Official Title: A Randomized Clinical Trial of Prophylactic Risedronate for Patients With Peripheral Lung Tumors Treated With SBRT
NCT03861091
IRB-Approved Date: 12/16/21

Department of Radiation Oncology

A RANDOMIZED CLINICAL TRIAL OF PROPHYLACTIC RISEDRONATE FOR PERIPHERAL LUNG TUMORS UNDERGOING STEREOTACTIC BODY RADIOTHERAPY

Informed Consent Form to Participate in Research
Michael Farris, MD. Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to help find ways to avoid bone loss which may be caused by radiation. You are invited to be in this study because you have a lung tumor that is located near your ribs or your backbone. In order to treat the tumor completely, it is very difficult to avoid getting some radiation to these normal bones because they are so close to the tumor. When radiation interacts with normal bones, it can cause bone loss and can lead to breaks in the bone or cracks which might cause pain. Sometimes, patients can have pain in these bones or in the chest even if there is not a break in the bone.

In this study, you will receive standard radiation treatments that would be offered regardless of your involvement in this study. On this study however, before you start the radiation, you will be given one tablet to take by mouth. The tablet will contain either a placebo or a medicine named risedronate. Risedronate is a type of drug called a bisphosphonate. This type of medicine is commonly used to decrease bone loss in people who have osteoporosis, but it has not been given to stop bone loss that is caused by radiation. The placebo tablet will look exactly like the risedronate tablet, but it will not have any active medicine inside of it. The placebo is believed to have no effect on your bones. A computer will choose if you get the placebo tablet or the risedronate medicine tablet. Neither you, nor your doctor will know if the tablet that you take contains medicine or placebo while you are on the study.

The only non-standard part of treatment in this trial is taking this tablet one time. Otherwise, you will receive standard of care radiation and standard of care follow-up scans that you would otherwise have regardless of your participation in this trial.

We will also collect one urine sample before you receive radiation, and at each follow up appointment. These urine samples will be stored in a laboratory freezer and will be tested for markers of bone breakdown. After the urine is tested it will be disposed of.

All research studies involve some risks. The most common risks from the risedronate tablet in with this study are bone and joint pain, or abdominal discomfort/indigestion

There is the possibility that you may benefit from participation in this study. Your participation in this study is voluntary. You do not have to participate in this study if you do not want to.

There may be other choices available to you. Some other choices may include radiation without the tablet. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Michael Farris MD, PI. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is: [redacted] (clinic & after-hours).

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have a lung tumor that is near your ribs or backbone. It will be difficult to avoid getting some radiation dose to these bones and radiation may cause some thinning of these bones after treatment is finished. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to test if a drug that is used to prevent bone loss in patients with osteoporosis, will also stop or decrease bone loss that is caused by radiation. This could potentially lead to fewer rib or backbone fractures and could mean participants experience less chest or back pain after radiation.

Risedronate has been approved by the US Food and Drug Administration (FDA), but it has not been approved for use to avoid bone loss caused by radiation.

In this study, risedronate will be compared to placebo. A placebo is a substance, like a sugar pill, that is not thought to have any effect on your disease or condition. In this study you will either receive the active study medication, risedronate or placebo, which is not active. Placebos are used in research studies to see if the drug being studied really does have an effect.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

There will be 84 people at Wake Forest University Baptist Medical Center will take part in this study. This hospital is the only research site.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will be randomized into one of the study groups receiving a

one-time dose of a tablet that is either placebo or risedronate before you receive radiation. Randomization means that you are put into a group by chance. Randomization will not affect your radiation treatment or your follow up after treatment. It is like flipping a coin. You will have an equal chance of being placed in either group.

You will take the tablet of risedronate or placebo about 1 to 3 weeks before you start radiation therapy. The only part of this study that is not standard of care is taking this one-time dose of a risedronate tablet or a placebo tablet before you start radiation. Otherwise, all aspects of your care will be standard of care that you would receive regardless of inclusion on this study.

Neither you, nor the investigator, will know if you are receiving risedronate or placebo until the study is completed, and you have finished 1 year of followup. This is done so that a fair evaluation of results can be made. This information is available to the researchers if needed in an emergency.

