Title: A Single Arm Phase II Study of Hypofractionated Radiotherapy Alone in Locally Advanced Nonsmall Cell Lung Cancer Patients Who Decline or Are Ineligible for Surgery or Chemotherapy
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Informed Consent

Departments of Radiation Oncology and Hematology Oncology

A SINGLE ARM PHASE II STUDY OF HYPOFRACTIONATED RADIOTHERAPY ALONE IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WHO DECLINE OR ARE INELIGIBLE FOR SURGERY OR CHEMOTHERAPY

WFBCCC # 62220

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

SUMMARY

You are invited to participate in a research study. The purpose of this research study is to improve control of lung cancer with high doses of very targeted radiation alone for patients who cannot be treated with surgery or chemotherapy. You are being asked to take part in this study because you have lung cancer that has not spread to distant parts of your body and is either confined to the lung where it started (Stage II) or has spread locally within your chest (Stage III) and your physicians do not feel that you are a good candidate for chemotherapy or surgery. Your participation in this research will involve multiple visits for treatment with radiation therapy. Radiation therapy will last for approximately five weeks. After treatment is completed, you will be seen for routine follow up visits that typically last 1 - 2 hours. They will occur one month after the last day of radiation and every 3 months after that for the next 2 years.

All research studies involve some risks. A risk to this study that you should be aware of is possible irritation of the lungs called pneumonitis. This also happens with standard chemotherapy and radiation therapy. Another risk is damage to the airways in your lungs or your swallowing tube called the esophagus. Damage to these organs can lead to narrowing or bleeding and death, but there is risk of these toxicities with standard chemotherapy and radiation as well. 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 lower doses of standard radiation therapy alone. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The rest 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 M.D. If you have questions, suggestions, or concerns about this study or you want to withdraw from the study his contact information is:

Michael Farris, M.D.
[redacted]

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 lung cancer that has spread to the lymph nodes in the middle of your chest and your physicians do not feel that you are a good candidate for chemotherapy or surgery. Your participation is voluntary. Please take your time in making your decision as to whether you wish to participate or not. 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 find out what effects (good or bad) may come from a new way of doing radiation therapy for lung cancers that involve lymph nodes in the middle of the chest, are very large, or located very close to major blood vessels or airways. This study is for patients who are not able to get surgery, stereotactic body radiation therapy (SBRT) or chemotherapy with their radiation.

The standard way of doing radiation in patients who cannot get chemotherapy with radiation therapy or SBRT for lung cancer is called hypofractionated radiation, where slightly larger amounts of radiation are given per day than when radiation is given with chemotherapy. A newer, more complex way of planning radiation that was not previously available on older trials has now become a standard technique across the country. This is called a simultaneous integrated boost or SIB. Planning radiation with an SIB allows the actual tumor to get an extra radiation dose while still protecting the organs that are near the tumor. This is how hypofractionated radiation will be planned in this study. It allows us to give the biggest parts of the tumors that are the most difficult to control a little more radiation every day than the lower risk areas. There is evidence that this might be a safer way to give radiation therapy than SBRT in patients with tumors very close to the center of the chest.

