NRG ONCOLOGY

NRG-LU001

(ClinicalTrials.gov NCT #: **02186847***)*

RANDOMIZED PHASE II TRIAL OF CONCURRENT CHEMORADIOTHERAPY +/- METFORMIN HCL IN LOCALLY ADVANCED NSCLC

Amendment 3: November 1, 2018

NRG ONCOLOGY
NCI Protocol NRG-LU001

Consent Form

Study Title for Study Participants: Testing the addition of the drug, metformin, to usual radiation and chemotherapy in locally advanced lung cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: NRG-LU001, Randomized Phase II Trial Of Concurrent Chemoradiotherapy +/- Metformin HCL In Locally Advanced NSCLC

What is the usual approach to my locally advanced lung cancer?

You are being asked to take part in this study because you have advanced lung cancer which has grown and cannot be treated with surgery. People with your type of disease who are not in a study are usually treated with a combination of radiation and chemotherapy. There are several FDA-approved chemotherapy drugs that are commonly used as part of this treatment. Typically, combinations of these are used at the same time with chest radiotherapy. Your doctor can explain these treatments in detail. Combined radiotherapy and chemotherapy can reduce symptoms, may stop the tumor from growing for several months or more, and in some cases, cure lung cancer.

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 example:

- you may choose to have the usual approach described above
- you may choose to take part in a different 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.

Why is this study being done?

The purpose of this study is to compare any good and bad effects of using the anti-diabetic drug, metformin along with the standard of care radiation therapy and chemotherapy to using the standard of care radiation therapy and chemotherapy alone. The addition of metformin to the usual radiation and chemotherapy could shrink your cancer more than the usual radiation and chemotherapy alone and help prevent it from returning, but it could also cause side effects. This study will allow the researchers to know whether adding metformin to radiation and chemotherapy is better, the same, or worse than radiation and chemotherapy alone. To be better, adding metformin should increase by 10 patients in 100 the ability of radiation and chemotherapy to prevent lung cancer from returning in 1 year compared to the standard of care. Metformin is already FDA-approved for use in diabetes, and studies have shown that it is safe for use in non-diabetic patients.

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

What are the study groups?

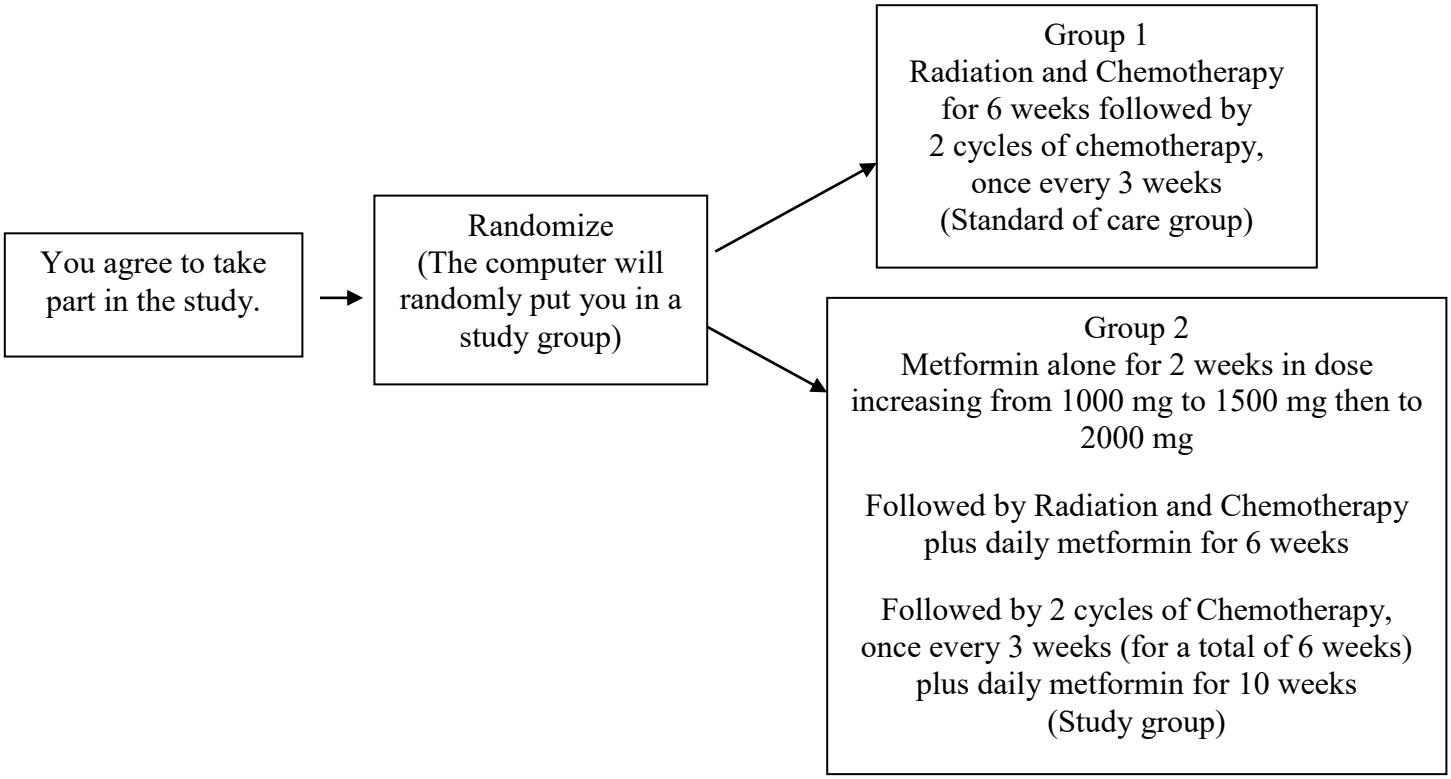
This study has two study groups. Group 1 will receive radiation therapy once a day, 5 days a week (for a total of 60 units of radiation, which are called gray [Gy] over 6 weeks) and chemotherapy, carboplatin and paclitaxel, through your vein once a week for 6 weeks. This will be followed 4 to 6 weeks later with 2 cycles of chemotherapy, carboplatin and paclitaxel, every 3 weeks (for a total of 6 weeks).

