NCI COMMUNITY ONCOLOGY RESEARCH PROGRAM – KANSAS CITY (NCORP-KC)

RTOG 1119

Phase II Randomized Study Of Whole Brain Radiotherapy In Combination With Concurrent Lapatinib In Patients With Brain Metastasis From HER2-Positive Breast Cancer- A COLLABORATIVE STUDY OF NRG Oncology AND KROG

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have HER2-positive breast cancer that has spread to your brain.

Why is this study being done?
Lapatinib is a drug that has been approved by the FDA for patients with progressive HER2-positive metastatic breast cancer. However, the combination of brain radiation and lapatinib for the treatment of brain metastases is experimental. The combination is being tested because lapatinib was found to improve the effectiveness of radiation therapy in the laboratory. An early study in patients showed that brain radiation and lapatinib can be combined safely.

The purpose of this study is to evaluate the effects of adding lapatinib to standard brain radiation therapy on you and your cancer. The study will try to find out whether radiation therapy alone or lapatinib plus radiation therapy is better at safely improving tumor control. In this study, you will receive either lapatinib plus radiation therapy or radiation therapy alone.

How many people will take part in the study?
About 143 people will take part in this study.

What will happen if I take part in this research study?
Before you begin the study ...
You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical examination
- MRI (magnetic resonance imaging) scan of your brain: An MRI is imaging using a strong magnetic field to look at one part of your body
- Blood tests for blood counts, liver function, and kidney function: About 2 teaspoons of blood will be drawn
- Pregnancy test, if applicable

During the study ...
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures.

- Evaluation of any side effects you are experiencing
- Blood work (if you are taking lapatinib): About 2 teaspoons of blood will be drawn at the end of the 3 weeks of radiation treatment. The purpose is to monitor for any changes in your blood counts, liver function, and kidney function that might have occurred because of the treatment with lapatinib.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

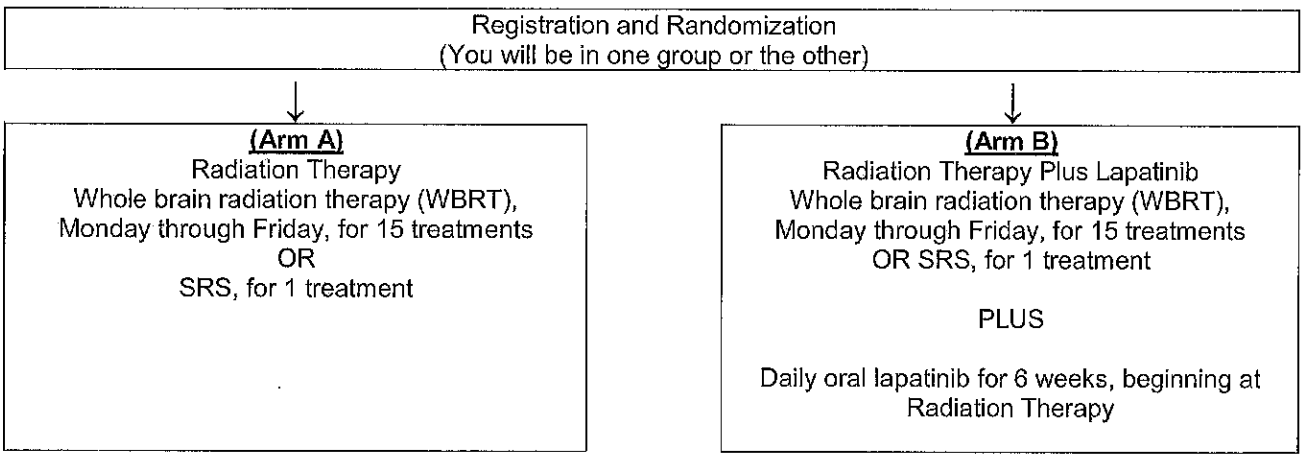
Both groups will receive radiation therapy. Your doctor will select which type of brain radiation is most appropriate for you. You will receive either whole brain radiation therapy (WBRT) or a type of radiation that targets your brain tumor(s) called stereotactic radiosurgery (SRS).

If you are in Arm A: You will receive radiation therapy alone. You will receive WBRT you will receive radiation once a day, 5 days a week for 3 weeks, for a total of 15 treatments. If you receive SRS, you will receive treatment on one day.

If you are in Arm B: You will receive radiation therapy plus lapatinib. You will receive radiation therapy as in Arm A. In addition, you will begin taking lapatinib once daily for 6 weeks starting on the first day of radiation therapy. You will also be asked to complete a pill diary to document the amount of lapatinib that you took each day. You should bring this pill diary with you to be checked by your study doctor or study nurse once each week during the 6 weeks you are on lapatinib treatment and at your follow-up visits at 4 and 12 weeks after treatment.

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



When I am finished treatment with WBRT with or without lapatinib...
You will be followed at regular check-ups, including MRIs, at 4 and 12 weeks after you complete treatment, and then every 12 weeks for the rest of your life.

