Research Study Informed Consent Document

Study Title for Participants: A study of chemotherapy and radiation therapy compared to chemotherapy and radiation therapy plus durvalumab immunotherapy for bladder cancer which has spread to the lymph nodes

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol EA8185, Phase II Study of Bladder-SparIng ChemoradiatioN With Durvalumab in Clinical Stage III, Node PosItive BladdeR CancEr (INSPIRE) (NCT04216290)

Version Date: May 16, 2024

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

Rev. Add3

We are asking you to take part in this research study because you have bladder cancer that has spread from your bladder to your lymph nodes, called node-positive bladder cancer. Node-positive bladder cancer behaves differently than cancers that have spread to distant areas in the body. In this study the researchers are investigating whether or not combining chemotherapy, radiation and immunotherapy in node positive bladder cancer patients would increase the number of patients whose cancer disappears completely on scans. This study is combining different kinds of treatment: chemotherapy and radiation therapy, with immunotherapy in one group, to attack bladder cancer after patients receive the usual chemotherapy.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are

answered. See the "Where can I get more information?" section for resources for more cancer studies and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Can we improve the treatment response in bladder cancer that has spread to lymph nodes by adding immunotherapy to chemotherapy and radiation therapy?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for node positive bladder cancer. The usual approach is defined as care most people get for bladder cancer involving the lymph nodes.

What is the usual approach to my bladder cancer with node involvement?

The usual approach for patients who are not in a study is treatment with surgery, radiation, and/or chemotherapy drugs. All of these are FDA-approved for treatment of bladder cancer. Sometimes, combinations of these treatments are used. Your doctor can explain which treatment may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get chemotherapy and radiation for 6-8 weeks, or you will get durvalumab immunotherapy in addition to chemotherapy and radiation for 6.5-8 weeks. This study has an initial (lead-in)safety phase, or period, during which the first 6 patients that receive durvalumab will be watched closely for major side effects. durvalumab is a type of immunotherapy that would be given during the chemotherapy and radiation period. After those 6.5-8 weeks of treatment you will have exams such as CT scan or MRI of your belly to take pictures of your bladder that will allow your doctor to see if the tumor has responded to treatment. If you are in the durvalumab Group 1 and the bladder cancer has responded (shrunk, gone away or remained stable) to treatment with chemotherapy, radiation and durvalumab, you will be offered more treatments with
Rev. Add4 durvalumab alone for up to 6 months. If you are in the arm with chemotherapy and radiation, and your cancer has responded, you will be watched closely without any additional
Rev. Add4 chemotherapy and radiation treatments. In special circumstances (if you did not get any

chemotherapy prior to chemotherapy and radiation), if you are in observation arm and your physician wishes to give you more chemotherapy post chemotherapy and radiation, it is allowed. If your cancer has not responded, your doctor may offer you surgery or some other treatment. You will still be followed by study team to see how you are doing.

After you finish your study treatment, your doctor will continue to follow you for up to 3 years. The follow-up will consist of visits to his or her office and CT scans of the bladder according to the following schedule: every 3 months for 1 year; every 6 months in the 2nd year; then once a year in the 3rd and 4th year. In addition, your urologist will also follow you with cystoscopy (a method of inserting a camera into the bladder and urinary tract) to have a look in your bladder every 3 months for 2 years, and then every 6 months until year 3. If you are in the group getting additional durvalumab after your radiation treatment, in addition to the above follow-up, you will be followed monthly with your doctor for treatment for up to 6 months. This has been explained in-depth in this consent form on page 6. After 4 years, you may still be followed closely by your doctors and they may do follow-ups if needed based on the usual care.

Rev. Add3
Rev. Add5
Rev. Add5

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study drug durvalumab combined with the usual approach for your cancer may not be as good as, or better than the usual approach for your cancer at treating your cancer.

There is also a risk that you could have side effects from the study drug. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

There is also a risk that the stage of your cancer may not be able to be classified accurately, if it is not able to be biopsied and tested in a lab. A biopsy is where doctors take a small piece of the tumor out of the body and run tests on it.

Rev. Add3 There is a risk that your disease may get worse if you do not get the cystectomy (surgery to remove the bladder) upfront, if the cancer does not respond to chemotherapy and immunotherapy drugs that will be given with radiation.

