Protocol Title: A Phase I Trial Of Intensity-modulated Radiation Therapy Using A Contralateral Esophagus Sparing Technique In Locally Advanced Non-Small Cell Lung Cancer and Limited-Stage Small Cell Lung Cancer

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A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have locally advanced lung cancer. This research study is examining the impact of a technique called Contralateral Esophagus Sparing Technique (CEST) on the likelihood of developing severe esophagitis (irritation and inflammation of the esophagus) during the course of radiation therapy which is associated with very painful and difficult swallowing.

For purposes of this research, you will be referred to as a "participant."

It is expected that about 20 people will take part in this research study.

Dana-Farber/ Harvard Cancer Center is supporting this research study by providing funding for the study procedures.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase I clinical trial, which tests the safety of an investigational intervention and also tries to define the appropriate dose of the

investigational intervention to use for further studies. "Investigational" means that the intervention is being studied.

The U.S. Food and Drug Administration (FDA) has approved radiation with chemotherapy as a treatment option for your disease.

There is no firm data to indicate that different chemotherapy regimens given at the same time of radiation therapy result in different rates of esophagitis. We will, therefore, allow any type of standard-of-care chemotherapy regimen at the discretion of your medical oncologist.

Currently, there are no established rules to avoid esophagitis in the treatment of lung cancer with radiation therapy. At MGH, we have developed an intensity-modulated radiation therapy (IMRT)-based technique, termed CEST, to reduce the radiation dose to the part of the esophagus that is located opposite to the tumor. The reason behind this approach is that a lower radiation dose causes less esophagus inflammation and irritation and, therefore, may preserve the swallowing function of the esophagus better. In our clinical experience, reducing the radiation dose to part of the esophagus (i.e, the contralateral side) in this manner has shown the potential to dramatically decrease the likelihood of severe esophagitis in many though not all people with lung cancer. We therefore wish to analyze this technique further.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Take part in another research study.
- Receive the same treatment, but not as part of a research study.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

All participants will receive standard concurrent chemotherapy as prescribed by their doctor. These regimens when combined with radiation are associated with comparable rates of esophagitis. Side effects in relation to chemotherapy will be managed per standard of care.

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. All of these tests and procedures are part of regular cancer care and would be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, smoking status/history, alcohol use, and acid reflux history
- **A physical exam,** Including weight and vital signs, blood pressure, heart rate and oxygen saturation
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Laboratory tests,** which may include complete blood counts and liver function tests. These tests will be up to the discretion of the treating medical oncologist depending on chemotherapy regimen and tolerance.
- **An assessment of your tumor** by all of the following standard assessment tools: Computerized Tomography (CT) scan, Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) scans
- **Optional FLT-PET scan (Refer to Section O)**

Additional research procedures
- **Radiation therapy** will consist of high-precision IMRT using CEST delivered to your tumor(s) over 7 weeks

Research Study Plan:

	Screening	**Concurrent radiation/chemotherapy (weeks)**[c]							**Follow-up**[b]
		1	2	3	4	5	6	7	
Medical History	X								

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	Screening	Concurrent radiation/chemotherapy (weeks)[c]							Follow-up[b]
		1	2	3	4	5	6	7	
Physical Exam	X	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X	X
Laboratory Tests	X	X	X	X	X	X	X	X	X[a]
Optional FLT-PET	X			X[d]					
CT Chest/(+/-)Abdomen	X								X[a]
Brain MRI, Head CT, PET	X								X[e]
Radiation Therapy		X----------							

a.) CT scans will be conducted every 3 months (+/- 4 weeks) per standard of care. CT scans outside this schedule, will be allowed if needed per standard of care. Laboratory studies will be conducted during follow up visits at the discretion of the treating physician

b.) Participants who have at least moderate (grade 2) esophagitis at the end of the radiation therapy course should be seen at least every other week until esophagitis is resolved.

c.) These may be obtained only in part or less often than once per week.

d.) Scan will be obtained in week 3 (+/- 1 week)

e.) As clinically indicated

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this research study for up to two years.

