The Ohio State University Consent to Participate in Research

Study Title:	A Phase II trial Combining Hypofractionated Radiation Boost with Conventionally-Fractionated Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer Not Suitable for Surgery
Principal Investigator(s):	Eric Miller, MD, PhD
Sponsor:	The Ohio State University

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

You have been asked to participate in this study because you have been diagnosed with lung cancer and have not received any chemotherapy. We know that a combination of chemotherapy and radiation therapy (chemoradiation) does have a benefit in treating your cancer and is the standard way your cancer is treated. Cisplatin and etoposide and carboplatin and paclitaxel are two chemotherapy drug combinations that have been approved for use by the Food and Drug Administration (FDA) for your type of cancer. In this study we want to add two higher doses of radiation (called boost doses) right before starting standard treatment

of chemotherapy with cisplatin and etoposide or carboplatin and paclitaxel and radiation to see if we can improve the benefit of therapy on your cancer.

Even with standard chemotherapy and radiation for your cancer, the risk of having the tumor come back where it started in the lung is about 1 in 3 patients with your type of cancer. The two boost doses of radiation will be a type of radiation called stereotactic, or hypofractionated radiation, which is a newer way to deliver radiation much more precisely and accurately, allowing us to deliver higher doses of radiation more safely. This study tests whether a higher dose of stereotactic radiation delivered in two boost doses prior to starting standard chemoradiation therapy, will prevent the cancer coming back in the location it started.

2. How many people will take part in this study?

Approximately 38 patients will take part in this trial.

3. What will happen if I take part in this study?

Before you begin the study…

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may or may not need to be repeated. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Some of the exams, tests, and procedures outlined in the study calendar may be completed via Telehealth visit (phone, video call, or email) if the investigator deems it appropriate. Ask your physician if you have questions about Teleheath or Telehealth visits.

Within 14 days of entering the study:

- Blood or urine pregnancy test (if necessary)
- MRI of the chest - research scan to study the effects of radiation boost doses to the tumor
    - If you elects to get an optional MRI, you will undergo two research MRI scans (total) to be performed over 1 to 1.5 hours (each) at the Wright Center.

      The Wright Center of Innovation in Biomedical Imaging Concourse Building, Martha Morehouse Medical Plaza, 2050 Kenny Road Columbus, OH 43221

The scans will be focused on a portion of the lung bearing the primary lung tumor, and will include several different sequences (perfusion-weighted, diffusion, and BOLD (Blood Oxygenation Level Dependent Imaging)) to measure tumor vessel blood flow, tumor cell density, and oxygenation. For the oxygenation (BOLD) portions of the study, you may be required to inhale oxygenated air through a nasal cannula or face mask temporarily.

Within 21 days of entering the study:

- CT (computed tomography) simulation scan- a scan we need to allow us to plan for the radiation you will be receiving

Within 30 days of entering the study:

- History and physical exam (including vital signs)
- Blood Tests – complete blood counts, chemistries and liver function tests
- CT scan of the chest

Within 60 days of entering onto this study:

- PET-CT scan (positron emission tomography)- to look for the tumor in the whole body (or CT chest/abdomen/pelvis)
- MRI (magnetic resonance imaging) of the brain (or CT of the head), providing you are able to get an MRI.

Within 90 days of entering onto this study:

- Tests to determine the function of your lungs (spirometry/pulmonary function tests)

Therapy consists of:

Week 1

- You will receive two boost doses of stereotactic radiation which will occur at a minimum of 20 hours apart.
- Optional MRI of the chest about 24 hours after the first dose of radiation- research scan to study the effects of radiation boosts to the tumor
    - Performed at The Wright Center of Innovation in Biomedical Imaging similar to first research MRI
- Physical exam (including vital signs)

Weeks 2-7

- You will receive standard chemotherapy with cisplatin and etoposide or carboplatin & paclitaxel and radiation for 6 weeks at the discretion of the medical oncologist. Your study doctor will decide which combination you are best suited for. You will receive chemotherapy treatment based on the standard treatment schedule of selected chemotherapy regimen.
- Blood tests (total blood count and chemistries) will be completed prior to chemotherapy or at the discretion of your study doctor.
- These treatments can be done at a James Cancer Network affiliate center.

Consolidation Therapy

- If you end up taking the carboplatin & paclitaxel chemotherapy combination you will be required to participate in 2 additional cycles of consolidation therapy. Consolidation therapy is typically done after initial treatment as a follow up attempt to ensure cancer cells are destroyed. Cycles are 21 days in length and are expected to begin 4-6 weeks after you end the initial treatment.
- If you end up taking immunotherapy (e.g. durvalumab), you may not have consolidation chemotherapy at the discretion of the medical oncologist.
- These treatments can be done at a James Cancer Network affiliate center.

Follow up Visits

After your treatment is complete, you will come back for a clinic visit and have all or some of the following tests/procedures at about 1 month post-treatment and every 3 months for 2 years at OSU or a James Cancer Network affiliate site:

- History and Physical Exam (including vital signs)
- Blood Tests – complete blood counts, chemistries and liver function tests (about 1 tablespoon)
- CT scan of the chest with intravenous contrast or Chest X-ray
- Pulmonary Function Test

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After 2 years of follow up, you will return to clinic every 6 months for an additional 3 years and have the following tests/procedures:

- History and Physical Exam
- CT scan of the chest with intravenous contrast
- Chest X-ray (or CT scan)

If there is a reason not to do a CT scan due to allergies or poor kidney function, MRI can be done instead (providing you are able to get MRIs).

If your cancer comes back before your follow-up period has ended, some tests/procedures may not be performed during the remainder of the follow-up period. Talk to your study doctor about your requirements if your cancer comes back.

Research Blood Samples

In addition to the blood samples listed above, whole blood samples (30mL/each) will be collected to identify Tumor Biomarkers. These samples will be collected prior to your first radiation treatment, at the start of the first chemotherapy cycle, towards the end of chemoradiation, and at 1 month, 6 months, and 12 months after you complete treatment on this study. If you are being treated or followed after treatment at a James Cancer Network affiliate site, these research blood samples are not required.

4. How long will I be in the study?

The chemotherapy and radiation therapy will last approximately 7 weeks. Follow up will continue for approximately five years after study treatment has been completed.

5. Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

6. What risks, side effects or discomforts can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may 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 drugs. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

You should talk to our study doctor about any side effects that you have while taking part in the study.

Risks from chemotherapy (Cisplatin)

- **Common (20-100 in 100 people):**
  - Nausea, vomiting

- Infection, especially when white blood cell count is low
- Anemia which may cause tiredness, or may require blood transfusions
- Bruising, bleeding
- Kidney damage which may cause swelling, may require dialysis
- Hearing loss including ringing in ears
- Numbness, tingling, or pain of the arms and legs

- **Occasional (4-20 in 100 people, or less):**
  - Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
  - Confusion
  - Difficulty with balance
- **Rare (3 in 100 people, or less):**
  - Cancer later in life caused by chemotherapy.
  - Seizures

Risks from chemotherapy (Etoposide)

- **Common (20-100 in 100 people):**
  - Hair loss
  - Chills
  - Sores in mouth which may cause difficulty swallowing
  - Diarrhea, loss of appetite, nausea, vomiting
  - Infection, especially when white blood cell count is low
  - Anemia which may require transfusion
  - Bruising, bleeding
  - Tiredness
  - Fever

- **Occasional (4-20 in 100 people, or less):**
  - Heart failure or heart attack which may cause chest pain, shortness of breath, swelling of ankles, and tiredness
  - Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body
  - Liver damage which may cause yellowing of eyes and skin, swelling

- **Rare (3 in 100 people, or less):**
  - Cancer of bone marrow caused by chemotherapy
  - Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Risks from chemotherapy (Carboplatin)

Most likely effects:

- Diarrhea, nausea, vomiting, loss of appetite or constipation. These are expected to be mild and brief but may be severe or long-lasting.
- Fatigue—expected to be mild but could be moderate or worse.
- Decreased white blood cell count (white blood cells fight infection) - Decreased white blood count may lead to an increased risk of infection at the surgical site (wound infection) or infection in another part of the body such as pneumonia.
- Lowering of the platelets (cells that stop bleeding), excessive bleeding that is hard to stop.
- Lowering of the red blood cells (anemia)

Less likely effects:

- Fevers and chills
- Infection if blood counts are low
- Abdominal pain
- Increase in liver tests-Damage to liver cells may result in abnormally high liver tests. This may reflect a decrease in your liver's ability to function normally, including metabolize chemicals and compounds such as food and medicine taken orally or intravenously. Routine tests will check liver tests and follow up any abnormal tests.
- Hearing loss
- Numbness or tingling in hands or feet
- Changes in your electrolytes in your blood (sodium, potassium, magnesium or calcium)

Unlikely effects:

- Low blood pressure from an infection
- Kidney damage
- Allergic Reaction

Risks from chemotherapy (Paclitaxel)

Likely effects:

