Cold symptoms such as stuffy nose, sneezing, sore throat • Infection, especially when white blood cell count is low • Loss of appetite • Dizziness, headache • Changes in taste • Damage to nerves that may interfere with walking or organ function which may cause numbness, tingling, weakness • Rash, itching

RARE, AND SERIOUS **In 100 people receiving crizotinib, 3 or fewer may have:**
• Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or hole in the bowels that may require surgery • Sores in the throat • Difficulty swallowing • Liver damage which may cause yellowing of eyes and skin, swelling • Change in the heart rhythm • Fainting • A sac in the kidney that is filled with fluid • Damage to the lungs which may cause shortness of breath

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 male patient must notify the investigator. The pregnant female partner should be advised to call her healthcare provider immediately.

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 90 days 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 new information becomes available
- If you do not follow the study rules
- 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, you may contact the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

The crizotinib will be supplied at no charge while you take part in this research study. It is possible that the crizotinib 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. Contact information for your study doctor is listed on the consent cover page. The study sponsors will not offer to pay for medical treatment for injury. 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.

No funds have been set aside to compensate you in the event of injury.

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 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:

- Montana Cancer Consortium
- The study sponsor, ECOG-ACRIN, and the drug company supporting the study, Pfizer, Inc.

- 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.

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.

You will not get health benefits from any of these studies. The researchers leading the optional studies hope the results will help other people with cancer in the future.

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 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 storage of samples of your blood for research projects that may be done later date. 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. About 2-3 tablespoons of blood will be collected using a needle before you begin treatment, after 3 months of treatment, and if your disease returns or becomes worse. The blood should be collected at the same time as the blood to monitor your health is collected. However, sometimes an additional stick may be done to collect the blood samples.

2. If your disease returns or becomes worse, a small piece of tumor tissue from your biopsy, if performed, will be sent to the Biobank for storage. Only samples from procedures performed as part of your standard care will be sent. No additional procedures will be done to collect these research tissues samples.
3. Your samples and some related information will be stored in the Biobanks, 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.
4. 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.
5. 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.
6. 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.

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, who will let the researchers know. Contact information for your study doctor is listed on the consent cover page. 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. Contact information for your study doctor is listed on the consent cover page.

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

SAMPLES FOR FUTURE RESEARCH STUDIES:

- **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 information for your study doctor is listed on the consent cover page.

Signature:

This study has been explained to me, and I have been told what my enrollment in the study involves. I have read all pages of this consent and have had my questions answered to my satisfaction at this time. I consent to participate in this study and any additional studies where I circled 'yes'. I understand that by signing this form I have not given up any of my legal rights. I will be given a copy of this consent form. I may also request a copy of the protocol (full study plan).

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)