The research doctor may decide to take you off the research study for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens
- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time; however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study treatments to keep track of your blood counts and organ function, as per standard-of-care. If you experience side effects, they may go away after you stop undergoing study treatments. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study treatments used with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Side Effects of Radiation

Radiation side effects are divided into those that occur acutely (during course of radiation therapy and up to 3 months after completion of treatment) and those that occur later (more than 3 months post-radiation). Acute side effects are common, while late normal tissue complications are generally rare but they can be severe and/or permanent. All participants will be seen weekly by their treating radiation oncologist while undergoing therapy.

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Greater than 10% chance this will occur:

- Fatigue
- Mild to moderate inflammation/redness of the skin (dermatitis)
- Mild, moderate, or severely difficult or painful swallowing (esophagitis)
- Dry cough
- Mild to moderate inflammation of lung tissue that may cause transient shortness of breath (pneumonitis). In rare cases, the risk can be severe and life-threatening, and requires oxygen support/mechanical ventilation

Between 1 and 10% chance this will occur:

- Moist peeling (desquamation) of skin
- Persistent swallowing difficulties due to narrowing (stricture) of the esophagus
- Permanent shortness of breath (dyspnea) or oxygen deprivation (hypoxia)
- Fracture of ribs or spine (vertebral body)
- Decreased white blood cell (neutrophil) count

Less than 1% chance this will occur (serious or life-threatening):

- Esophageal obstruction, which is a blockage in the esophagus. This creates a problem with food and liquid intake.
- Esophageal perforation, which is a hole in the esophagus. This creates a problem with food and liquid intake.

- An abnormal connection between two different organs (fistula). This side effect may lead to life-threatening complications including serious infections, bleeding or dysfunction of the organs.
- Severe coughing up of blood (hemoptysis)
- Heart attack (myocardial infarction)
- Inflammation around the heart (constrictive pericarditis)
- Severe congestive heart failure
- Cardiac irregularities (arrhythmias)
- Injury to the spinal cord (transverse myelitis)
- Impairment of nerves that affect the arm and hand which might also cause pain (brachial plexopathy)
- Irritation or destruction of skin or other body tissues (skin ulceration)
- Radiation-induced cancer

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, CT scans, PET scans, and/or other scans utilizing radioactivity may be used to evaluate your disease. The frequency of these exams is slightly greater than what you would receive as standard care. In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

Risks Associated with MRI Scans:
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 research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

This study may or may not help you. Taking part in this research study may reduce the risk of you developing severe esophagitis, meaning you may have less painful and less difficult swallowing than you would experience with standard radiation therapy. However, it is unlikely that this technique will completely eliminate any swallowing difficulty associated with radiation therapy. Taking part in the research study will help us learn more about the Contralateral Esophagus Sparing Technique that will allow us to further refine the technique or/and apply it to other patients with lung cancer in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid to take part in this research study.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services is:

- Massachusetts General Hospital: (617) 726-2191
- Newton-Wellesley Hospital: (617) 243-6824

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

K. WHAT HAPPENS IF I AM INJURED OR SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. The treating hospital may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for any of the sponsors of this study to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The results of this research study may be published. You will not be identified in publications without your permission.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can

identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Massachusetts General Hospital

- Henning Willers, MD: (617) 726-5184
- Joanna T. Tansky, MD PhD : (617) 219-1200

24-hour contact: please call Massachusetts General Hospital at (617) 726-5130 or Newton-Wellesley Hospital at (617) 219-1200 and ask that your doctor to be paged.

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

N. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;

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- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the treatments for the purpose of this or other research relating the study treatment and its use in cancer; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor of the study, its subcontractors, and its agent(s): Dana-Farber/ Harvard Cancer Center
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies

- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"

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O. OPTIONAL RESEARCH STUDIES:

Please Note: You do not have to agree to this test and your refusal to do so will not affect your participation in the main study. Optional scans are currently only being offered to participants at Massachusetts General Hospital.

18F-Fluorothymidine-PET (FLT-PET): You are being asked to participate in two additional PET scans during the course of treatment. With these scans we hope to obtain information on early tumor response to chemotherapeutic agents.

The difference between the FLT-PET scan and the standard FDG-PET scan is that the FLT tracer has higher tumor specificity than FDG.

I agree to participate in two additional PET scans during treatment.

Please initial and date one of the following options:

Yes:_____ No:_____

Date:_____

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O. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant or Legally Authorized Representative — Date

Relationship of Legally Authorized Representative to Participant

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Adult Participants

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is illiterate

The consent form was read to the participant who was given the opportunity to ask questions.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate

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