- Low red blood cell count (anemia), which can lead to tiredness and shortness of breath and may require a blood transfusion.
- Feeling weak or tired
- Hair loss
- Numbness, tingling, or burning in your hands or feet
- Joint and muscle pain
- Nausea and vomiting
- Hypersensitivity reaction – trouble breathing; sudden swelling of your face, lips, tongue, throat, or trouble swallowing; hives or rash
- Diarrhea

- Abdominal pain
- Mouth or lip sores
- Low white blood count, placing you at risk for infection
- Infections – if you have a fever (temperature above 100.4ºF) or other sign of infection, tell your healthcare provider right away
- Swelling of your hands, face, or feet
- Bleeding events
- Irritation at the injection site
- Low blood pressure
- Abnormal liver function tests
- Rash, which may cause itching

Less likely effects:

- Low platelet count, which can increase the risk of bleeding or bruising
- Nail changes

Rare, but Serious:

- Inflammation of the lung that can cause difficulty breathing
- Abnormal heart rhythm
- Blood clot in an extremity (leg, arm) or lung
- Death

Risks-from radiation therapy (both standard fractionation and high-dose radiation boost doses) include some or all of the following side effects:

Chest Radiation Therapy may cause:

- Sore throat.
- Loss of appetite, nausea, weight loss, weakness.
- Irritation of the large blood vessels that surround the heart (e.g. atherosclerotic changes or vasculitis). Very rarely this can cause bleeding (coughing up blood).
- Narrowing of the food pipe (esophageal strictures), which may require dilation. (Your throat will be numbed and a balloon or plastic device will be used for stretching your throat.)
- Spinal cord damage and/or irritation may cause weakness, tingling or numbness of the lower body and legs. This can lead to inability to move or control the lower half of the body (paralysis), but this is extremely rare.
- Scar tissue or changes in heart that may cause heart attacks or heart failure.
- Problems with your blood vessels (vascular complications).
- Brachial plexus (a network of nerves in your neck) injury which may lead to loss of sensation or function of arm.
- Radiation may cause a permanent unhealing skin ulcer.

- Difficulty, pain, or a burning sensation on swallowing. This effect is from irritation of the food pipe (esophagus). The side effect usually begins after the second week of radiotherapy and usually goes away within one month of completion of radiotherapy.
- Fatigue (tiredness). It is usually a temporary effect which resolves within several months after completion of treatment.
- Skin reaction within the radiation fields. The skin may develop a sunburn-like appearance which may itch, feel dry, or burn. Although skin color and the sunburn-like reaction improve within 2-6 weeks after treatment, the skin may be permanently drier than other skin and may be tanner. Chest hair (if any) may not re-grow.
- Decrease in white blood cells and platelets. A decrease in white blood cell production may predispose you to infection. A decrease in platelets may make you bleed or bruise easily.
- Scarring of the lung (i.e. radiation fibrosis) may result in chronic shortness of breath and a cough. Chemotherapy may make the above side effects worse and may increase normal tissue damage.
- Collapse of a portion of your lung may result in shortness of breath and cough. This is due to irritation of the airways from radiation or from a tumor that is pushing the airways closed. This is uncommon.
- Chest wall discomfort if your tumor lies close to the outside of the lung where the chest wall is. Radiation can irritate the chest wall requiring medications to relieve the pain until it resolves. Much more rarely, radiation can cause a rib to weaken and break.
- Inflammation of the lungs by radiation (i.e. radiation pneumonitis) which may result in low grade fevers, chest discomfort, cough, and shortness of breath and thus resemble a lung infection. You may need to receive antibiotics and/or steroids to help relieve these symptoms. Hospitalization due to this risk may occur. In similar trials with similar patients where the radiation dose was escalated beyond the standard dose, the risks of symptomatic (requiring steroids) or severe radiation pneumonitis were 17-25%.In addition, if pneumonitis becomes severe, it can be life-threatening. In these trials, the risk of life-threatening symptoms or death from pneumonitis were very uncommon. It is not clear how infection with COVID19 would alter these risks.
- Collection of fluid around the lungs in the chest cavity (i.e. pleural effusion), which can cause shortness of breath and may require treatment. This risk is less likely.
- Difficulty breathing with low levels of oxygen in the blood (i.e. respiratory failure), which could be serious and life threatening and require you to have a tube inserted into your windpipe that is hooked up to a machine to help you breathe. This risk is rare but serious.
- Inflammation of the sac around the heart (i.e. radiation pericarditis) which may result in chest pain, irregular or rapid heartbeat, shortness of breath, low-grade fever, weakness, heart failure as well as fluid around the heart. You may need to receive steroids or have fluid drained to help relieve these symptoms. Hospitalization or surgery may be required to correct this symptom. This risk is uncommon.
- Chest pain
- Muscle spasm

Other Risks

You may feel discomfort from some of the procedures during this study.

