Title of Study: Checkpoint Inhibitor and Radiation Therapy in Bulky, Node-positive Bladder Cancer (CIRTiN-BC)

Consent to be part of a Research Study
To be conducted at
The University of Texas Southwestern Medical Center

Key Information about this Study

This study is for patients with bladder cancer that has spread to the lymph nodes near the bladder and who are planning to start treatment with a drug called an Immune Checkpoint Inhibitor (ICI). The purpose of the study is to evaluate the benefit of combining radiation therapy with ICI treatment. Although radiation therapy is an approved treatment for bladder cancer, its combination with ICI and surgery has not been evaluated before and hence we are conducting this trial.

Patients with bladder cancer that has spread to the lymph nodes are at very high risk of having their cancer return or spread elsewhere in the body after surgery. Our hope is that adding radiation to ICI treatment will reduce this risk Radiation itself can kill cancer cells, and it is possible that radiation may combine with the ICI treatment to increase its activity against the cancer.

If you participate in this study, after starting your ICI treatments, you will receive three doses of radiation to your bladder and to the lymph nodes where the disease has spread. The three visits for radiation treatment will be 12-16 days apart and each visit will take approximately three hours. You will have another office visit following radiation treatments to discuss your symptoms and whether you have had any problems caused by the radiation. During this time you will continue to receive your ICI drug. Four to eight weeks after receiving radiation, you will undergo surgery to remove the bladder (radical cystectomy) unless you and your doctor decide that you will not benefit from the surgery. After surgery, you will follow up with your doctor as you normally would, at least once every six months for at least two years. You will receive phone calls from the study team every six months for two years to discuss how you are doing.

Possible risks of participating in the study include the risks of radiation, such as injury to the blood vessels, bowels, or other organs near the treated area of the body. It is possible that radiation will make surgery more difficult or risky. It is possible that radiation will not reduce the risk of your cancer returning or spreading.

If you are interested in learning more about this study, please continue to read below.

Information about this form

You may be eligible to take part in a research study. This form gives you important information about the study.

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Please tell the researchers or study staff if you are taking part in another research study.

Your doctor is a research investigator in this study. S/he is interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you decide to stop taking part in this research study, it will not affect your relationship with the UT

Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

General Information – "Who is conducting this research?"

Principal Investigator
The Principal Investigator (PI) is the researcher directing this study; the PI is responsible for protecting your rights, safety and welfare as a participant in the research. The PI for this study is Solomon Woldu, M.D., Department of Urology at UT Southwestern Medical Center.

Purpose – "Why is this study being done?"

Bladder cancer which has spread to lymph nodes near the bladder (called "node-positive bladder cancer") often returns (recurs) or spreads elsewhere in the body (metastasizes) after surgery. Patients with node-positive bladder cancer are usually given chemotherapy before surgery because this has been shown to cure more patients. However, some patients cannot receive chemotherapy for medical reasons, and in others the cancer does not respond to the chemotherapy. For these patients, one treatment option is a type of drug called an Immune Checkpoint Inhibitor (ICI). These drugs are designed to "rev up" your immune system and cause it to attack the cancer. However, only about half of patients who receive an ICI drug will respond to treatment. Radiation therapy (RT) can kill cancer cells, and some studies in animals have suggested that it may also work with ICI treatment to make the ICI more effective.

You are asked to participate in this research study, in which patients with node-positive bladder cancer are given radiation therapy in addition to ICI before undergoing surgery. The radiation therapy may directly kill tumor cells and in addition it may improve the effectiveness of the ICI drug by helping your immune system recognize and attack the cancer. This may result in your immune system recognizing and attacking cancer cells in your body even after the bladder is surgically removed.

The researchers hope to learn if it is possible to add radiation therapy to ICI before radical cystectomy and if this will result in improved outcomes for patients. Some possible areas where improvement might be seen could be in the number of patients with node-positive bladder cancer who are able to receive surgery, the number of patients who are found to have remaining cancer in the lymph nodes at the time of surgery, and in the number of patients whose disease returns or spreads elsewhere in the body after surgery.

Novel Use of Radiation Treatment

This study involves the combination of ICI, a treatment that has been approved by the U.S. Food and Drug Administration (FDA) in patients with advanced bladder cancer, with radiation therapy which is another FDA approved modality for the treatment of bladder cancer. The combination of radiation therapy and ICI in this study is investigational, and we will use a type of radiation therapy called Personalized Ultrafractionated Sterotactic Ablative Radiation (PULSAR) in a novel way. In this case, "novel" means that we will take an established treatment (radiation therapy) and use it in a way which is new or different from how it has been used in the past.

This study will help find out what effects, good and/or bad, the combination of ICI and radiation therapy have in people who receive them and on their effect on node-positive bladder cancer. This study will be among the first in people in whom this combination of treatments will be used. The safety of this radiation therapy combined

with ICI treatment in humans has been tested in prior research studies; however, it has not been used in this particular situation before and some side effects may not yet be known.

Information about Study Participants – "Who is participating in this research?"

You are being asked to be a participant in this study because you have bladder cancer which your doctor believes has spread to lymph nodes near the bladder, based on your scans; and additionally, you are either unable to receive chemotherapy, have refused to accept chemotherapy, or you have received chemotherapy but your cancer does not appear to have responded to treatment based on your scans. Patients with bladder cancer that has spread to the lymph nodes ("node-positive bladder cancer") have a very high risk of their disease returning or spreading to other parts of the body, even if they undergo surgery in an attempt to cure them.

How many people are expected to take part in this study?
This study will enroll approximately 27 study participants.

Information about Study Procedures – "What will be done if you decide to be in the research?"

While you are taking part in this study, you will be asked to attend approximately five visits with the researchers or study staff, including your visits for radiation treatment. All of the other visits, tests, and scans you receive will be the same as if you had not participated in the study. The study staff will follow up on your routine doctor visits after surgery and will contact you every six months for two years in order to discuss how you are doing.

Screening – After you sign this consent to participate, exams, tests, and/or procedures may be done as described below to find out if you can continue in the study; this is called screening. We may be able to use the results of exams, tests, and/or procedures you completed before enrolling in this study. You will be told which results we will obtain and which procedures will not have to be repeated. Many of the procedures are described below as "**standard care**" and would be done even if you do not take part in this research study. You will be told which ones are for "**research only**".

Screening Procedures

- We will review your medications and the plan of care that you have made with your medical oncologist in order to determine that you are eligible for the study.
- We will review your medical and surgical history with you.
- The physical examination done as part of your standard of care will be used.
- The results of blood tests done as part of your standard of care will be used.
- The results of your scans (CT scan, MRI, etc.) done as part of your standard of care will be used.
- If you are capable of becoming pregnant, a pregnancy test will also be done before you receive study treatment.
- We will ask you to sign this form, documenting that you understand the reason for the study and its risks and benefits, and that you agree to participate.

The research procedures will add approximately 45 minutes to the length of a routine care visit.

The results of the screening exams, tests, and/or procedures will be reviewed to determine whether you will be allowed to continue in the study. If you are not allowed to continue in the study, the researcher will discuss the reasons with you and will discuss other possible options.

As part of the study, you will receive one appointment with the radiation oncologists to discuss the radiation treatment in more detail including its risks and benefits. You will have three visits to receive radiation treatments and another visit after treatment is completed to discuss whether you have had any side effects of treatment. All of the other visits you receive and blood tests or scans you undergo are part of your standard of care.

Assignment to Study Groups –

All patients who participate in this study will receive the same treatment. There will not be a "placebo" group or other control group not receiving the investigational treatment.

Study Procedures - as a participant, you will undergo the following procedures:

- You will have an enrollment visit to determine if you are eligible for the trial. During this visit, you will be asked about your medical history and symptoms, you will undergo a physical examination, and the doctor will review your medical records including lab tests and imaging. You may be asked to provide additional blood and urine samples. The design and intent of the study will be discussed with you and you will sign this informed consent form. This study will be similar to a standard medical office visit and will require approximately one hour.

- If you decide to participate in the study, you will receive three radiation treatments. Radiation therapy is considered one of many appropriate treatments for patients in your clinical situation; however it would not necessarily be performed in all cases. Each appointment will involve an outpatient visit to the radiation oncology clinic, a brief physical examination and discussion of your symptoms, and a radiation treatment. The radiation treatment may require you to lie still in the treatment machine for a period of time, but it will not be painful. The three visits will be approximately 12-16 days apart. Each visit will likely require a total of 2-3 hours.

- You will have an additional follow up visit with the radiation oncology doctors following your final radiation treatment, to discuss any side effects you may have had. This will be similar to a standard office visit and will likely require between 15 and 30 minutes.

- Before, during, and after your radiation treatments, it is expected that you will have office visits with your medical oncologist to receive your checkpoint inhibitor therapy. These visits are **standard care**, meaning that you would undergo them regardless of whether or not you were on the trial. It is expected that after completing your radiation treatments and several doses of checkpoint inhibitor therapy, your medical oncologist will order another CT or MRI scan to determine if your disease has gotten better, worse, or remained the same. You will have an appointment with your urologist (surgeon) to discuss whether or not to proceed with surgery. These visits and tests are also **standard care**.

- Approximately four to eight weeks after completing radiation therapy, you will undergo surgery (radical cystectomy or removal of the bladder). This is a major surgery that usually involves a hospital stay of five to ten days in the hospital and carries a significant risk of complications. Your urologist will discuss this surgery with you in detail. The surgery is considered **standard care**.

- You will see your urologist 30 days after surgery and you will continue to follow up with your medical oncologist at regular intervals. You will have labs and CT or MRI scans at every three to four months to determine if your disease has returned or progressed. Your medical oncologist may decide to resume you on checkpoint inhibitor treatments following surgery. All of these visits, and all of the care you receive after completing your radiation treatments, are considered **standard care**.

Could your participation end early? There are several reasons why the researchers may need to end your participation in the study (early withdrawal). Some reasons are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is stopped.

The researchers will discuss your options for medical care when your participation in this study ends.

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 known genes 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 genetic information to identify you.

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 data and/or tissue samples.

It is possible that this type of testing will identify information about you that was previously unknown, such as disease status or risk. There are no plans to provide this information to you or your physician.

Risks – "What are the risks of participation in the research?"

Risks from the research

The investigators have designed this study to learn how well the addition of radiation therapy to checkpoint inhibitors compares to the commonly accepted treatment of checkpoint inhibitors alone. There is a risk that the addition of radiation will not be effective in treating the disease. It is possible, though unlikely, that the radiation treatments could make the disease worse. It is possible that receiving the radiation and checkpoint inhibitor treatments will cause a delay in surgery (for example, if you have complications from the radiation or if the cancer fails to respond to treatment) that will reduce your chances of being cured by surgery.

Risks from the specific research procedures (drug(s), interventions, or procedures)

There are risks to taking part in this research study. One risk is that you may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, the study doctors don't know all the side effects that may happen. Be sure to tell your study doctor immediately, about any side effect that you have while taking part in the study.

Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or fatal (could cause death). The frequency that people experience a certain side effect can range from many (likely), few (less likely) or only one or two (rarely).

There may be additional unforeseeable side effects that could be life threatening or fatal (could cause death).

By combining radiation therapy with immune checkpoint inhibitor therapy, you will be exposed to the risks of both treatments as listed below. However, it is also possible that the combination of the two treatments could

lead to additional complications that we are unable to predict or anticipate, or could increase the chance that you suffer a known complication. You and other patients participating in the study will be monitored closely for the development of any such complications.

Risks associated with radiation therapy:

The radiation therapy (PULSAR) in this research is similar to a standard technique called Stereotactic Ablative Radiation Therapy (SAbR), which is often used in patients with bladder and other cancers that have spread elsewhere in the body.