Some of the most common side effects that the study doctors know about are:

- Itching; rash
- Fatigue or feeling really tired
- Joint or muscle pain
- Infections, such as of the nose, lungs, throat, mouth, or other parts or organs of the body
- Inflammation of the intestines, lung, or liver

- Hormonal abnormalities

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that durvalumab immunotherapy is effective in shrinking or keeping your cancer stable. It is not possible to know now if the addition of the study drug durvalumab to the usual approach (chemotherapy and radiation) will improve the shrinking of your tumor compared to the usual approach alone. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing. Stopping your taking part in this study may mean slowly stopping the study drugs.

Rev. Add3

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- For men: You wish to father children while on the study.
- The study is stopped by the National Cancer Institute (NCI) Institutional Review Board (IRB), Food and Drug Administration (FDA), study sponsor. The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the usual treatment of chemotherapy and radiation to adding durvalumab immunotherapy to the usual treatment. The addition of durvalumab immunotherapy to the usual treatment may help shrink your cancer better than the current standard of care or usual approach for bladder cancer. But, it could also cause side effects,

which are described in the risks section.

This study will help determine if this different approach is better than the usual approach. To decide if it is better, the study doctors will be looking to see if the study approach increases the life of patients compared to the usual approach.

Rev. Add3
Rev. Add5

This immunotherapy drug, durvalumab, is already approved by the FDA for use in bladder cancer that has spread, or metastasized, to other parts of the body. But, most of the time it is not used until chemotherapy stops working. There will be about 95 people taking part in this study.

What are the study groups?

This study includes 2 main study groups, Group 1 and Group 2. Group 1 is the group where patients would get chemotherapy along with radiation and durvalumab. Group 2 is the group where patients would get chemotherapy and radiation alone. There will be a total of about 95 patients taking part in this study. You will only participate in one group. You may or may not have completed chemotherapy (per your physician's choice) prior to being on this study and prior to being assigned to one of these arms and your bladder cancer must not have progressed (gotten worse).

After chemotherapy, CT scan and cystoscopy (a procedure to look in your bladder) would be done to evaluate the response to treatment. In addition, your urologist would do a trans-urethral resection of bladder tumor (TURBT), a procedure to scrape out any visible cancer in the bladder, if possible when performing cystoscopy.

Your doctor will determine how your cancer responded to the first rounds of chemotherapy. If your cancer shrinks or stays the same size to this first chemotherapy, you will get assigned to either Group 1 or 2.

Groups 1 and 2

- You will receive radiation treatment 5 days a week for 6 to 8 weeks. You will get the radiation through a machine called a linear accelerator that creates the radiation beam.
- You will also get the chemotherapy together with the radiation that your doctor thinks is best for you. He/she will choose one of the following three options of chemotherapy:

Option	Chemotherapy agents	Description
1	Cisplatin	This would be given by IV (into your vein) once a week for 6 weeks.
2	Gemcitabine	This would be given by IV twice a week for 6 weeks.
3	5-Fluorouracil (5-FU) and mitomycin-C	5-FU would be given by IV on the same days as your first 5 radiation treatments and your 16th through 20th radiation treatments. Mitomycin-C would be given by IV on the same day as your first radiation treatment.

- For Group 1 ONLY: you will get durvalumab during the radiation treatment every 3 weeks. If the cancer responds to the radiation, chemotherapy, and durvalumab after the treatment is over, you will continue durvalumab once every month for a total of 6 months. You will not be able to get additional doses of the drug. This drug is currently not approved by the FDA for treatment of your stage of disease.

Rev. Add5

There will be at least 51 patients in each Group.

Additional Study Drug Treatment and Follow-up:

After the study treatment is completed, your doctor would do CT scan and another cystoscopy (a procedure to have a look in your bladder) with additional biopsy (to take some scrapings from bladder wall to examine it under the microscope) to determine response to treatment.

Rev. Add5

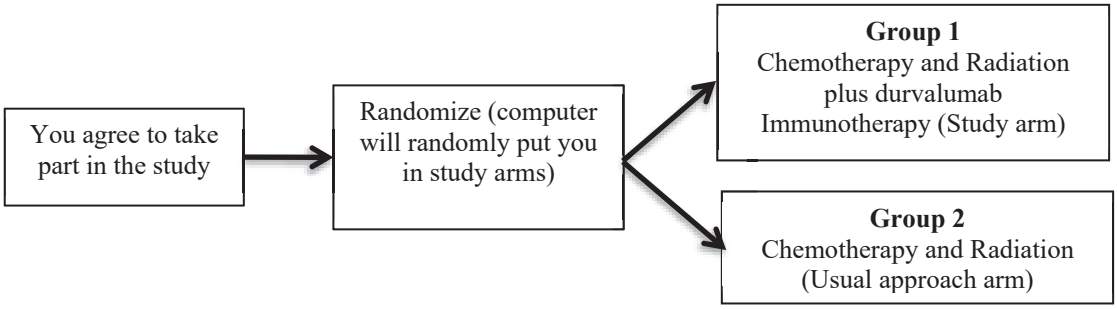
In Group 1, if your cancer responds to treatment, you will get additional 6 doses of monthly durvalumab in your vein. Every 3 months for year 1, you will get CT scan and cystoscopy (a procedure to have a look in your bladder) to determine response to treatment. After completion of treatment your doctor will monitor you to ensure no progression of cancer with CT scan and cystoscopy. CT scan will be done every 3 months for year 1, then every 6 months for year 2 then annually until year 3. Cystoscopy would be done every 3 months for 2 years, then every 6 months until year 3. After this, your doctor will determine future frequency of these tests.

In Group 2, if your cancer responds to treatment, your doctor will observe you without giving you any additional treatment with CT scan and cystoscopy. CT scan will be done every 3 months for year 1, then every 6 months for year 2 then annually until year 3. Cystoscopy would be done every 3 months for 2 years, then every 6 months until year 3. Thereafter your doctor will determine future frequency of these tests.

However, if your cancer did not respond to treatment in any arm, then your doctor may offer surgery or any other treatment. The study team will still follow you up to see how you are doing, but your treatment would be guided by your doctor.

We will use a computer to assign you to one of the study arms. This process is called “randomization.” It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance (50% chance) of being in Group 1 or 2.

Another way to find out what happens during this study is to read the chart below. Start reading from left to right, following the lines and arrows.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Some exams, tests, and procedures need to be done as part of this study to monitor your safety and health and are part of the usual care. The blood work, CT scans and cystoscopies (to have a look in your bladder) along with the biopsy to evaluate for response are part of your usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- Blood counts done during the day of your infusions during the course of your treatment

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study drug may not be as good as the usual approach for your cancer or condition at shrinking your cancer.

You also may experience the following:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The chemotherapy, radiation and durvalumab immunotherapy used in this study could be very harmful to an unborn or newborn baby. It is very important that you check with your doctor about what birth control or pregnancy prevention to use during the study treatment and for 3 months after the last dose of study treatment. There may be some risks that doctors do not yet know about.

Rev. Add3

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

Any leftover specimens from the biopsy may possibly be stored for future research, as will be discussed in the section below under "Optional studies."

Side Effect Risks

The chemotherapy, radiation and durvalumab immunotherapy used in this study may affect how different parts of your body such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the radiation therapy, chemotherapy, and durvalumab immunotherapy.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have or conceive children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 - In addition to side effects listed above, people who are in Group 1 may also have some side effects from durvalumab.

Possible Side Effects of MEDI4736 (durvalumab)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving durvalumab (MEDI4736), more than 20 and up to 100 may have:

- Cough

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving durvalumab (MEDI4736), from 4 to 20 may have:

- Anemia which may require blood transfusion
- Pain in the muscles, joints
- Diarrhea, nausea, vomiting
- Swelling of the body
- Tiredness, fever
- Infections. Infections can be severe and involve jaws and fatty tissues
- Loss of appetite
- Painful urination
- Shortness of breath
- Changes in voice
- Increased sweating

Durvalumab (MEDI4736) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems include but are not limited to:

- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin: itching; rash, patches of light skin color

RARE, AND SERIOUS
In 100 people receiving durvalumab (MEDI4736), 3 or fewer may have:

- Pain and swelling of thyroid
- Reaction during or following a drug infusion which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

RARE, AND SERIOUS

In 100 people receiving durvalumab (MEDI4736), 3 or fewer may have:

Durvalumab (MEDI4736) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems include but are not limited to:

- Damage to blood cells that may cause bruises and bleeding
- Blood clots in small blood vessels, which may cause kidney failure, fever, and confusion
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body or abnormal heartbeat
- A condition with high blood sugar (diabetes) which leads to tiredness, frequent urination or excessive thirst which may require treatment with insulin
- Swelling and redness of the eye
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness
- Damage to the pancreas which may cause belly pain and hospitalization
- Problem of the muscle (myositis), which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Problem of the nervous system that can cause weakness and paralysis, which may include: numbness, tingling of hands and feet, and may also cause problems with breathing
- Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling
- Severe skin reactions with blisters and peeling which can involve mouth and other parts of the body

Study Group 1 and Group 2 – Possible side effects of chemotherapies used with radiation have been listed below.

