Official Title: Wake Forest NCORP Research Base - A Single Arm, Pilot Study of Ramipril for Preventing Radiation-Induced Cognitive Decline in Glioblastoma (GBM) Patients Receiving Brain Radiotherapy - Coordinating Center

NCT03475186

IRB Approval Date: 11/21/2022

Informed Consent

Study Title for Study Participants: Testing Ramipril to prevent memory loss in people with glioblastoma

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol WF-1801, A Single Arm, Pilot Study of Ramipril for Preventing Radiation-Induced Cognitive Decline in Glioblastoma (GBM) Patients Receiving Brain Radiotherapy (NCT03475186)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer. We are asking you to take part in this research study because chemoradiation treatments for your cancer can cause side effects such as at increased risk for memory loss.

Taking part in this study is your choice.

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

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

Why is this study being done?

This study is being done to answer the following question:

Can we lower the chance of memory loss in patients with glioblastoma by adding a drug Ramipril to the usual chemoradiation treatment?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your increased risk of memory loss from chemoradiation during the treatment of your glioblastoma. The usual approach is defined as care most people get for glioblastoma.

What is the usual approach to preventing memory loss from chemoradiation treatment of glioblastoma?

The usual approach for patients who are not in a study is to be followed closely by their doctor to watch for the development of symptoms of memory loss at brain radiation. Some patients may receive formal memory testing. Patients are encouraged to "stay mentally active" by reading, using word games, puzzles and other brain stimulating activities. Other interventions may include memory training programs, or use of other medications that may help memory loss.

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

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.

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

If you decide to take part in this study, you will get Ramipril for up to 22 weeks (6 weeks during radiation, followed by 4 additional months after radiation).

After you finish the 22 weeks of Ramipril your doctor will continue to follow your condition for 1 month and watch you for side effects. This will be done by a phone call 30 days after you have completed taking Ramipril.

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

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

Risks

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

If you choose to take part in this study, there is a risk that the Ramipril may not be as good as being closely watched by your doctor at preventing memory loss from your chemoradiation.

There is also a risk that you could have side effects from the Ramipril. These side effects may be worse and may be different than you would get with the usual approach for preventing memory loss from chemoradiation. Ramipril has already been approved by the U. S. Federal Drug Administration (FDA) to treat high blood pressure.

Ramipril is not FDA approved for the condition being investigated in this study, that is, lowering the chance of memory loss in patients with glioblastoma.

Some of the most common side effects that the study doctors know about Ramipril are:

- blurred vision
- confusion
- dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position
- sweating
- unusual tiredness or weakness
- cough
- headache

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

Benefits

This study may or may not help you because we do not know how Ramipril will compare to the usual approach for preventing memory loss from chemoradiation. This study may help us learn things that could help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

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

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

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

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

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

What is the purpose of this study?

You will be getting chemoradiation to treat your cancer. This treatment may cause memory loss. The purpose of this study is to test if Ramipril can reduce your chance for memory loss. The effects of Ramipril will be compared to the usual approach of being followed closely by your doctor. Ramipril has already been approved by the FDA to treat high blood pressure, but has not been approved by the FDA for reducing the chance for memory loss during chemoradiation treatment.
There will be about 75 people taking part in this study.

What are the study groups?

In this study, you will get the usual chemoradiation. You will also get the study drug Ramipril.

There are no study groups in this study. Every patient will receive Ramipril. The dose of Ramipril will be gradually increased as you can tolerate it over the first 3 weeks. Ramipril will be provided in capsule form and taken orally.

- Week 1 – 1 capsule (1.25 mg) once daily
- Week 2 – 2 capsules (2.5 mg) once daily
- Week 3 – 4 capsules (5.0 mg) once daily
- Week 4 to Week 22 – Maximum tolerated dose, but not higher than 4 capsules (5.0 mg) once daily

You will be followed from Week 22 to Week 26 or 1 month after finishing Ramipril for potential side effects.

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

What exams, tests, and procedures are involved in this study?

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

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

These exams, tests, and procedures to monitor your safety and health include:

- Blood tests (Comprehensive Metabolic Panel) done weekly during radiation therapy, at the end of radiation therapy and one month post radiation therapy. This blood test will help your doctor determine if you are having any side effects to taking Ramipril that will require them to change the amount you are taking.

This study will use a genetic test that may identify changes in the genes in DNA or deoxyribonucleic acid. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer.