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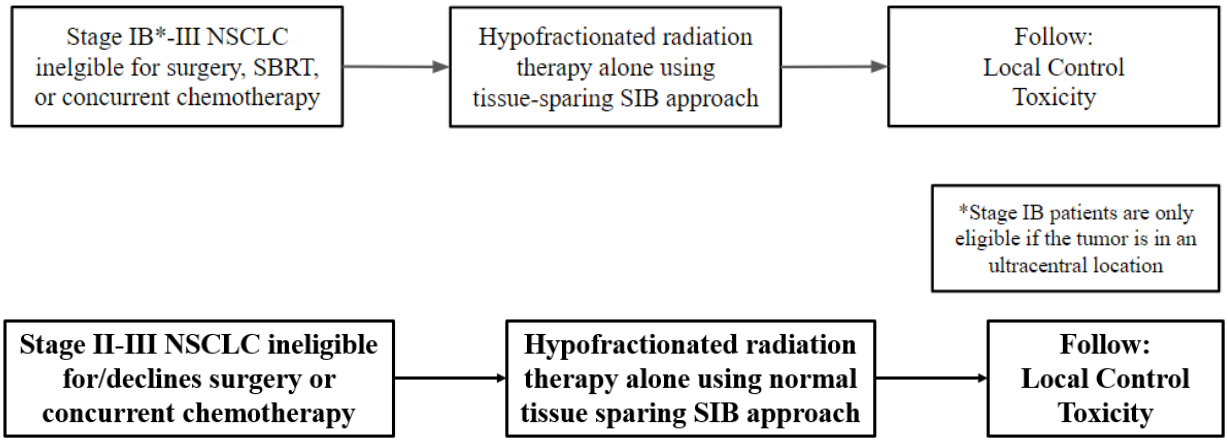
Radiation therapy to the tumor is a standard treatment. However, it is not typically planned in this way. In standard radiation, all parts of the tumor are given the same amount of radiation every day. However, this does not always work as well, and we think there may be a better approach. There are still questions we need to answer to make sure that this is a safe and effective treatment option. We do not know that this special radiation technique will be better at controlling the tumor. We also are not sure that the specialized radiation planning will not increase the risks compared to standard radiation.

How Many People Will Take Part in the Study?

There will be 30 patients on this study. This is the only institution where this study is being done.

What Is Involved in the Study?



We will make sure you qualify for the study by performing a PET/CT scan and a brain MRI before you are enrolled on the trial. These two scans tell us exactly where the cancer has spread. If you do qualify for the study, you will be asked to provide written informed consent (by signing this form) to join the study. Then you will undergo a standard radiation planning CT scan, and start radiation therapy around 2 weeks after that. You will get radiation therapy once a day for 25 days, Monday through Friday (around 5 weeks).

Before you take part in this study, you will have the following standard tests and procedures:

- History and Physical examination
- Whole Body Positron Emission Tomography (PET/CT) to assess where cancer has spread
- Magnetic Resonance Imaging (MRI) of the brain to determine if cancer has spread to the brain
- Blood or urine pregnancy test for women who can become pregnant

The history and physical examination, PET/CT scan, MRI brain scan, and pregnancy test would be standard tests before any radiation therapy, regardless if you were enrolled on this trial or not.

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 use contrast. Contrast would be given as an injection in the vein and helps us see the areas that we are trying to treat more clearly. Radiation treatments will be given over the course of 25 treatments, one treatment per day given Monday through Friday. The radiation will be planned with a simultaneous integrated boost (SIB). This means that the biggest parts of the tumor that are the most difficult to control will receive slightly more radiation per day than other areas at lower risk of tumor spread.

After completing radiation you will have routine follow-up visits. You will have CT scans of your chest, and abdomen at 1 month, then every 3 months for the next two years. These CT scans may be performed with contrast that is given as in injection in the vein. You and your doctor will decide if contrast is needed. After this, you will likely continue to be followed by your physician for the rest of your life but will not continue to be followed for the purposes of the study.

How Long Will I Be in the Study?

You will be in the study for a total of 25 months after completion of radiation therapy. After this you will likely continue to follow with your oncologists but will not be specifically followed per this study protocol and results will not be collected past 2 years.

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.

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may

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happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the radiation. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death. The side effects of hypofractionated radiation therapy are similar for tumors that are typically treated with surgery or SBRT and chemotherapy and radiation because the organs that can be hurt by radiation are the same.

Risks and side effects related hypofractionated radiation to the chest:

Likely

- Difficulty, pain, or a burning sensation when swallowing, which is temporary
- Damage to surrounding normal lung and/or collapse of a portion of treated lung
- Changes in the lungs as the tumor shrinks; these changes will be recognized by your radiation doctor on your x-rays or scans as expected "scarring" that is developing. In most patients, no noticeable symptoms will result from this lung damage.

