NRG ONCOLOGY

NRG-CC003

(ClinicalTrials.gov NCT #: **02635009***)*

RANDOMIZED PHASE II/III TRIAL OF PROPHYLACTIC CRANIAL IRRADIATION WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE FOR SMALL CELL LUNG CANCER

Amendment 5: July 1, 2022

NRG ONCOLOGY
NCI Protocol NRG-CC003

Consent Form

Study Title for Study Participants: Testing whether avoiding the hippocampus during whole-brain radiation therapy prevents cognitive side effects in patients with small cell lung cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer (NCT #02635009) (14-FEB-2019)

What is the usual approach to treating small cell lung cancer? (11Aug2017)

You are being asked to take part in this research study because you have small cell lung cancer, which can spread to the brain. People who are not in a study are usually treated with radiation to the whole brain to reduce the chance of the cancer spreading to the brain.

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? (15-JUNE-2020)

The purpose of this study is to compare any good and bad effects of avoiding the hippocampus during whole-brain radiation to the usual whole-brain radiation. The hippocampus is part of the brain that is important for memory. Avoiding the hippocampus during whole-brain radiation could decrease the chance of side effects on memory and thinking. It also is possible that avoiding the hippocampus could have no benefit or could cause other side effects. Hippocampal avoidance also could lessen the effectiveness of whole-brain radiation. This 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 addition of the hippocampal avoidance technique to whole-brain radiation therapy should decrease the chance of side effects on memory or thinking by at least 14.5%.

The first portion of this study will test if avoiding the hippocampus during whole-brain radiation is as effective as the usual treatment, whole-brain radiation, in decreasing the chance of cancer spreading to the brain. The second portion of the study will test if hippocampal avoidance decreases side effects related to memory and thinking.

There will be about 172 people taking part in both the first and second portions of this study and about 220 additional people taking part in only the second portion of this study (a total of about 392 participants).

What are the study groups?

This study has two study groups:

- Group 1 will receive whole-brain radiation (usual care).

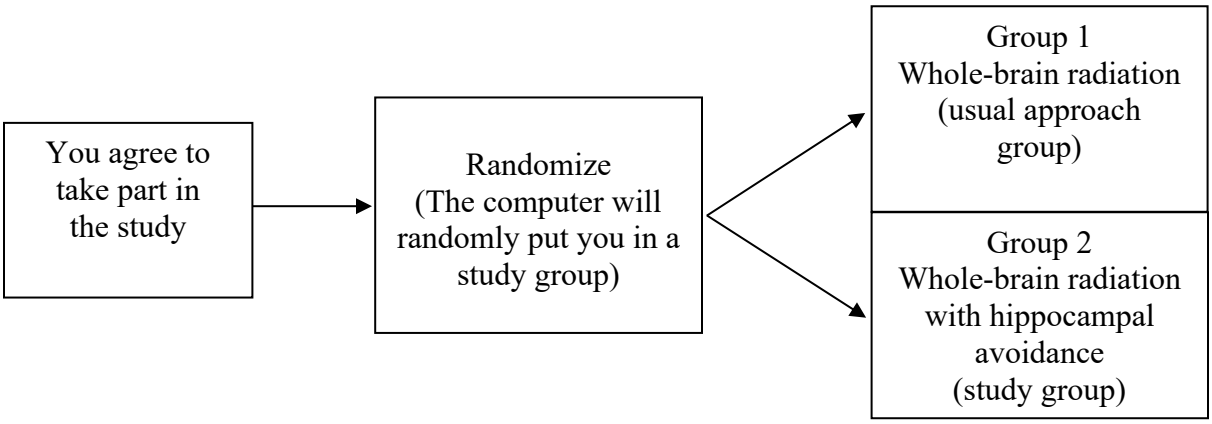
- Group 2 will receive whole-brain radiation with hippocampal avoidance.

These study groups are the same for the first and second portions of the study.