Before radiation begins, you will have a treatment planning session. You will lie in a specific position, possibly within a frame device or on a large plastic bag filled with tiny foam balls like a bean bag. The purpose of the frame or bag is to hold your body as still as possible for planning and treatment. After you are positioned, doctors will check your breathing and see how your organs move. The doctors will try to limit the effect of that movement on the position of your tumor by timing your breathing. They may use a device to control the depth of your breathing. They may use a device to monitor the rate and pattern of your breathing. This is so that they will be able to deliver the radiation to the tumor while accounting for the effect of breathing. In order to plan the radiation, you will have a CT scan that may or may not use contrast. Contrast would be given as an injection in the vein and sometimes helps us see the areas that we are trying to treat more clearly. Radiation treatments will generally be given over the course of 3 – 10 treatments. This is often with one treatment per day given Monday through Friday or sometimes given every other day. When radiation is given in this short course it is typically called stereotactic body radiotherapy (SBRT).

After radiation therapy is completed, you will receive a phone call 30 days afterward to ask about any side effects or illnesses you may have experienced during this time. You will see your radiation doctor in clinic every 3 months with a new CT scan of your chest, and you be asked questions about any chest or back pain or soreness that you may have experienced after radiation. Your cancer doctor will follow your standard CT chest scans to see how well the radiation controlled your tumor, and to check that there are no new lung tumors. For the purposes of this study, we will use these same CT scans to check the bone thickness of your ribs and backbone which may have received some radiation dose. You will likely continue to follow your cancer every 3 – 6 months for a much longer time with your radiation doctor, but for the purposes of this study, you will only be asked specific questions about this study for one year after you finish radiation. On this study we will also collect one urine sample before you receive radiation, and at each follow up appointment. These samples will be stored in a laboratory freezer and will be tested for markers of bone breakdown. After the urine is tested it will be disposed of. After 1 year has passed from your radiation treatment, you will no longer be asked to provide a urine

sample at your follow-up visits.

How Long Will I Be in the Study?

You will be in this study for one year after you complete radiation treatment. This study will not require any extra visits to the hospital or extra imaging outside of your routine standard of care treatment and follow up.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

What Are the Risks of the Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff.

A risk to this study that you should be aware of is the possibility of jaw bone pain with bisphosphonate medications. This is a small risk, generally less than 5%, but it can happen any time that bisphosphonates are used

There are currently no clearly reported side effects from the combination of bisphosphonates and radiation therapy to the lungs. These medications have been given at the same time as radiation in patients undergoing radiation for to various sites in the body and no excess toxicities were reported. There is no contra-indication (meaning warnings or known side effects that prevent use) for the use of bisphosphonates and radiation to the lung. These medications are not routinely discontinued during radiation therapy. However, bisphosphonates are not currently FDA approved for use as a preventative bone loss medication before radiation therapy.

Because some patients on this study will receive placebo, there is a risk of bone loss near the treated tumor and chest or back pain or soreness. This risk would be present regardless of inclusion on this trial. It is not clear if the bisphosphonate medicine studied in this trial will prevent radiation therapy from causing these problems. However, it is clear that patients with tumors near the chest wall who receive a high dose of radiation, will likely experience some bone loss. The risk of rib fracture or chest wall pain can exceed 30 – 40%.

Risks and side effects related to the radiation and separately risk related to the risedronate medication that we are studying are detailed below.

The side effects of SBRT are listed below with likelihood:

<u>Likely risk and side effects</u>

- Fatigue
- Redness of irritation of the skin in the treatment area
- Hair loss in the treatment area

- For tumors near the esophagus, irritation of the esophagus and sore throat/difficulty swallowing
- Some soreness of the ribs with an increased risk of rib fracture
  - Treatment for such symptoms usually consists of rest, heat, and pain medication.
- Damage to surrounding normal lung and/or collapse of a portion of treated lung
- Changes in the lungs as the tumor shrinks
  - This includes expected "scarring".
  - In most patients, no noticeable symptoms will result from this lung damage.