- Fatigue, which is temporary
- Tanning, redness of the skin, and hair loss within the treatment area, which is temporary
- Skin in the treatment area may remain permanently dry, and chest hair may not grow back

Less Likely

- Cough and some difficulty in breathing due to lung inflammation, which can require steroids or supplemental oxygen, either short term or permanently, and may in rare case be life-threatening
- Narrowing of the esophagus causing difficulty swallowing meals (rarely requiring internal dilation or a feeding tube)

Rare but serious (late)

- Pericarditis – irritation of the heart sac causing a rapid heart rate, or chest pain.
- Myocarditis – irritation of the heart muscle causing shortness of breath, chest pain, or permanent heart muscle damage
- Damage to the spinal cord, which can cause numbness, weakness, tingling, and/or inability to use the arms and/or legs
- Bleeding from the airway
- Narrowing of the airway causing shortness of breath
- Damage to the stomach or bowel which can lead to ulceration or perforation with a risk of infection and death.
- Damage to the large blood vessels surrounding the heart, which could cause coughing up of blood and possibly death
- Death from treatment complications above.

During the process of treatment planning we decide where the radiation will go in your body. You will lie in a specific position on a firm flat surface and hold very still. We will take pictures of the inside of your body with CT scans. You might be inside a frame device. Sometimes patients can get nervous while they are being scanned but we can give medications to make you feel more comfortable if needed. Also, your study doctor may give you pain medication before each treatment if needed. This would decrease discomfort from laying on a hard surface while receiving treatment or from holding your arms up over your head for a long time. The focused radiation treatments involve exposure to radiation from a machine called a linear accelerator. This machine is used to treat cancer using high energy x-rays. These radiation planning scans are no different than the planning scans that you would have if you were being treated off protocol.

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. If you are a woman able to have children and are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant or suspect that you have caused anyone to become pregnant while you are on this study, you must tell your study doctor immediately.

Risks of Radiation Exposure
If you participate in this study, 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 from your participation in this study, 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 research study that involves radiation exposure.

Risks Associated with Providing Confidential Information
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. 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.

Reproductive Risks and other Issues to Participating in Research

Pregnant women are excluded from participation in this study. Because some methods of birth control are not 100% reliable, 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. There could be a risk of radiation affecting sperm in men, and these sperm usually are replaced with healthy sperm in your body every 3 – 6 months. This could be harmful to any children that are fathered by men immediately after they receive radiation. We strongly encourage men not to father children for at least 6 months to 1 year following treatment with radiation.

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 that this treatment will increase the control of the tumor, but this is not certain. We hope the information learned from this study will aid in the understanding of cancer and help in the development of new approaches to its treatment and benefit other people in the future

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. The usual treatment for your disease radiation therapy with chemotherapy followed by immunotherapy if possible, or in some cases surgery or SBRT.

You could be treated with hypofractionated radiation even if you do not take part in the study.

WHAT ARE THE COSTS?

The costs of all medications, radiation treatment, x-rays, tests, physician's fees, diagnostic and laboratory studies, drug handling charges, transportation, and hospital or clinic visits will be billed to you. Some of these costs may or may not be covered by your insurance provider. In addition, the use of medications to help control side effects could result in added costs.

You will receive no payment or other compensation for taking part in this study. Parking validation will be provided for all study-related visits.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest Baptist Comprehensive Cancer Center. The sponsor is providing money or other support to help conduct this study. The researchers do not, however, hold a direct financial interest in the study.

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 safety and effectiveness of radiation treatment with pembrolizumab or pembrolizumab alone; 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 National Institutes of Health which is funding 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.

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:

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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

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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 MD Michael Farris M.D. at [redacted], or [redacted].

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

Legally Authorized Representative Name (Print):_____

The above named Legally Authorized Representative has legal authority to act for the research subject based upon (specify health care power of attorney, spouse, parent, etc.)

Relationship to the Subject:_____

Legal Representative Signature: _____ Date:_____ Time:_____ am pm

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