How long will I be in the study?
If you are in Arm A, you will receive either 3 weeks of WBRT or one treatment of SRS depending on your tumor location(s). If you are in Arm B, you will receive either 3 weeks of WBRT or one treatment of SRS and will take lapatinib for a total of 6 weeks beginning with radiation therapy. After you have finished receiving treatment on

either Arm A or Arm B, the study doctor will ask you to visit the office for follow-up exams every 12 weeks for the rest of your life.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so your study doctor can evaluate any risks from the radiation therapy and/or lapatinib. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?
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 lapatinib and radiation therapy 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 drug(s)/ study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may 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.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Possible Side Effects of Brain Radiation

COMMON, SOME MAY BE SERIOUS In 100 People receiving brain radiation, more than 20 and up to 100 may have:
▪ Scalp redness or soreness ▪ Hair loss, which may be temporary or permanent ▪ Temporary hearing decrease or loss ▪ Tiredness ▪ Temporary increase of brain tumor symptoms such as headaches, seizures, or weakness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving brain radiation, from 4 to 20 may have:
▪ Change in thinking patterns, decrease ability to concentrate, behavior changes, difficulty walking, difficulty talking ▪ Permanent hearing decrease or loss ▪ Cataracts ▪ Nausea, vomiting ▪ Dry mouth, changes in taste ▪ Loss of appetite ▪ Abnormal hormone levels related to changes to the pituitary gland may cause symptoms such as low blood sugar, low blood pressure, and fatigue which may require hormone replacement

RARE, AND SERIOUS In 100 people receiving brain radiation, 3 or fewer may have:
▪ Damage to the brain ▪ Swelling of the brain ▪ Blurred vision with chance of blindness ▪ A new cancer resulting from treatment of earlier cancer

Receipt of prior radiation may increase the risk of side effects in some patients, depending on the radiation dose previously received.

Possible Side Effects of lapatinib

COMMON, SOME MAY BE SERIOUS In 100 people receiving lapatinib, more than 20 and up to 100 may have:
▪ Diarrhea ▪ Rash

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

- Anemia which may require blood transfusion
- Bloating, heartburn, passing gas, vomiting
- Pain
- Sores in mouth which may cause difficulty swallowing
- Tiredness
- Flu-like symptoms including fever, chills, body aches, muscle pain
- Infection
- Loss of appetite, dehydration
- Changes in taste
- Headache
- Cough, sore throat
- Nose bleed
- Hair loss, itching, acne
- Dry skin
- Chang in or loss of some or all of the finger or toenails
- Flushing, hot flashes

RARE, AND SERIOUS
In 100 people receiving lapatinib, 3 or fewer may have:

- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Liver damage which may cause yellowing of eyes and skin, swelling
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Change in heart function
- Change in the heart rhythm
- Swelling of the lungs which may cause shortness of breath
- Redness, pain or peeling of palms and soles
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study and for 12 months after you stop study treatment. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you are a woman of childbearing potential, you must have a negative pregnancy test before enrolling in this study. You will not be allowed to continue in the study if you become pregnant.

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

Are there benefits to taking part in the study?
Taking part in this study may or may not make your health better. While doctors hope that the combination of radiation therapy and lapatinib will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about this combination as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Standard treatment (WBRT or SRS alone)
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- NRG Oncology
- Other organizations in the National Clinical Trials Network (NCTN): Alliance for Clinical Trials in Oncology (ALLIANCE), ECOG-ACRIN Cancer Research Group (ECOG-ACRIN), SWOG, and Imaging and Radiation Oncology Core (IROC)
- 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 National Cancer Institute (NCI) and other government agencies (in the U.S. or other countries), like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), an organization sponsored by the NCI to provide greater access to cancer trials
- Novartis (the drug supplier of lapatinib) and its authorized agents

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.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The NCI will provide the lapatinib at no charge while you take part in this study. The NCI does not cover the cost of getting the lapatinib ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the NCI may not be able to continue to provide the lapatinib for some reason. If this would happen, the study may have to close. Your study doctor will talk with you about this, if it happens.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment. Novartis will not pay any money to you or your medical bills.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the NCI Community Oncology Research Program – Kansas City Institutional Review Board (a group of people who review the research to protect your rights) at 913-948-5588.

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to taking part in the additional research.

You can say "yes" or "no" to the following study. Please mark your choice.

Consent Form for Use of Tissue for Research
About Using Tissue for Research
You have had a biopsy (or surgery) to see if you have cancer. Your doctor removed some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases.

As a result of your participation in the trial, you will have blood tests performed before you start treatment. We would like to collect for future research about 3 tablespoons of blood taken at that time. In addition, we would like to collect about 3 tablespoons of blood at 4 and 12 weeks after you finish radiation therapy; the blood taken at these times would be an extra blood draw, since you would not otherwise need to have blood taken at those times as part of

your participation in the main part of the trial. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care and will not identify you.

Things to Think About
The choice to let us keep the tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any tissue that remains will be returned to the institution that submitted it and any blood that remains will be destroyed.

In the future, people who do research may need to know more about your health. While the Radiation Therapy Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits
The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks
The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

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. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

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.

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.

Many states have laws to protect against genetic discrimination. Additionally, a federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law prohibits health insurer or employer discrimination. 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 your study doctor.

Making Your Choice
Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No".

If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number. No matter what you decide to do, it will not affect your care.

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
Yes No
2. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
Yes No
3. My blood may be kept for use in research to learn about, prevent, or treat cancer.
Yes No
4. My blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
Yes No
5. Someone may contact me in the future to ask me to take part in more research.
Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Release

By signing this form you authorize NCORP-KC to access and obtain information that is required for the study. This may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant Name_____

Participant Signature _____ **Date** _____

Person Obtaining Consent_____

Signature of Person Obtaining Consent_____

Date _____