You will receive one of several possible chemotherapy regimens. Only the side effects listed under the drugs you will receive are relevant to you.

Please note that your doctor will also choose the type of chemotherapy to be given prior to the combined chemotherapy and radiation therapy, if you have not received it prior to the enrollment on the study and will discuss the side effects separately. So, you will not get the side effects from drugs you are not getting.

Possible Side Effects of 5- Fluorouracil (Table Version Date: April 10. 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving 5-Fluorouracil, more than 20 and up to 100 may have:
• Diarrhea, nausea • Sores in mouth which may cause difficulty swallowing • Heartburn • Swelling and redness at the site of the medication injection • Redness, pain or peeling of palms and soles • Increased risk of sunburn, itching

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving 5-Fluorouracil, from 4 to 20 may have:
• Chest pain • Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may require blood transfusions • Sores in stomach which may cause belly pain • Internal bleeding which may cause black tarry stools • Difficulty with balancing • Tiredness • Skin changes

RARE, AND SERIOUS In 100 people receiving 5-Fluorouracil, 3 or fewer may have:
• Damage to the heart which may cause shortness of breath • A new cancer resulting from treatment of a prior cancer

Possible Side Effects of Cisplatin (Table Version Date: November 8, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Kidney damage which may cause swelling, may require dialysis • Hearing loss including ringing in the ears • Nausea, vomiting • Confusion

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
• Numbness and tingling of the arms and legs

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• Change in taste • Diarrhea • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Hair loss

RARE, AND SERIOUS In 100 people receiving Cisplatin, 3 or fewer may have:
• Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness • Seizure • A new cancer resulting from treatment of a prior cancer

Possible Side Effects of Gemcitabine (Table Version Date: October 17, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may require a blood transfusion • Blood in urine • Nausea, vomiting • Flu-like symptoms of muscle pain, fever, headache, chills and fatigue • Muscle weakness • Feeling of "pins and needles" in arms and legs • Numbness and tingling of the arms and legs • Swelling of arms, legs • Tiredness • Difficulty sleeping • Rash • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, from 4 to 20 may have:
• Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles • Scarring of the lungs • Shortness of breath • Liver damage which may cause yellowing of eyes and skin, swelling • Diarrhea, constipation • Sores in mouth which may cause difficulty swallowing • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Swelling and redness of the area of radiation • Blisters on the skin

RARE, AND SERIOUS In 100 people receiving Gemcitabine, 3 or fewer may have:
• Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness • Blockage of the airway which may cause cough • Blood clot • Severe blood Infection • Anemia, kidney problems which may require dialysis

Possible Side Effects of Mitomycin (Table Version Date: October 17, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Mitomycin, more than 20 and up to 100 may have:
• Infection, particularly when white blood cell counts are low • Anemia which might require blood transfusion • Bruising, bleeding • Tiredness • Swelling of the body • Difficult, painful or frequent urination (when the drug is administered into the bladder) • Blood clot

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Mitomycin, from 4 to 20 may have:
• Loss of appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Mitomycin, from 4 to 20 may have:
• Nausea, vomiting • Sores in the mouth • Rash • Hair loss • Loss of fertility • Swelling and redness at the site of the medication injection • Fever • Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis

RARE, AND SERIOUS In 100 people receiving Mitomycin, 3 or fewer may have:
• Shortness of breath, cough, scarring of the lungs • Kidney failure that could require treatment with dialysis

Possible Side Effects of Radiation Therapy
EARLY REACTIONS:

COMMON, SOME MAY BE SERIOUS: In 100 people receiving radiation, more than 20 and up to 100 may have:
• Inflammation of bowel causing cramping and diarrhea • Inflammation of rectum and anus causing pain, spasm, discharge • Bladder inflammation causing burning, frequency, spasm, pain, incontinence • Skin changes: redness, irritation, coloration, thickening, hair loss, scaliness, blistering • In women there could be disturbance in menstrual cycle, vaginal discharge, pain, irritation, bleeding and painful intercourse.