Group 2 will receive daily metformin (a pill) 7 days per week for 2 weeks prior to starting chemotherapy in a dose increasing from 1000 mg to 1500 mg and then to 2000 mg, taking metformin 1-2 hours before meals. After 2 weeks of metformin, Group 2 patients will receive radiation therapy once a day, 5 days a week (for a total of 60 units of radiation, which are called gray [Gy] over 6 weeks) and chemotherapy, carboplatin and paclitaxel, through your vein once a week, plus daily metformin (2000 mg) 7 days per week for 6 weeks. This will be followed 4 to 6 weeks later by 2 cycles of chemotherapy, carboplatin and paclitaxel, through your vein every 3 weeks, (for a total of 6 weeks) and daily metformin (2000 mg) 7 days per week for 10 weeks.

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other. You have an equal chance at being placed in either study group.

This study has two study groups.

- Group 1 will get the standard of care radiation therapy and chemotherapy drugs, carboplatin and paclitaxel.
- Group 2 will get the standard of care radiation therapy and chemotherapy drugs, carboplatin and paclitaxel, plus the study drug, metformin before, during, and after radiation therapy.



How long will I be in this study?

Group 1 patients will receive radiation and chemotherapy for 6 weeks followed by 2 cycles of additional chemotherapy (for a total of 6 weeks) given 4-6 weeks later.

Group 2 patients will receive metformin alone for 2 weeks followed by radiation and chemotherapy with metformin for 6 weeks and then 2 cycles of additional chemotherapy (for a total of 6 weeks) given 4-6 weeks later plus 10 weeks of metformin.

After you finish treatment, your doctor will continue to watch you for side effects, check your disease, and see you in follow-up visits every 3 months for years 1 and 2, every 6 months for years 3, 4, and 5, then once a year for your lifetime.

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 approach for your cancer. However, there are some extra blood tests that you will need to have if you take part in this study.

During the study:

- Group 2 patients will need weekly blood sugar testing that requires a finger stick to test a drop of blood.
- Group 2 patients will be asked to keep a diary of what metformin they take and when it was taken.

What possible risks can I expect from taking part in this study? (8/10/16)

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

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- The study drug/study approach may not be better, and could possibly be worse, than the usual approach for your cancer.

The radiation therapy, chemotherapy drugs, and metformin 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 be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

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 Metformin Table Version Date: January 19, 2016)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Metformin, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Metformin, from 4 to 20 may have:
• Heartburn, passing gas • Headache • Tiredness • Abdominal discomfort • Vitamin B12 deficiency

RARE, AND SERIOUS In 100 people receiving Metformin, 3 or fewer may have:
• Lactic acid build up which may cause muscle aches, shortness of breath, or severe belly pain

Possible Side Effects of Paclitaxel (Table Version Date: August 23, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, more than 20 and up to 100 may have:
• Anemia which may cause tiredness, or may require blood transfusions • Infection, especially when white blood cell count is low • Diarrhea, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Bruising, bleeding • Pain • Muscle weakness • Numbness, tingling, or pain of the arms and legs • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Paclitaxel, from 4 to 20 may have:
• Abnormal heartbeat • Damage to the lungs which may cause shortness of breath • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving Paclitaxel, 3 or fewer may have:
• Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or a hole in the stomach which may cause belly pain or that may require surgery

Possible Side Effects of Carboplatin (Table Version Date: March 24, 2015)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Carboplatin, more than 20 and up to 100 may have:
• Hair loss • Vomiting, nausea • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require blood transfusions • Bruising, bleeding • Belly pain

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Carboplatin, from 4 to 20 may have:
• Diarrhea, Constipation • Numbness and tingling in fingers and toes • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Changes in taste • Changes in vision

RARE, AND SERIOUS In 100 people receiving Carboplatin, 3 or fewer may have:
• Damage to organs which may cause hearing and balance problems

Possible Side Effects of Lung Radiation Therapy (5/7/15)

COMMON, SOME MAY BE SERIOUS In 100 people receiving lung radiation therapy, more than 20 and up to 100 may have:
• Swelling and redness, tanning, thickening, numbness, or peeling of the skin in the area of radiation • Difficulty and/or pain with swallowing • Hair loss in the treatment area, may be permanent • Shortness of breath • Cough with or without increased phlegm production • Tiredness • Diarrhea, nausea • Anemia, which may require blood transfusion • Infection, especially when white blood cell count is low • Bleeding, bruising • Rib pain, increased risk of rib fracture

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving lung radiation therapy, from 4 to 20 may have:

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving lung radiation therapy, from 4 to 20 may have:
• Inflammation of the lung that may cause difficulty breathing and can be life-threatening • Narrowing of the throat which may cause vomiting, difficulty swallowing • Scarring in the lung • Lung collapse • Fluid around lungs • Bleeding from the lungs which may cause coughing up blood • Fever • Narrowing of the esophagus • Pain in chest wall

RARE, AND SERIOUS In 100 people receiving lung radiation therapy, 3 or fewer may have:
• Abnormal opening in internal organs which may cause pain and bleeding • Irritation of the heart causing heart failure, heart attack, chest pain, abnormal heartbeat, shortness of breath, swelling of ankles, cough or tiredness • Transverse myelitis – irritation of the spinal cord causing weakness, tingling or numbness of the lower body and legs, or paralysis of the lower half of the body • Brachial plexopathy – irritation of the nerves controlling the arm, causing weakness or paralysis • Bleeding from the airway (windpipe) • Narrowing of the airway causing shortness of breath • Death • Lung damage, may be life threatening • Damage to the large blood vessels surrounding the heart, which could cause coughing up of blood and possibly death Sores and skin damage causing bleeding and severe pain and may lead to an open wound

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 get pregnant, breastfeed, or father a baby while in this study. The radiation and drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the addition of metformin to radiation therapy and chemotherapy is better than the usual approach of radiation and chemotherapy, so this study may or may not help you. This 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 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? (5/7/15)

NOTE TO PARTICIPATING SITES: Most insurers will not pay for metformin. Neither NCI nor NRG Oncology are able to support the central distribution of this drug. Therefore, sites have the option to cover costs of metformin for patients on this trial as stated in protocol section 7.1.5, or require patients to pay for metformin out of pocket. Sites should tailor the section below, based on site policy, when submitting this Consent Form for local IRB review.

You and/or your health plan/insurance company will need to pay for the costs of the radiation therapy, chemotherapy drugs, and metformin HCL while in this study, including the cost of tests, procedures, or medicines to manage any side effects. Because metformin HCL is investigational for your cancer, in most cases your health plan/insurance company will not pay for the drug; however, it is a commonly used, generic drug, and the cost is very low. Before you decide to be in the 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 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 study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for 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 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.

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:

- NRG Oncology
- 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.

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).*

THIS SECTION IS ABOUT OPTIONAL STUDIES YOU CAN CHOOSE TO TAKE PART IN (8/10/16)

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.

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

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

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your 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.

If you choose to take part, a sample of tissue from your previous biopsy and blood will be collected. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by NRG Oncology and supported by the National Cancer Institute.

WHAT IS INVOLVED?

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

1) About 3-4 tablespoons of blood will be collected from a vein in your arm and a sample from the tissue that was collected at the time of your biopsy will be sent to the Biobank.
2) Your sample and some related information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review 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) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included

WHAT ARE THE POSSIBLE RISKS?

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 kept about you. Someone may 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.
3) There can 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 research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

4) Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information. Some states have laws to protect against genetic discrimination [*list appropriate state information if your state has such laws]*. A federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law does not allow discrimination by insurers or employers. The law does not include other types of misuse by life insurance, disability, or long term care insurance. To learn more about the GINA Law, please ask [*Note to local investigator: List contact information here for patient representatives or other individuals who take calls regarding clinical trials but who are not on the site IRB or research team.*]

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 samples are 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 NRG Oncology staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom NRG Oncology 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?

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?

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?

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 (*include only applicable questions)*:

SAMPLES FOR FUTURE RESEARCH STUDIES:

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

YES NO

I agree that my study doctor, or their representative, may contact me or my physician 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 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_____