The radiation therapy treatment for this study is standard of care, however, its combination with ICI is not. Your radiation doctor will discuss the known risks of radiation therapy with you and ask you to sign a separate specific treatment site consent form. Possible side effects of radiation therapy include:

Prostate/Testicular Short Term Effects:

1. Inflammation of bowel causing cramping and diarrhea.
2. Inflammation of rectum and anus causing pain, spasm, discharge, bleeding.
3. Bladder inflammation causing burning, frequency, spasm, pain, and/or bleeding.
4. Skin changes: redness, irritation, scaliness, blistering or ulceration, coloration, thickening, hair loss,
5. Depression of blood counts leading to increased risk of infection and/or bleeding.
6. In children, there reactions are likely to be intensified by chemotherapy before, during, or after radiation therapy.
7. In children, depression of blood counts leading to increased risk of infection and/or bleeding is more common.

Prostate/Testicular Long Term Effects:

1. Bowel damage causing narrowing or adhesions of the bowel with obstruction, ulceration, bleeding, chronic diarrhea, or poor absorption of food elements and may require surgical correction or colostomy.
2. Bladder damage with loss of capacity, frequency of urination, blood in urine, recurrent urinary infections, pain, or spasm which may require urinary diversion and/pr removal of bladder.
3. Changes in skin texture and/or coloration, permanent hair loss, and scarring of skin/
4. Bone damage leasing to fractures.
5. Testicular damage causing reduced sperm counts, infertility, sterility, or risk of birth defects.
6. Impotence (loss of erection) or sexual dysfunction.
7. Swelling of the genitalia or legs.
8. Nerve damage causing pain, loss of strength or feeling in legs, and/or loss of control of bladder or rectum
9. Fistula between the bowel and other organs.
10. In children, there may be additional late reactions as follows:

a. Disturbances of bone and tissue growth.
b. Bone damage to pelvis and hips, causing stunting of bone growth and/or abnormal development.
c. Secondary cancers developing in the irradiated areas

Female Pelvis Short Term Effects:

1. Inflammation of bowel causing cramping and diarrhea.
2. Inflammation of rectum and anus causing pain, spasm, discharge, bleeding.
3. Bladder inflammation causing burning, frequency, spasm, pain, bleeding.
4. Skin changes: redness, irritation, scaliness, blistering or ulceration, coloration, thickening, hair loss.
5. Disturbance of menstrual cycle.

6. Vaginal discharge, pain, irritation, bleeding.
7. Depression of blood counts leading to increased risk of infection and/or bleeding.
8. In children, these reactions are likely to be intensified by chemotherapy before, during, or after radiation therapy.
9. In children, depression of blood counts leading to increased risk of infection and/or bleeding is more common.

Female Pelvis Long Term Effects:

1, Bowel damage causing narrowing or adhesions of the bowel with obstruction, ulceration, bleeding, chronic diarrhea, or poor absorption of food elements and may require surgical correction or colostomy.
2. Bladder damage with loss of capacity, frequency of urination, blood in urine, recurrent urinary infections, pain, or spasm which may require urinary diversion and/or removal of bladder.
3. Changes in skin texture and/or coloration, permanent hair loss, and scarring of skin.
4. Bone damage leading to fractures.
5. Ovarian damage causing infertility, sterility, or premature menopause.
6. Vaginal damage leasing to dryness, shrinkage, pain, bleeding, or sexual dysfunction
7. Swelling of the genitalia or legs.
8. Nerve damage causing pain, loss of strength or feeling in legs, and/or loss of control of bladder or rectum.
9. Fistula between the bladder and/or bowel and/or vagina.
10. In children, there may be additional late reaction as follows:
a. Disturbances of bone and tissue growth.
b. Bone damage to pelvis and hips, causing stunting.
c. Secondary cancers developing in the irradiated area.

Risks associated with immune checkpoint inhibitor (ICI) therapy

These drugs are approved by the Food and Drug Administration, and you are receiving them as part of the "standard of care", meaning that they are not experimental. Being on one of these drugs is a requirement to participate in the study, but it is not part of the study. The risks of these drugs are listed below.