OCCASIONAL, SOME MAY BE SERIOUS: In 100 people receiving radiation, from 4 to 20 may have:
• Inflammation of rectum and anus causing bleeding • Bladder inflammation causing bleeding

RARE AND SERIOUS: In 100 people receiving radiation, 3 or fewer may have:
• Skin changes: ulceration • Inflammation of bowel causing bleeding

RARE AND SERIOUS: In 100 people receiving radiation, 3 or fewer may have:
• Depression of blood count leading to increased risk of infection and/or bleeding

LATE REACTIONS:

COMMON, SOME MAY BE SERIOUS: In 100 people receiving radiation, more than 20 and up to 100 may have:
• Loss of bladder capacity • Inability to hold urine for a long time • Frequency of urination • Bladder spasms or pain • Changes in skin texture and/or coloration, permanent hair loss, scarring of skin. • Testicular damage causing reduced sperm counts, infertility, sterility, or risk of birth defects. • Impotence (loss of erection) or sexual dysfunction • Ovarian or Uterine damage causing infertility, sterility, or premature menopause. • Vaginal damage leading to dryness, shrinkage, pain, bleeding, or sexual dysfunction.

OCCASIONAL, SOME MAY BE SERIOUS: In 100 people receiving radiation, from 4 to 20 may have:
• Blood in urine • Recurrent urinary tract infections • Chronic diarrhea or poor absorption of food elements

RARE AND SERIOUS: In 100 people receiving radiation, 3 or fewer may have:
• Bowel damage causing narrowing or adhesions of the bowel with obstruction, ulceration, bleeding, or tears and may require surgical correction or colostomy. • Bladder damage which may require urinary diversion and/or removal of bladder. • Bone damage leading to fractures. • Swelling of the genitalia or legs. • Nerve damage causing pain, loss of strength or feeling in legs, and/or loss of control of bladder or rectum. • Fistula between the bowel and other organs. • Second cancer due to the radiation

Let your study doctor know of any questions you have about possible side effects. You can

ask the study doctor questions about side effects at any time.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your appointments.
- Tell your doctor about:
  - all medications and supplements you are taking before study enrollment and during study treatment.
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.
  - if you are planning to receive a live attenuated vaccine during the study or within 30 days after your last dose of study drug.
  - if you plan to donate blood while on the study.

For women: Do not get pregnant or breastfeed while taking part in this study.

For men: Do not father a baby while taking part in this study.

For all: Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 3 months after your last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- Cost of tests, exams, procedures, and drugs including chemotherapy and radiation therapy that you get during the study to monitor your safety, and prevent and treat side effects.

Rev. Add4

- The costs of preparing and administering the Durvalumab
- Your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You or your insurance provider will not have to pay for the durvalumab while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.

- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups with which it works to review research.
- The NCI and the groups with which they work to review research.
- The NCI's National Clinical Trials Network and the groups with which they work to conduct research.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked for your consent to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the National Cancer Institute (NCI) web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

You can talk to your doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that you can choose to take part in.

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample collections for storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, samples of tumor tissue and blood will be collected and stored. Storing samples for future studies is called "bio-banking." The biobank is being run by ECOG-ACRIN and is supported by the NCI.

This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use.

Right now, we don't know what research may be done in the future using your blood and/or tissue samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.

- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

- We would like tissue samples from your diagnostic biopsy as well as tissue from your restaging biopsy performed to assess response for storage at the biobank. These tissue samples are from procedures performed as part of your routine care.
- Approximately eight (8) teaspoons of blood will be collected prior to the start of treatment post randomization, and approximately six (6) teaspoons of blood will be collected post therapy at restaging (week 16). Your samples will be stored in the biobank.
- Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.

Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.

Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.

Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.

In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/.

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your samples and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your samples and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, Dr. (*insert name of study doctor*), at (*insert telephone number of study doctor*), who will let the biobank know. Then, any samples that remain in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, (*insert name of study doctor*), at (*insert telephone number of study doctor*).

Please circle your answers below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:

May we have samples of your tumor tissue and blood for future research?

- **I agree that my samples and related health information may be kept in a Biobank for use in future health research.**

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature _____

Date of signature _____

Signature of person(s) conducting the informed consent discussion _____

Date of signature _____