Informed Consent Document for Treatment with LDK378 (Ceritinib)

Study Title for Participants: Targeted Treatment for ALK Positive Patients Who Have Previously Been Treated for Non-Squamous Non-Small Cell Lung Cancer **(NCT03737994)**

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol NRG-LU003: A Biomarker-Driven Protocol for Previously Treated ALK-Positive Non-Squamous NSCLC Patients: The NCI-NRG ALK Protocol **(NCT03737994)**
(20-May-2019)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have non-small cell lung cancer and your cancer has a change in the gene called ALK. You have received treatment with an ALK-targeting drug for your ALK positive lung cancer and you are no long responding to treatment. Once a patient no longer responds to an ALK- targeted therapy it is not clear which other ALK-targeted therapy or chemotherapy is the best. This study will treat patients with different ALK inhibitors or chemotherapy based on a change in their ALK gene or other changes in the tumor that developed after treatment with a second generation ALK inhibitor drug.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You can also change your mind at any time while on study. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Can we find a better treatment based on gene resistant changes found on biopsy results?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your cancer. The usual approach is defined as care most people get for non-small cell lung cancer.

What is the usual approach to my lung cancer?

The usual approach for patients with ALK-positive lung cancer who are no longer responding to an ALK targeting drug is treatment with a different ALK targeting drug or chemotherapy. Platinum-based chemotherapy is an FDA-approved treatment option that may improve survival, although this has not been formally tested in patients with ALK+ lung cancer. There are a number of ALK targeting and chemotherapy drugs approved by the Food and Drug Administration (FDA) to treat ALK-positive lung cancer. LDK378 (ceritinib) is approved by the FDA for treating ALK-positive lung cancer for patients who have progressed after crizotinib, but it is not approved after progression on other ALK inhibitors. The choice of drug is not based on a specific tissue mutation. Your doctor can explain which treatment may be best for you if you decide not to participate in the study. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

What are my choices if I decide not to take part in this study?

- 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.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will receive treatment based on the results of the test on your tumor biopsy and your previous treatment. You will receive the study drug, LDK378 (ceritinib) until you are no longer benefitting from the treatment or the side effects become too severe.

After you finish your treatment your doctor will continue to follow your condition for 30 days and watch you for side effects.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study drug may not offer any benefit to you and you could have side effects from the study drug.

Some of the most common side effects of LDK378 (ceritinib) the study doctors know about are:

- Pain, constipation, diarrhea, nausea, vomiting, tiredness, cough, weight loss, loss of appetite
- Some serious side effects include abnormal heartbeat and liver damage

There may be some risks that the study doctors do not yet know about.

Benefits
It is not possible to know at this time if the study approach to genetic screening of your tumor sample to help select treatment drugs is better than the usual approach, so this study may or may not help you. Even if the study drug may not be of any benefit to you, this study will help researchers learn things that will help people in the future.

If I decide to take part in this study, can I stop later?
Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your 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.

Are there other reasons why I might stop being in the study?
Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsors, National Cancer Institute and NRG Oncology. The study sponsor is the organization who oversees the study.
- The drug is no longer available and/or provided by the pharmaceutical company.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study? (17-FEB-2020)
Patients who stop responding to ALK targeting drugs often have developed other resistant changes or mutations in the ALK gene. The purpose of this study is to learn if a gene mutation is helpful to decide which different ALK targeting drug to give you compared to the usual treatment of chemotherapy and or another ALK inhibitor not based on gene mutations. Using a biomarker helps to select an ALK targeting drug or chemotherapy that could control your cancer. But, the ALK targeting drug or chemotherapy could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better, the same, or worse than the usual approach. To decide if it is better, the study doctors will be looking to see if the study drug will shrink tumors.

This chemotherapy drug, LDK378 (ceritinib), is already approved by the FDA for use in non-small cell lung cancer.

Another purpose of this study is for the study doctors to learn if a tumor DNA blood test provides the same information as the tumor biopsy result. Two extra tubes of blood were drawn during screening and two more will be drawn at the time of disease progression. The study doctors do not know if using the test is similar to the biopsy. If similar, this test could replace having a tissue biopsy in the future.

There will be about 660 people taking part in this study.