ICI drugs act by "turning up" your own immune system, making it easier for the immune system to recognize and attack tumor cells. In rare cases, it is possible for the drugs to cause the immune system to attack the body's own healthy cells in various parts of the body, which can cause a wide variety of symptoms. These reactions are often mild and improve when the ICI treatment is stopped; however, in rare cases they may be severe or life-threatening and may result in irreversible complications.

It is possible that administering radiation therapy together with the ICI drug will cause the drug to work better, because the radiation therapy will cause tumor breakdown which will allow the immune system to recognize and attack the tumor better. It is also possible that administering the two together will increase the risk of the immune system attacking your own normal tissues. Your doctor will monitor you closely for any adverse reaction.

As for any cancer treatments, ICI drugs may not work for all patients. If the drug is not effective, it is possible that your cancer will progress while you are being treated.

In general, risks of ICI drugs include the following:

Common (> 10%)

- Edema (swelling)

- Arrhythmia (irregular heartbeat)
- Skin itching or rash
- Blood sugar disturbances
- Electrolyte disturbances
- Weight loss
- Diarrhea
- Constipation
- Appetite loss
- Nausea or vomiting
- Blood in urine
- Infections
- Decreased blood counts
- Fatigue
- Headache
- Aches and pains
- Impaired kidney function
- Cough
- Shortness of breath
- Fever

Less likely (1-10%)

- Thyroid function disturbances
- Bowel irritation
- Difficulty swallowing
- Liver function disturbances
- Neuropathy (nerve injury causing “tingling” or loss of sensation)
- Neck pain
- Eye inflammation
- Kidney failure
- Lung inflammation

Rare, but serious (< 3%)

- severe autoimmune disease including myasthenia gravis, Guillian-Barré syndrome (GBS), lupus, hypophysitis, type 1 diabetes, pancreatitis, nephritis, vasculitis, pneumonitis, colitis, adrenal insufficiency, hepatitis, Stevens-Johnson syndrome (SJS)
- heart attack

Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Males: Being in this research may damage your sperm, which could cause harm to a child that you may father while on this study. If you take part in this study and are sexually active, you must agree to use a medically-acceptable form of birth control. Medically-acceptable forms of birth control include:

(1) surgical sterilization (vasectomy), or
(2) a condom used with a spermicide (a substance that kills sperm).

Females: If you are part of this study while pregnant or breast-feeding an infant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females cannot participate in the study. If you can become pregnant, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you participate in this study. If you take part in this study and you are sexually active, you and any person that you have sex with must use medically-acceptable birth control (contraceptives) during the study and for 90 days following completion of therapy. Medically-acceptable birth control (contraceptives) includes:

(1) surgical sterilization (such as hysterectomy or "tubes tied"),
(2) approved hormonal contraceptives (such as birth control pills, patch or ring; Depo-Provera, Implanon),
(3) barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm), or
(4) an intrauterine device (IUD).

If you do become pregnant during this study, you must tell the researchers immediately.

Radiation exposure to a woman's reproductive organs may harm an embryo or fetus. Also, if radioactive materials are used for certain types of scans, harm may come to an embryo, fetus, or an infant who is breast feeding.

The following section will describe the risks related to each your participation in this research study. You should talk to your study doctor about any side effects or other problems that you have while taking part in the study.

For more information about risks and side effects, ask one of the researchers or study staff.

Genetic Informational risks

This research study does not include genetic testing.

Are there risks related to withdrawing from the study?

If you decide to withdraw from this study early, please discuss your decision with the principal investigator. The researcher may ask you to complete study withdrawal procedures at a final study visit. This visit will include a discussion of your symptoms and an examination. There is no risk to you if you do not complete the final withdrawal procedures and you can choose not to participate in them.

Reproductive Risks -

Concerns for sexually active women: You should not become pregnant while taking part in this study because we do not know how the study drugs/procedures could affect a fetus, if a woman becomes pregnant during the study. It is important that you talk to your study doctor about avoiding pregnancy during this study. If you think you might have become pregnant while you are in this study, you must tell one of the study doctors right away so that management of the pregnancy and the possibility of stopping the study can be discussed.