You and your doctor will decide if you will also receive the medicine, memantine. Memantine is not being studied in this trial. Memantine is a pill commonly given during radiation to the brain that may decrease the risk of side effects on memory and thinking. Memantine is FDA-approved for use in patients with dementia.

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 will have an equal chance at being placed in either study group.

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.



How long will I be in this study?

You will receive whole-brain radiation therapy (usual treatment or with hippocampal avoidance) daily for 2 weeks. After you finish radiation, your doctor will continue to watch you for side effects and follow your condition for your lifetime.

What extra tests and procedures will I have if I take part in this study? (11Aug2017)

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

Before you begin the study:

- Three tests to see how the study is affecting your thinking abilities, such as memory, administered by a trained test administrator in the clinic that take about 20 minutes to complete.
- You will be asked to fill out five forms with questions about how you are feeling physically and emotionally. These forms will take a total of 15 to 20 minutes to complete. Researchers will use this information to learn more about how cancer and cancer treatment affects people. The forms will ask about things like fatigue, hopefulness, or cognitive functioning. You may feel uncomfortable answering some of the questions, and you can skip any you do not want to answer.

During the study:

- Three tests at 3, 6, 12, 18, and 24 months from the start of radiation to see how the study is affecting your thinking abilities, such as memory, that take about 20 minutes to complete. At the 6-month time

point, you also will be asked to fill out two forms regarding hopefulness, which take about 5 minutes to complete.

- You will be asked to fill out three forms at the end of radiation therapy, and at 6, 12, and 24 months about how the study is affecting your ability to work and do daily activities. You also will be asked about the number of times you have seen a doctor or visited the emergency room between clinic visits. These forms will take 10-15 minutes to complete.
- You will be asked to fill out three forms at months 3, 6, 12, 18 and 24 months from the start of treatment with questions about how you are feeling physically and emotionally that will take a total of 10 to 15 minutes to complete.
- You will be asked to maintain a diary to keep track of all the health services you require while on this study. Your caregiver may help you complete this diary. We will ask for your caregiver's contact information in case we need to contact them if the diary is not completed. Their information will not be shared with NRG Oncology.

In the past, patients often have filled out these quality of life forms on paper. NRG Oncology is working with a company, VisionTree Software, Inc., that has a web site where patients can fill out these forms anywhere there is a computer with Internet access. This option is being offered as some patients may find it more convenient to fill out the forms electronically from any location, including home. When you log on to the web site, it will take you through the process of completing the forms step by step. You will need an e-mail address that you agree to use for this purpose. The e-mail address is needed to identify you on the VisionTree web site and for e-mail reminders that will be sent to you when the forms are due. Your e-mail address will only be used for the purpose of this study, not for mail or marketing purposes. If you are interested in filling out quality of life forms electronically but do not have an e-mail address, you may obtain one (quickly and for no charge at web sites such as Yahoo!, Hotmail, or AOL). You will only be sent e-mail reminders at the time that the forms are due (a maximum of 3 e-mail reminders per time point). Your access to the VisionTree web site is password protected and secure. You can use your e-mail address to retrieve your password if you forget it or lose your login card. You will receive a login card either by regular mail or e-mail, and it will include the information you need to log in to the VisionTree web site the first time. All patients will complete the forms before treatment on paper. After that, you can choose to complete the remaining forms online or on paper. The choice is up to you.

Please circle your answer: I choose to use the VisionTree Software. I agree to fill out the Quality of Life forms electronically (after treatment has started) using the VisionTree web site.

YES NO

What possible risks can I expect from taking part in this 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 study approach may not be better, and could possibly be worse, than the usual approach for your cancer.

The radiation used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood.

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.
- If you decide to take memantine, the study doctor may adjust the dose of memantine to try to reduce side effects.

The tables below show the most common and the most serious side effects of whole-brain radiation 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.