Interactions with Other Drugs:
There are many drugs (prescription and over the counter medications) and dietary supplements (including what are sometimes called "complementary" or "alternative" medicines), which may interact with the experimental drugs. The doctor will review all of the medications and supplements you are currently taking before starting these experimental drugs. You should not take any new medications or dietary supplements without discussing it with your doctor first.

Blood drawing risks:
There may be bruising, bleeding, inflammation (redness and swelling) or, rarely infection, or nerve damage at the sites where blood samples are taken. There is a chance that you also may experience fainting. Care will be provided to avoid these complications.

CT scan/PET scan:
You will get a small amount of radiation. Please discuss with your study doctor the amount of radiation for each scan if you have questions. During the CT scans, and PET scan, you will get dye that will be injected into one of your veins. There is a risk of allergic reaction to the dye and in rare cases kidney damage. This reaction may be mild (such as a skin rash or hives) to severe (such as breathing difficulties and shock). There is also a risk that the injection of dyes may cause pain, swelling, bruising, irritation or redness at the site, infection at the site of the needle puncture, or feeling faint. Your study doctor will take steps to prevent this from happening, and may recommend medications that may help with these particular side effects.

MRI Scan
When having an MRI (magnetic resonance imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your study doctor. Your study doctor may give you a medication to make you feel more comfortable in a confined space. If severe anxiety/claustrophobia persists despite mediations to relieve these symptoms, an MRI will not be performed. MRIs use powerful magnets to make images. Therefore, persons with certain metal implants, such as pacemakers, should not have an MRI. If you have an implant or any metal in your body, please check with your study doctor to find out whether or not you can have an MRI. For people without metal implants, there are no known health risks associated with exposure to the magnet.

The risks associated with the MRI research portion of this study include:

- Bleeding and /or infection at the site of the administration of the contrast into one of your veins

- Fainting during the injection
- Anxiety associated with claustrophobia (i.e. fear of closed spaces) during the MR procedure [Please note: you may ask for a relaxation medicine before your MR scans],
- Allergic reaction to the contrast agent, which occurs very rarely and/or decrease in kidney function.

Note: If you have a pacemaker, implantable defibrillator, aneurysm clip, or if you are pregnant, nursing, weigh greater than 350 pounds, allergic to gadolinium contrast or have severe anxiety/claustrophobia related to MRIs despite medications to relieve your anxiety/claustrophobia, an MRI would not be safe for you, and thus you would not receive these scans during this study.

Reproductive Risks:

Females are required to use an effective method of contraception from the time of negative serum pregnancy test, throughout the study duration, and until 4 weeks after the last dose of chemotherapy. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of study drug administration.

Infection complications

The risks of complications from infections, including COVID-19, that may be contracted during and after study therapy is unknown. The study team will follow all of the standard infectious disease precautions for the medical procedures you will receive in this study, as well as any additional COVID-19 specific guidelines from the University.

7. What benefits can I expect from being in the study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with lung cancer in the future.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

Your other choices may include:

- Receiving treatment or care for your cancer without being in a study which would likely include the standard combination of chemotherapy and radiation therapy.

- Taking part in another study.
- Getting no treatment.

Please talk to your regular doctor about these and other options.

9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

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 the website at any time.

You may also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

10. What are the costs of taking part in this study?

The following tests/procedures will not be charged to you or your insurance company:

- Optional MRI scans (two) before Week 1 and during Week 1
- Whole blood for research

Most of the tests/procedures required while on this study are considered routine care for your disease. This includes the two boosts of radiation, PET scans, CT and MRI scans, and lung function testing. You and/or your insurance will need to pay for some or all of the costs of these routine services. You will be responsible for any deductibles, co-insurance, and/or co-payments required by your health plan/insurance company.

Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company about your insurance coverage and to find out if there are any limitations to your plan. To find out more about costs, you can ask the study doctor or study staff. If you have any questions about study expenses like medical bills and hospital bills, please speak with the study doctor.

11. Will I be paid for taking part in this study?

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

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

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University does not have funds set aside for the payment of health care expenses for this study.

13. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subject's research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact **Dr. Eric Miller at 614-293-8415 (office) or 614-293-8000 (24 Hours).**

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact **the Office of Responsible Research Practices at 1-800-678-6251.**

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact **Dr. Eric Miller at 614-293-8415 (office) or 614-293-8000 (24 Hours).**

I agree to participate in the following optional study:

☐ Two research MRIs

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form**.**

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
Relationship to the subject	**AM/PM**
	Date and time

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time