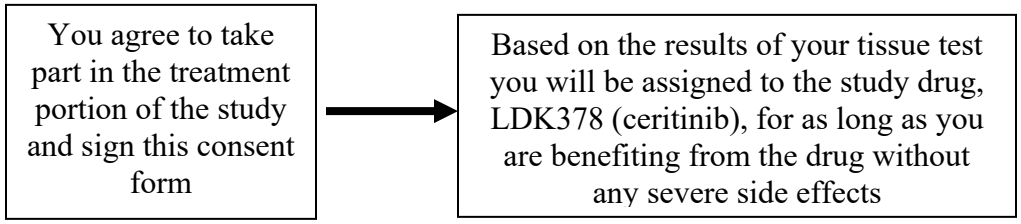
What are the study groups? (20-May-2019)
The study has two steps: the initial screening step which you already consented to and the treatment step which will be discussed in this consent form.

Based on gene mutation results from your tumor tissue, you will receive the study drug, LDK378 (ceritinib).

You will take the study drug LDK378 (ceritinib) by mouth once a day with food. Do not open or dissolve capsule contents. You will take LDK378 (ceritinib) until your cancer gets worse or the side effects become too severe.

You also will keep a pill diary. This helps you keep track of when you take your pills. The study doctor will show you how to use this diary. Each time you visit the clinic, you must bring the pill diary, any remaining pills, and the pill bottle.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



What exams, tests, and procedures are involved in this study? (17-FEB-2020)
Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to

carefully follow the effects of the study treatment, including preventing and managing side effects.

The following test is to monitor your safety and health:

- A fasting blood sample for glucose testing if your blood sugar is high on the usual labs
- A blood sample for pancreas enzymes every 21 days during treatment and 30 days after the end of treatment

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done after patient enrollment for research purposes only.

- Two tubes of blood will be collected at disease progression. This blood sample will use genetic tests that may identify changes in the genes in your tumor DNA. Finding these changes would not affect your treatment in this study. However, they could give information about your and or your family's risk of certain diseases in future. If there are changes found that could cause health problems for you or your family in future, then, your study doctor will discuss your options with you and a genetic counseling referral will be made.
- If you agree, some tumor tissue will be collected if you have a biopsy if your disease progresses.
- About 1 ½ tablespoons of blood will be collected, if you agree during study treatment, 30 days after treatment and if your disease progresses.

The optional blood draws and any leftover tumor tissue will be stored in the Biobank and used for future studies. This will be discussed in the section on optional studies below.

What risks can I expect from taking part in this study? (13-NOV-2019)

General Risks

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

You also may have the following discomforts:

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

The study drug used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during and after you have completed the study.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Genetic Testing Risks
The genetic test used in this study will test your tumor for a panel of gene mutations to find out if your tumor has genetic changes that occurred after treatment with a second generation ALK drug. You have been assigned to a study drug based on the genetic changes in your tumor. Because we do not know if a genetic change will respond better to any one of the ALK targeting drugs, you may receive a drug that you do not respond to. There is a chance of a false positive or a false negative result. A "false positive" refers to the identification of a biomarker that is not present. A "false negative" is the failure to find a biomarker that indeed exists. The tests have been designed to ensure that the possibility of incorrect results is low. Either a false positive or a false negative test would mean that your treatment assignment would not include the correct targeted treatment. However, because we do not know whether targeted treatment will work for you, we cannot say whether an incorrect treatment assignment would be worse.

A genetic change that could be passed down to your children may be found in this test. Since this study is only testing tumor tissue, we will not know if a genetic change in your tumor is also in your normal tissue. If you want to find out if the change is in your normal tissue, then you will need to get other tests done outside of this study.

Genetic tests of normal tissue can reveal information about you and also about your relatives. Your study doctor will talk with you about what testing your normal tissue may mean for you and your family. He or she also may suggest that you talk with a genetics counselor to learn more. You or your insurance plan would have to pay for any genetic tests and visits to a genetic counselor done outside of this study.

Biopsy Risks
Depending on the area from where tissue biopsy is taken, the risks may vary. Your doctor will discuss this with you in depth and a separate consent will be provided to you at the time to explain explicitly the risks based on the site to be biopsied. Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection can occur. You may lose time at work or home and spend more time in the hospital or doctor's office than usual.

Side Effect Risks
The study drug 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 let you know if changes occur that may affect your health.

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

Here are important things to know about side effects:
1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. 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.

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

Risk Profile for LDK378 (ceritinib) (CAEPR Version 2.1, October 2, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving LDK378 (ceritinib), more than 20 and up to 100 may have:
• Pain • Diarrhea, nausea, vomiting • Tiredness • Weight loss, loss of appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving LDK378 (ceritinib), from 4 to 20 may have:
• Anemia which may require blood transfusion • Visual disturbances • Constipation • Fever • Infection • Cold symptoms such as stuffy nose, sneezing, sore throat • Change in the heart rhythm • Dizziness, headache • Difficulty sleeping • Cough, shortness of breath • Rash

RARE, AND SERIOUS In 100 people receiving LDK378 (ceritinib), 3 or fewer may have:

- Abnormal heartbeat
- Liver damage which may cause yellowing of the eyes and skin
- Kidney damage which may cause swelling, may require dialysis
- Damage to the lungs which may cause shortness of breath
- Increased risk of sunburn

Additional Drug Risks
There could be potential interactions with drugs you are taking. Please discuss further with your study doctor. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.

What are my responsibilities in this study? (13-NOV-2019)
If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study
  - write down in your medication diary when you take the study drug at home.

For women: Do not get pregnant or breastfeed while taking part in this study and for 6 months after your last dose of study drug. Women must use an adequate method of contraception to avoid pregnancy for the duration of the study and for 6 months after the last dose of LDK378 (ceritinib). **For men:** Do not father a baby while taking part in this study or within 3 months of your last dose of study drug. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant.

What are the costs of taking part in this study? (20-May-2019)

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- The costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- The costs of getting the study drug ready and giving it to you.
- Your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- The required and optional blood samples (collected before the first dose, during treatment, at disease progression and after treatment)
- Study drug

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?
If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information? (20-May-2019)
Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsors, NRG Oncology and the National Cancer Institute (NCI) and any drug companies supporting the study
- The IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research, including the Cancer Trials Support Unit (CTSU)

- The NCI's National Clinical Trials Network and the groups it works with to conduct research, including the Imaging and Radiation Oncology Core (IROC)
- Foundation Medicine, Inc., the laboratory that will test tumor tissue and blood

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Where can I get more information? (17-FEB-2020)
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.

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 in this study, call the _____ *(insert name of organization or center) or* Institutional Review Board at _____ *(insert telephone number).*

Optional studies that 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. They are separate from the main study described above. These optional studies will not benefit your health. 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.

Taking part in this optional study is your choice. You can still take part in the main study even if you say "no" to this optional study. There is no penalty for saying "no." You and your insurance company will not be billed for this optional study. If you sign up for, but cannot complete this optional study for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for the following study.

Optional sample collections for storage for possible future studies (20-May-2019)
Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies
If you choose to take part in this optional study, blood samples will be collected and stored. If your disease progresses and you have a biopsy, tissue from the biopsy will be collected stored. Storing samples for future studies is called "biobanking." The biobank is being run by NRG Oncology and is supported by the NCI. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use.

We don't know what research may be done in the future using your blood and tissue samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- Future research studies may include sequencing of all or part of your DNA called genomic sequencing. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. This is usually done to look for changes in your genome that may cause health problems.
- You will not get reports or other information about any research that is done using your samples.

What is involved in this optional sample collection?
If you agree to take part, here is what will happen next:

1. About 1 ½ tablespoons of blood will be collected from a vein in your arm about 2 ½ months after starting treatment, 30 days after treatment and if your disease progresses.
2. Tissue from your biopsy taken if your disease progresses will be sent to the biobank.
3. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
4. Researchers can only get samples from the biobank after their research has been approved by experts.
5. Researchers will not be given your name or contact information.
6. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find 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 and get or keep health insurance. *(For non-US participants, adapt the following two sentences as needed.)* There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

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

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

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 to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

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 biobank know. Then, any sample that remains in the biobank will be

destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?
If you have questions about the use of your samples for research, contact the study doctor, _____ *at* _____.

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:
I agree that my samples and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research
I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the 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 and dated copy of this form. I agree to take part in the main study. I also agree to take part in 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 _____