Less likely risk and side effects

- Cough
- Difficulty breathing
  - Decrease in lung function parameters
  - May result in temporary or permanent need for supplemental oxygen
- Increased phlegm production
- Fever
- Severe pain or skin damage leading to an open wound
- Damage to the stomach or bowel
  - This can lead to ulceration or perforation with a risk of infection and death.
- Damage to the spinal cord
  - can cause numbness, weakness, tingling, and/or inability to use the arms and/or legs
- Damage to the large blood vessels surrounding the heart
  - This could cause coughing up of blood and possibly death
- Damage to the heart muscle, which can cause heart attack, heart failure, or death
- Damage to the lining of the heart, which can cause fluid accumulation around the heart
  - This may cause chest pain, shortness of breath, and/or irregular or rapid heart beat
- Tumors near vertebrae there is increased risk of vertebral compression fracture
  - If vertebral fracture is already present, there is risk of progression of fracture.
- With any radiation therapy, there may be a very small chance that the radiation could cause a secondary cancer. The excess cancer risk from the radiation is estimated to be about 1 - 3% with at least 7 years between the receipt of radiation and the second cancer forming.

The side effects of Risedronate are listed below with likelihood:

Likely risk and side effects

- Bone and joint pain
- Abdominal discomfort/indigestion

Uncommon/Rare risk and side effects

- Eye pain, redness, swelling, sensitivity to light and or decreased vision
- Glossitis (swelling of the tongue)
- Jaw osteonecrosis with pain in the mouth or teeth
- Numbness or feeling of heaviness in the jaw
- Poor healing of gums
- Loose teeth

Very rare

- Allergic and skin reactions
  - Hives, rash with or without blisters
  - Facial/tongue/lip swelling, trouble swallowing or breathing
- Symptoms of low blood calcium (Numbness, tingling, muscle spasms)

In addition to these risks above there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

Whether or not you participate in this study, treatment with SBRT means you will be exposed to amounts of radiation above what you would normally receive in daily life. To be sure that you do not receive an unhealthy amount of radiation during your participation in this study or otherwise, you should let your study doctor know if you have had, or are going to have, any other scans or x-rays as part of your medical or dental care. It is very important that you let your study doctor know if you already are participating in, or plan to participate in, any other treatment or research study that involves radiation exposure.

Reproductive Risks

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel

and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study because radiation has clear teratogenic and potentially abortifacient risks. Some methods of birth control are not 100% reliable, therefore a pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential. This can be done by testing the blood or the urine and must be performed within 1 week of starting radiation treatments.

Contraceptive Measures for Males

Your participation in this research study may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should also promptly notify her doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. Based on animal studies and some human studies, researchers believe that bisphosphonate medications like the one used in this study can stop or slow the loss of bone that is caused by radiation therapy. This has not been studied in the case of high dose radiation to tumors near the ribs or backbone. Because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have these options: the same standard-of-care SB Radiation Therapy (as outlined in this consent) without the risedronate medicine.

WHAT ARE THE COSTS?

Research study costs, including any study medications and procedures related directly to the study, will be paid for by the study. However, tests and procedures that are done as part of your routine cancer care, which would be done regardless of your participation in this study, will be the responsibility of you or your insurance company. For this study in particular, we will extract data and results from the following routine-care procedures: physical exams, CT scans, blood labs, and pregnancy testing (if applicable.)

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published

in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the effectiveness of risedronate to prevent bone loss that is caused by radiation. The results will be provided to the sponsor, the Food and Drug Administration, and other federal and regulatory agencies as required.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH which is funding in part this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment or other compensation for taking part in this study.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the Wake Forest Thoracic Multidisciplinary Tumor Committee and in part by the NIH, as it utilizes support of cancer center personnel in the departments of statistics and protocol editing. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a

direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Michael Farris, M.D. at [redacted] or [redacted].

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** History and physicals, pathology, labs, imaging and lung function tests.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to

provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research

2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center

3) Representatives from government agencies such as the Food and Drug Administration (FDA), NCI (National Cancer Institute), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups, it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed, or it will be de-identified. Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Farris that you want to take away your permission to use and share your

Protected Health Information at any time by sending a letter to this address:

Michael Farris M.D.
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form, you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part, or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first to learn about any potential health or

safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is felt by the treating physician to be in your best medical interest, your condition worsened, new information becomes available, or you had an unexpected reaction. Additionally, this could occur because you failed to follow instructions, or because the entire study has been stopped

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Michael Farris M.D. at [redacted] (clinic & after-hours) or [redacted] (office).

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm