Official Title:	Adaptive-Dose to Mediastinum With Immunotherapy (Durvalumab MEDI4736) and Radiation in Locally-Advanced Non-Small Cell Lung Cancer
NCT number:	NCT04372927
Document Type:	Informed Consent Form
Date of the Document:	11/18/2021

University of Washington
Seattle Cancer Care Alliance
Fred Hutchinson Cancer Research Center

Consent to take part in a research study:

Adaptive-Dose to Mediastinum with Immunotherapy (Durvalumab MEDI4736) and Radiation in Locally- advanced non-small cell lung cancer

ADMIRAL Trial

Principal Investigator:
Jing Zeng, MD.
University of Washington Department of Radiation Oncology;
SCCA Proton Therapy Center. 206-598-4100

Emergency number (24 hours): 206-589-3300

Ask to speak to the Radiation Oncologist on-call.

If you are serving as a legally authorized representative the terms "participant", "you", and "your" refer to the person for whom you are providing consent.

Important things to know about this study.

You are invited to participate in a research study. The purpose of this research is to improve cancer control in stage III non-small cell lung cancer patients by using a combination of immunotherapy (durvalumab), chemotherapy, and radiation.

People who agree to join the study will be asked to attend roughly 60 clinic visits over 2 years. The study involves imaging appointments, daily radiation for 6 weeks with weekly chemotherapy, and immunotherapy once every 4 weeks for 2 years.

We do not know if durvalumab would help treat stage III non-small cell lung cancer, and it could even make your condition/disease worse. Durvalumab could cause side effects such as hepatitis, as described below in this form.

You do not have to join this study. You can choose to receive standard methods to treat stage III non-small cell lung cancer instead of participating in this study. We will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the study. If you join this study, we will give you a signed copy of this form to keep for future reference.

FHCRC IRB Approval
11/18/2021
Document Released Date

We invite you to join this research study.

Your doctor is inviting you to join this research study because you have stage III non- small cell lung cancer. Research is not the same as treatment or medical care. The purpose of this research is to answer scientific questions.

You do not have to join this study. You are free to say yes or no, or to drop out after joining. If you say no, you will have no penalty or loss of benefits. Whatever you decide, your regular medical care would not change.

Your study doctor will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study. Please take the time to read this form and ask questions. You may also discuss your decision with your family, friends, and healthcare team.

If you join this study, we will give you a signed copy of this form to keep for future reference.

Why are we doing this study?

You are being asked to join this study because you are beginning treatment for stage III non-small cell lung cancer. The purpose of the research is to examine two things:

1) does it improve cancer control to add the drug durvalumab, a type of immunotherapy, earlier in the treatment course (starting at the same time as chemotherapy and radiation instead of waiting until after chemotherapy and radiation are over), and giving the drug for 2 years instead of 1 year.

2) could we skip part of the radiation treatment (radiation to lymph nodes in the middle of the chest) so we can decrease side effects, without decreasing cancer control.

We want to know if the two changes above could improve cancer control and decrease side effects from treatment. If you join this study, we would give you immunotherapy (durvalumab), chemotherapy, and radiation and watch carefully for any side effects.

How many people will take part in this study?

Our goal is to enroll up to 40 people in this study.

What research tests, procedures, and treatments are done in this study?

Chemotherapy will be given per standard clinical care in this study. Durvalumab will be given during chemotherapy and radiation as part of the research study, and continue for 2 years total, whereas the current standard of care is to give durvalumab for 1 year after chemotherapy and radiation. Typically, standard of care radiation is given to the tumor and lymph nodes for 30 treatments over 6 weeks. For this study, the radiation will be split into two parts. The initial part to the primary tumor will be a short course of 8-15 treatments. The second part, if needed (for patients who still have cancer in the lymph nodes), will be given for 30 treatments over 6 weeks.

FHCRC IRB Approval
11/18/2021
Document Released Date

Patients will undergo a second mediastinal lymph node evaluation procedure as part of the study, in order to see if the initial radiation/chemotherapy/durvalumab was able to eliminate all the cancer in the lymph nodes.

There is also an optional PET/CT scan at baseline and after the initial radiation/chemotherapy/durvalumab treatment course. Standard of care blood draws will be drawn prior to every infusion during chemotherapy and durvalumab therapy. Study blood draws will take place a maximum of 9 times per patient during the 24-month study period and coupled to the standard of care blood draws if possible. Optional repeat lung tumor biopsy will be performed 1 month after radiation to the primary tumor (±2 weeks).

Study blood draws

Study blood draws will take place:

-Prior to any treatment

-1 week after completion of radiation to the primary tumor (±7 days)

-Prior to mediastinal radiation for applicable patients

-Every 4 months (±1 month) afterwards for 2 years or until disease progression

Study blood draws will take place a maximum of 9 times per patient during the 24-month study period and coupled to the standard of care blood draws if possible.

How long would you stay in this study?

If you join this study, you would stay in this study for around 2 years. For the first 3 months, you will be receiving chemotherapy, radiation therapy, and durvalumab. After you are finished with radiation and chemotherapy, you will receive durvalumab for a total of 2 years.

All patients will be followed per standard clinical care after completion of 2 years of durvalumab: at least every 6 months until 3 years from diagnosis, and yearly until 5 years from diagnosis. The follow-up period of this study is until disease progression.

Doctors could take you out of this study at any time. This would happen if:

- They think it is in your best interest not to continue in the study.
- You are not able or willing to follow study procedures.
- The whole study is stopped.

If you withdraw from the study for any reason, previously collected information would remain in the study records and would be included in the analysis of results.
This information could not be removed from the study records.

What are the risks?

In this part of the consent form, we describe the side effects we expect from the tests and treatments in this study. We carefully watch everyone in the study for side effects.

FHCRC IRB Approval
11/18/2021
Document Released Date

If you join this study, we would tell you if we discover new side effects that could affect you.

While the goal of this clinical trial is to both improve survival and decrease toxicity, it is possible that the opposite results will be seen. Potential for increased toxicity could come from the following:

- Receiving immunotherapy sooner could compromise administration and completion of standard-of-care regimens due to additional toxicities (e.g., pneumonitis). Please see below for additional risks with immunotherapy.

FHCRC IRB Approval
11/18/2021
Document Released Date

Risks with durvalumab include, but are not limited to:

- Diarrhea/colitis pneumonitis (respiratory and lung disease caused from inflammatory bowel disease)
- Interstitial lung disease (scarring of the lungs)
- Hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis (inflammation of the pituitary gland) and adrenal insufficiency
- Hepatitis (inflammation of the liver)/increases in transaminases
- Nephritis (inflammation of the kidney)/increases in creatinine
- Pancreatitis (inflammation of the pancreas) /increases in amylase and lipase
- rash/pruritus/dermatitis
- myocarditis (inflammation of the heart)
- myositis/polymyositis (inflammation of muscles)
- other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.

Risks with radiation used along with immunotherapy include:

- fatigue
- pneumonitis (inflammation of the lungs)
- Patients could have higher toxicity rates from receiving a higher biological dose of radiation to the primary tumor.

Side effects of research blood draw include:

- Bruising or minor swelling at the site of needle injection
- Light headedness or dizziness
- Pressure from the rubber band around your upper arm to increase blood flow

Side effects may be mild or very serious.

Another potential risk is decreased survival due to worse cancer control, since mediastinal radiation is not given upfront in the induction phase, but given at week

FHCRC IRB Approval
11/18/2021
Document Released Date

12 if there is residual disease in the mediastinum. This could provide an opportunity for disease progression in the mediastinum, which otherwise might have been controlled by upfront radiation

Radiation risks

Some of the tests that you will have in this research study will expose you to radiation. Everyone receives a small amount of radiation every day called "background radiation". This radiation is natural and comes from space, air, water, soil, and the food you eat. Each year you are exposed to about 3 milliSieverts (mSv) of this background radiation. A milliSievert is a unit of radiation dose. For comparison, the estimated radiation dose from each of these tests is listed below. The risk to your health from this level of radiation exposure is too low to be detectable and may be nonexistent.

- Chest CT: 7mSv
- Abdomen CT: 8 mSv
- Pelvis CT: 6 mSv
- Biopsy CT: 5 mSv
- Head CT: 2 mSv PET/CT: 19 mSv

Reproductive risks

Female Patient of child-bearing potential:

Durvalumab and radiation therapy may involve unknown risks to an embryo, fetus (unborn baby) or nursing infant. Therefore, you could not join this study if you are pregnant, if you are planning to become pregnant, or if you are breast-feeding.

If you join this study, you would have to use an effective method of birth control from the time this form is signed until at 90 days after the last dose of durvalumab. If you are already using a method of birth control, you would have to check with the study doctor or a member of the study staff to make sure it is acceptable.

If you became pregnant after joining this study, you would have to notify the study doctor immediately. Study drugs should be discontinued immediately.

Male Patient reproductive risks:

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

What are the benefits?

We do not know if this study would help you. We are conducting this study to see its effects on people with non-small cell lung cancer. Overall, we believe the potential

FHCRC IRB Approval
11/18/2021
Document Released Date

benefits of the trial outweigh the risks. You might get better treatment results than standard of care treatments if you receive durvalumab and radiation treatment concurrent with chemotherapy, but your results could be the same or even worse. We hope the information from this study will help other people with stage III non-small cell lung cancer in the future.

You have other choices besides this study.

You do not have to join this study. You are free to say "yes" or "no". Your regular medical care would not change if you decide to say "no".

You have other choices for treatment. Each of these choices has risks and benefits. You should talk to your doctor or healthcare provider about these choices.

Other choices include:

- Getting treatment or care for your cancer without being in a study (according to the discretion of your treating oncologist). This could include standard therapies that may include radiation, chemotherapy, other targeted therapies or even immunotherapies that may be FDA approved.
- Receiving no treatment
- Getting comfort care. This type of care addresses pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly.

Enrollment in this study may exclude you from other research studies.

Protecting Privacy as an Individual and the Confidentiality of Personal Information

If you join this study, some people or organizations might need to look at your medical records and research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- AstraZeneca (the sponsor of the study) and their agents.
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Research Center IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Fred Hutchinson Cancer Research Center, University of Washington, and Seattle Cancer Care Alliance.
- Food and Drug Administration, and other regulatory agencies as required.

FHCRC IRB Approval
11/18/2021
Document Released Date

We will do our best to keep personal information confidential. But we cannot guarantee total confidentiality. Personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests. Or a court may order study information to be disclosed. Such cases are rare.

We will not use personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

If you join this study, information about your participation would be made part of your permanent medical record. This information would include a copy of this consent form. If an insurance company or employer or anyone else were authorized to see your medical record, they would see a copy of this consent form.

How is my genetic information protected?

A federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect genetic information about people who join research studies.

GINA restricts access to genetic information so that it cannot be used for health insurance coverage decisions. GINA prevents health insurance companies or group health plans from:

- Asking for genetic information obtained in research studies, or
- Using genetic information when making decisions regarding your eligibility or premiums

GINA *does not* help or protect against genetic discrimination by companies that sell life, disability or long-term care insurance.

Would we pay you if you join this study?

The sponsor will provide study drug for this study. There is no payment for being in this study.

Would you have extra costs if you join this study?

The tests that are done exclusively for research will not be billed to you or your insurance company. These tests include:

- Research blood collection
- Optional research biopsy
- Optional PET/CT scans

FHCRC IRB Approval
11/18/2021
Document Released Date

If you join this study, you or your insurance company would have to pay for the costs of standard treatment in this study.

What if you get sick or hurt after you join this study?

For a life threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is over or as soon as you can.

For all other medical problems or illness related to this research, immediately contact the study doctor, Dr. Jing Zeng. She will treat you or refer you for treatment. You or your health insurance will have to pay for the treatment. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family. State or national law may give you rights to seek payment for some of these expenses. You do not waive any right to seek payment by signing this consent form.

You or your insurer will be billed for treatment of problems or complications that result from your condition or from standard clinical care.

You would not lose any legal right to seek payment for treatment if you sign this form.

What will my information and/or tissue samples be used for?

Your information and tissue samples (such as blood and tumor cells) will be used for the purposes of this study.

Your tissue samples might help researchers develop new products. This research could be done by for-profit companies. There is no plan to share with you any revenue generated from products developed using your tissue samples.

During this study, if the researchers learn new information that may be important to your general health or to your disease or condition, they will share that information with you.

In addition, be aware that by agreeing to participate in this study, your information or tissue samples could be used for future research studies or sent to other investigators for future research studies without additional consent from you. These future research studies will be reviewed by an oversight group known as an institutional review board if required by law. The information that identifies you will first be removed from your information or tissue samples. If you do not want your information or tissue samples to be used for future research studies without your consent, you should not participate in this study.

