NRG ONCOLOGY

NRG-CC001

(ClinicalTrials.gov NCT #: **02360215***)*

A RANDOMIZED PHASE III TRIAL OF MEMANTINE AND WHOLE-BRAIN RADIOTHERAPY WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE IN PATIENTS WITH BRAIN METASTASES

Amendment 3: September 26, 2017

NRG-CC001 Consent Form

Study Title for Study Participants: Testing whether avoiding the hippocampus in addition to memantine during whole-brain radiation therapy better prevents cognitive side effects in people with brain metastases

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

NRG-CC001, A Randomized, Phase III Trial Of Memantine and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Patients With Brain Metastases

What is the usual approach to the cancer that has spread to my brain? (8/17/16)

You are being asked to take part in this research study because you have cancer that has spread to the brain. People who are not in a study are usually treated with radiation therapy along with memantine. Memantine is an oral tablet given during and after radiation therapy that can decrease the risk of cognitive side effects after radiation therapy 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?

The purpose of this study is to compare any good and bad effects of avoiding the hippocampus during whole-brain radiation plus memantine to using the usual whole-brain radiation plus memantine. The hippocampus is a brain structure that is important for memory. The addition of the hippocampal avoidance technique to the usual whole-brain radiation plus memantine will decrease the dose of radiation to your hippocampus. It is hoped hippocampal avoidance technique will decrease the chance of cognitive side effects, however it is possible hippocampal avoidance could have no impact on cognitive side effects and could even cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. Memantine is already FDA-approved for use in patients with dementia and is commonly used off-label (that is, for a purpose for which it is not FDA approved) for patients receiving whole-brain radiation therapy for cancer that has spread to the brain.

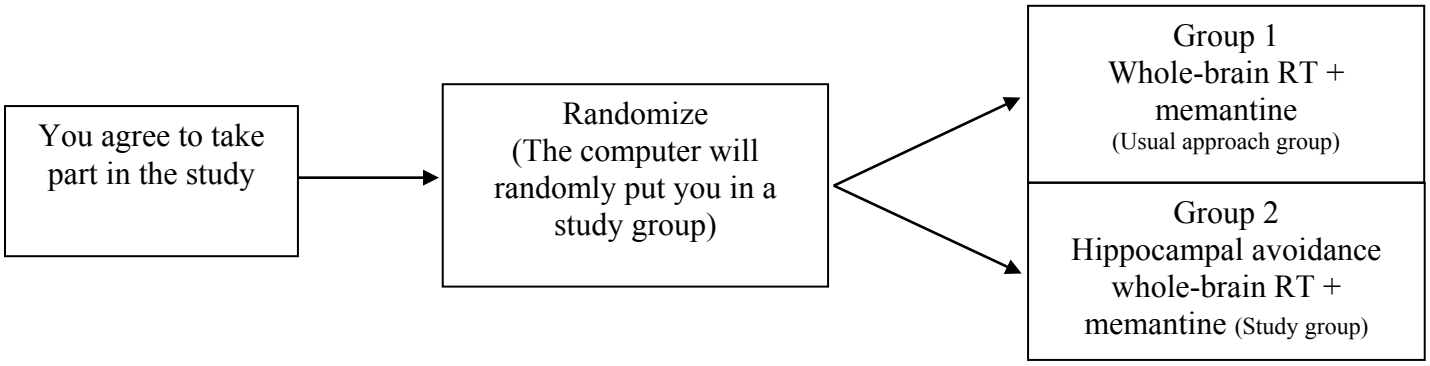
There will be about 510 people taking part in this study.

What are the study groups?

This study has two study groups.

- Group 1 will get the usual whole-brain radiation therapy plus memantine.
- Group 2 (investigational or "study" group) will get whole-brain radiation therapy using the hippocampal avoidance technique plus memantine.

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 others. 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.



Whether you are in Group 1 or Group 2 you will be prescribed memantine to begin taking while you are receiving radiation therapy. Memantine is well absorbed after oral administration and absorption is not affected by food and therefore can be taken with or without food. Either extended release memantine or twice daily memantine dosing will be allowed. The dosing and schedule are outlined below separately for each. All study participants will be given a Pill Diary to document their daily dose. The Pill Diary is to be returned to the clinic prior to each treatment cycle.

Twice Daily Dosing Memantine

On Week 1, starting on Day 1, take one 5 mg tablet in the morning, each day.
On Week 2, starting on Day 8, take one 5 mg tablet in the morning and one 5 mg tablet at night, each day.
On Week 3, starting on Day 15, take one 10 mg tablet in the morning and one 5 mg tablet at night, each day.
On Week 4, starting on Day 22, take one 10 mg tablet in the morning and one 10 mg tablet at night, each day.