Finding these changes would not affect your treatment in this study. However, they could affect your health in other ways. As part of this research project, your DNA will be studied in an effort to find out if there are genes that contribute to medical conditions that are part of this study. We will specifically be studying the Apolipoprotein E (APOE) gene. Because we do not know how the results of this DNA/APOE genotyping study relate to your individual health, the results of the research will not be given to you or your doctor. These results will also not be placed in your medical records.

If you are an English speaker and choose to take part in this study, you will be asked to fill out forms with questions about mood, well-being, memory, pain, daily schedule and how you organize your thoughts. Researchers will use this information to help estimate any memory loss and your well-being throughout the study.

Since these forms are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

You will be asked to fill out these forms 4 times:

- Before chemoradiation treatment starts
- After chemoradiation treatment is complete
- 1 month after chemoradiation
- 4 months after chemoradiation

Each form will take about 45 minutes to complete. You don't have to answer any question that makes you feel uncomfortable.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that Ramipril may not be as good as being closely watched by your doctor at preventing memory loss from your chemoradiation.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.

- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The Ramipril used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 1 month after you have completed the study.

Genetic Testing Risks

The genetic test used in this study will test for the presence of the Apolipoprotein E (APOE) gene, which is associated with a greater risk of developing memory loss from the chemoradiation treatment. Because we do not know how the results of this DNA/APOE genotyping study relate to your individual health, the results of the research will not be given to you or your doctor. These results will also not be placed in your medical records; therefore minimizing any risk.

Your blood sample and results will be stored with a unique identifier. The unique identifier will be a randomly assigned number and only the principal investigator or select study personnel identified by him will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

Your sample will be processed in theWake Forest NCORP Biospecimen Laboratory. The sample will be stored in the Wake Forest NCORP Biospecimen Laboratory and it will be given only to researchers approved by Dr. Michael Chan. An Institutional Review Board (IRB) must also approve any future research study using your blood sample.

Side Effect Risks

The Ramipril used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

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

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

Drug Risks

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

Possible Side Effects of Ramipril

COMMON, SOME MAY BE SERIOUS
• blurred vision • confusion • dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position • sweating • unusual tiredness or weakness • cough • headache

OCCASIONAL, SOME MAY BE SERIOUS
• arm, back, or jaw pain • chest pain or discomfort • chest tightness or heaviness • chills • cloudy urine • cold sweats • decrease in urine output or decrease in urine-concentrating ability • diarrhea • fainting • fast or irregular heartbeat • shortness of breath

RARE, SOME MAY BE SERIOUS
• seizures • unexplained bleeding or bruising • loss of liver function • lowered white blood cell count

Additional Drug and Food Risks

The study drug could interact with other drugs and food.

- Dehydration can be a risk while taking Ramipril, so adequate water should be ingested and the use of diuretic medications (also called "water pills" or "fluid pills") should be avoided unless specifically prescribed by your treating physician.
- Avoid the use of salt substitutes that are high in potassium, as well as, potassium supplements unless instructed to take by your treating physician.
- Before using nonsteroidal anti-inflammatory agents (Advil, Motrin, ibuprofen, naproxen, etc.) contact your treating physician, because their use with Ramipril can occasionally lead to decreased renal function.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

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

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 1 month after your last dose of study drug.

What are the costs of taking part in this study?

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

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

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

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

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

- Blood tests - Comprehensive Metabolic Panel (CMP) at weeks 1, 2, 3, 4, 5 & 6 during your radiation therapy
- APOE genotyping
- Neurocognitive Function Tests (required by study only)
- Ramipril

You or your insurance provider will not have to pay for the Ramipril while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

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

What happens if I am injured because I took part in this study?

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

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

Who will see my medical information?

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

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

There are organizations that may look at 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:

- The study sponsor supporting the study now or in the future.
- The study investigator and his/her staff or a representative working on their behalf.
- Wake Forest NCORP Research Base or a representative working on its behalf.
- 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 National Cancer Institute (NCI) and the groups it works with to review research.
- The Food and Drug Administration (FDA) and the groups it works with to review research.

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 also will be stored 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.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

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.

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, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study.

Participant's signature _____

Date and Time of signature _____ _____ AM PM

Signature of person(s) conducting the informed consent discussion

_____

_____

Date and Time of signature(s) _____ _____ AM PM