Your tissue contains DNA. DNA makes up the genes that serve as the "instruction book" for the cells in our bodies. By studying genes, researchers can learn more about diseases such as cancer. There are many different types of genetic tests. The testing on your tissue samples might include genetic testing called whole genome sequencing. Whole

genome sequencing looks at all the genetic information in your cells. This type of testing can provide useful information to researchers. It can also present risks if the test results became known to others, for example you could have problems with family members or insurance companies. There is also a risk that these test results could be combined with other information to identify you.

Your rights

- You do not have to join this study. You are free to say "yes" or "no".
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we might learn new information that you need to know. For example, some information may affect your health or well-being. Other information might make you change your mind about being in this study. If we learn these kinds of information, we would tell you.
- If you join this study, you would not have to stay in it. You could stop at any time (even before you start). Your regular medical care would not change. You would have no penalty for stopping, but it would be better not to join the study if you think that you would change your mind later.
- If you decide to drop out, we would want you to tell the study doctor. The doctor could tell you about the effects of stopping your treatment. You and the doctor could talk about the follow-up care and testing that would help the most.
- Before you leave the study, the doctor might ask you to continue in the follow-up part of the study.

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.

Your responsibilities

If you join this study, you would have some responsibilities.

- Follow the schedule of study visits and procedures.
- Take study medications as directed.
- Prevent pregnancy.
- Tell us about side effects

FHCRC IRB Approval
11/18/2021
Document Released Date

For more information

If you have questions or concerns about this study, you can talk to your doctor anytime. Other people you could talk to are listed below.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	206-598-4100 (Dr. Jing Zeng)
If you get sick or hurt in this study	206-598-4100 (Dr. Jing Zeng)
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center) 206-543-0098 (Human Subjects Division, University of Washington)
Your bills and health insurance coverage	The financial services department at the medical center where you will be treated: Seattle Cancer Care Alliance: Patient Financial Services 206-606-6226 (phone)1st Floor Seattle Cancer Care Alliance (in-person) 825 Eastlake Ave. E Seattle, WA 98019 University of Washington Medical Center Patient Financial Services 206-598-1950 (phone) UW Tower (in-person) 4333 Brooklyn Ave. NE Seattle, WA 98195

Emergency number (24 hours): 206-589-3300

Ask to speak to the Radiation Oncologist on-call.

FHCRC IRB Approval
11/18/2021
Document Released Date

Making Your Choice

Please think about your choice on whether to participate in this optional portion of the study. When you decide, please circle YES or NO. Please initial and date in the spaces provided.

Tumor Biopsy (Optional)

The additional research biopsy part of this study is completely optional. You can still participate in this study without undergoing the research biopsy. It is important to understand that the results of this research biopsy are not designed specifically to help you. This is an opportunity for us to get more information regarding your type of cancer. Information from this research will not be included in your medical record. For those who give permission for the research tumor biopsy, the biopsy will be scheduled before you begin radiation treatment and 16- weeks after you end radiation treatment. There will be a separate procedure consent form that will outline the risks associated with the area planned for biopsy. You and your insurance company will not be charged for this research procedure.

Do you agree to donate your tumor tissue to study cancer?

YES NO Initials:_____ Date: _____

PET/CT Scan (Optional)

The optional PET/CT scan will replace the pre-treatment CT scan and the Week 9 restaging CT scan. You can still participate in this study without undergoing the PET/CT imaging. You and your insurance company will not be charged for this research procedure.

Do you agree to receive the PET/CT scan?

YES NO Initials: _____ Date:_____

FHCRC IRB Approval
11/18/2021
Document Released Date

Signatures

Please sign below if you:

- have read this form (or had it read to you);
- had the opportunity to ask any questions you have;
- had the opportunity to discuss the research with the person obtaining consent; and
- agree to participate in this study.

Participant:

Printed Name	Signature	Date

Legally Authorized Representative: Please sign below if you:

- have read this form (or had it read to you);
- had the opportunity to ask questions;
- had the opportunity to discuss the research with the person obtaining consent; and
- agree to consent on behalf of the participant for him or her to participate in this study.

Legally authorized representative:

Printed Name	Signature	Date

Relation to the participant

If you served as an interpreter or impartial witness during the consent process, sign below to indicate you attest to the accuracy of the presentation and the participant's apparent understanding of and willingness to participate in the research.

Impartial Witness or Interpreter:

Printed Name	Signature	Date

FHCRC IRB Approval
11/18/2021
Document Released Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

Person obtaining consent signature:

Printed Name	Signature	Date

Current consent version date: 2.0

FHCRC IRB Approval
11/18/2021
Document Released Date