You will continue taking memantine for 20 more weeks or until your doctor tells you to stop.

Below is the *same* dosing schedule provided in table format:

	Daily AM Dose	**Daily PM Dose**
Week 1	5 mg	None
Week 2	5 mg	5 mg
Week 3	10 mg	5 mg
Weeks 4-24	10 mg	10 mg

Extended Release Memantine

On Week 1, starting on Day 1, take one 7 mg tablet each day.
On Week 2, starting on Day 8, take one 14 mg tablet each day.
On Week 3, starting on Day 15, take one 21 mg tablet each day.
On Week 4, starting on Day 22, take one 28 mg tablet each day.

You will continue taking memantine for 20 more weeks or until your doctor tells you to stop.

Below is the *same* dosing schedule provided in table format:

	Daily Dose Extended Release Memantine
Week 1	7 mg
Week 2	14 mg
Week 3	21 mg
Weeks 4-24	28 mg

How long will I be in this study?

You will receive whole-brain radiation therapy (standard treatment or using hippocampal avoidance) daily for 2 weeks, and will also take memantine daily during and after radiation for 24 weeks. After you finish radiation plus memantine, your doctor will continue to watch you for side effects and follow your condition for 12 months.

What extra tests and procedures will I have if I take part in this study? (8/17/16)

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:

- Completion of three tests administered by a trained test administrator in the clinic that take about 20 minutes to complete to see how the study is affecting your thinking abilities such as memory.
- You will be asked to fill out two forms with questions about how you are feeling physically and emotionally that will take 5 to 10 minutes to complete.

During the study:

- Completion of three tests administered by a trained test administrator in the clinic that take about 20 minutes to complete to see how the study is affecting your thinking abilities such as memory during months 2, 4, and 6 of memantine treatment, and at 12 months.
- You will be asked to fill out two forms with questions about how you are feeling physically and emotionally during your cancer treatment that will take 5 to 10 minutes to complete during months 2, 4, and 6 of memantine treatment, and at 12 months from the start of memantine.
- Patient pill diary

What possible risks can I expect from taking part in this study? (24AUG2017)

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.

There is also a risk that you could have side effects from the radiation and memantine.

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.
- Tell the study doctor if you start any new prescribed medications or over the counter medications to avoid potential interactions with memantine.

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.

Study Group 1 and Group 2: Possible Side Effects of Brain Radiation Therapy

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:
• Changes in thinking patterns, decreased ability to concentrate, behavior changes, difficulty walking, difficulty talking • Permanent hearing decrease or loss • Cataracts • Nausea, vomiting • Dry mouth, change 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

Study Group 1 and Group 2: Possible Side Effects of Memantine
Memantine is well-tolerated and is not associated with frequently occurring side effects.

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving memantine, from 4 to 20 may have:
• Dizziness • Headache • Constipation • Diarrhea • Pain • Shortness of breath • High blood pressure • Coughing • Nervousness • Changes in behavior • Confusion, Restlessness • Inability to obtain enough sleep • Depression • Tiredness, lack of energy • Vomiting

RARE, AND SERIOUS In 100 people receiving memantine, 3 or fewer may have:
• Seeing or hearing things that aren't there • Increased seizure frequency • Damage to kidney function

NOTE: Stevens Johnson Syndrome (SJS) is a severe skin rash with blisters and can involve the inside of mouth and other parts of the body and can include fever. Stevens Johnson Syndrome is very rare and, at this time, it is unknown if memantine causes this skin reaction. However, there have been reports of SJS while taking memantine. If you notice any skin reactions during treatment, inform your health care provider immediately.

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 development of cancer in or near the hippocampus

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 therapy and memantine 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 plus memantine) is better than the usual approach (whole-brain radiation therapy plus memantine) 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), Institutional Review Board (IRB) or the Food and Drug Administration (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?

You and/or your health plan/insurance company will need to pay for all of the other 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 be responsible for paying any deductibles, coinsurance, and co-payments as required under the terms of your insurance plan(s) including the costs of the memantine.

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:

- The study sponsor (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).*

ADDITIONAL STUDIES SECTION: This section is about optional studies you can choose to take part in.

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

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 study.

Optional Sample Collections for 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 in this study, the study doctor for the main study would like to collect blood and serum for research on memory and thinking in patients undergoing radiation therapy to the brain.

WHAT IS INVOLVED? (24AUG2017)

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 and at 2, 4, 6 and 12 months after you started radiation.
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 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 stored about you.
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.

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. To learn more about the GINA Law, please ask *[Note to local investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*.

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:

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_____