Study Group 1 and Group 2: Possible Side Effects of Whole-brain Radiation Therapy*(11Aug2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving whole-brain radiation therapy, more than 20 and up to 100 may have:
• Hair loss, which may be permanent • Dry mouth and/or change in taste • Scalp reddening or tanning and irritation (Your skin will be examined once a week during radiation therapy) • Memory loss, problems thinking clearly, or difficulty managing multiple tasks, which can occur in the first few months after whole-brain radiotherapy and may be permanent • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving whole-brain radiation therapy, from 4 to 20 may have:
• Temporary worsening of tumor-like symptoms such as seizures or weakness • Drainage of clear fluid from the ears or plugging of the ears with decreased hearing • Behavioral change and/or increased sleepiness (occurring four to ten weeks after radiotherapy is complete and lasting for several days up to two weeks) • Cataracts and eye damage with the possibility of impaired vision • Nausea and/or vomiting • Headaches

RARE, AND SERIOUS In 100 people receiving whole-brain radiation therapy, 3 or fewer may have:
• Severe local damage to or death of normal brain tissue, which may require surgery to remove • Hardening of the arteries in the brain, which may lead to strokes • A second new cancer caused by radiation, in the brain or nearby organs • Eye damage with the possibility of permanent blindness

*** NOTE: The risks above are possible side effects of whole brain radiation. Standard prophylactic cranial irradiation (PCI) doses for Small-Cell Lung Cancer, however, are usually lower and therefore, some of these risks may have a lower incidence than described in the table.**

Study Group 2: In addition to side effects outlined above, people who are in Group 2 also may experience the possible side effects of avoiding the hippocampus during whole-brain radiotherapy.

Possible Side Effects of Avoiding the Hippocampus During Whole-brain Radiotherapy

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving hippocampal avoidance whole-brain radiation therapy, from 4 to 20 may have:
• The risks of whole-brain radiotherapy listed above • The development of cancer in or near the hippocampus

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The radiation (and memantine, if taken) 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 study approach (hippocampal avoidance whole-brain radiation therapy) is better than the usual approach (whole-brain radiation therapy). 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 study sponsor, (NRG Oncology) or the Institutional Review Board (IRB).

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?

You and/or your health plan/insurance company will need to pay for all of the costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. 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? (15-JUNE-2020)

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, 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 or receive copies of some of the information in 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:

- NRG Oncology and any company supporting the study now or in the future. This would include any organization helping the company with the study
- The NCI Central 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).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now 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? (13-APR-2021)

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).*

ADDITIONAL STUDIES SECTION: This section is about optional studies you can choose to take part in. It is not about the main study.

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 each of the following studies.

Optional Sample Collections for Laboratory Studies and/or storage for Possible Future Studies (14-FEB-2019)

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

Known future studies

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If you choose to take part in these studies, we will collect blood samples for research on medical signs (called biomarkers) within the blood cells that may indicate that some people experience mental decline if they have the type of radiation in this study.

Unknown future studies
If you choose to take part in this study, we will collect blood samples for future research that 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.

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. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your blood 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.

WHAT IS INVOLVED?
If you agree to take part, here is what will happen next:
1) About 3 tablespoons of blood will be collected from a vein in your arm before treatment begins. In addition, blood will be collected at 3, 6, 12, and 18 months from the start of radiation therapy.
2) Your sample and some related health information will be stored in the Biobank, along with samples and information from other people who take part, for use in the study described above. The samples will be kept until they are used up.
3) Qualified researchers can submit a request to use the materials stored in the Biobank. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There also will 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? (14-FEB-2019)
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.

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 *[list appropriate state information if your state or locality 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 health insurers or employers. The law does not include other types of misuse by life insurance, disability, or long term care insurance.

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 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 in this optional study. 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 for these additional blood samples. 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? (15-JUNE-2020)

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

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

SAMPLES FOR KNOWN FUTURE STUDIES:

I agree that my samples and related health information may be used for the *miRNA Signature* studies described above.

YES NO

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_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____