Concerns for sexually active men and women: Women should not become pregnant and men should not father a baby while taking part in this study because we do not know how the study drugs/procedures could affect a man's sperm (for some drugs/procedures, the concern may be that the sperm might be affected and in some cases, drugs could being carried by the semen into the vagina and cause harm) or a fetus, if a woman becomes pregnant during the study. It is important that you talk to your study doctor about avoiding pregnancy during this study. If you think you might have become pregnant or if you believe your female partner has

become pregnant while you are in this study, you must tell one of the study doctors right away so that management of the pregnancy and the possibility of stopping the study can be discussed.

If you are a woman who is pregnant or could be pregnant, you cannot take part in this study because we do not know how the procedures might affect a developing fetus. We will do a pregnancy test before you start treatment to make sure you are not pregnant.

Risks to babies who are being breastfed: Women who are breastfeeding cannot take part in this study because we do not know what effect the procedures might have on their breast milk.

Are there risks if you also participate in other research studies?
Being in more than one research study at the same time, or even at different times may increase the risk to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers.

What if a research-related injury occurs?
The researchers have taken steps to minimize the known or expected risks. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. In the event of a research-related injury or if you experience an adverse reaction, please immediately contact your study doctor. See the section "Contact Information" for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We have no plans to give you money if you are injured. The investigator can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study.

Benefits – "How could you or others benefit from your taking part in this study?"

The possible benefit of your participating in this study is that you may have a reduced risk of having your bladder cancer return (recur) or spread elsewhere in your body (metastasize) after surgery.

There is no guarantee or promise that you will receive any benefit from this study.

We hope the information learned from this study will benefit other people with similar conditions in the future.

Alternative procedures or course of treatment – "What other options are there to participation in this study?"

There are other options available to you. Your other choices may include:

- participating in another clinical trial, if any is available
- receiving ICI treatment, with or without surgery, without receiving radiation
- receiving surgery only, without any additional treatment (however, patients being screened for this study will already have decided to start ICI and so this will likely not apply to you)
- receiving "trimodal" therapy, with chemotherapy and a higher dose of radiation, instead of surgery (however, patients being screened for this study will likely have already received chemotherapy or will be ineligible for chemotherapy and so this will likely not apply to you)

- refusing treatment for your bladder cancer, with the understanding that this will likely lead to the disease spreading elsewhere in the body and becoming incurable

Payments – Will there be any payments for participation?

No. You will not be paid to take part in this research study. There are no funds available to pay for parking expenses, transportation to and from the research center, lost time away from work and other activities, lost wages, or child care expenses.

Costs – Will taking part in this study cost anything?

You or your health insurance company will be responsible for the cost of treatments and procedures performed on this protocol, as all are considered within the "standard of care". This includes office visits, blood tests, imaging studies (CT scans or MRI scans), surgery, radiation, and hospital admissions. It is important to understand that some insurance companies do not cover some costs (for example, approved drugs used in a way different from the package instructions). If your insurance company does not cover these treatments or procedures, you will be required to pay for them. Ask the researchers if you have any questions about what it will cost you to take part in this study (for example bills, fees, or other costs related to the research).

Confidentiality – How will your records be kept confidential?

Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

How will my information and/or tissue samples be used?
With appropriate permissions, your samples and collected information may also be shared with other researchers here, around the world, and with companies.

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. 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.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study. Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your medical record. The information included in your medical record will be available to health care providers and authorized persons including your insurance company.

What is Protected Health Information (PHI)?
Protected Health Information is information about a person's health that includes information that would make it possible to figure out whose it is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for this research study. In carrying out this research, the health information we will see and use about you will include:

- your name, age, sex, and race
- clinical details related to your bladder cancer including stage, grade, pathologic details, and results of any other testing you undergo
- details related to the cancer treatments you have received previously or will receive in the future
- results of your lab tests and scans
- details related to your surgical treatment including time in the operating room, blood loss, postoperative length of stay
- details related to complications of treatment including hospital readmissions
- details related to your cancer outcomes (for example, whether or not your disease recurs and when)

We will get this information by asking you, asking your doctor, and/or by reviewing your chart at UT Southwestern Medical Center or Parkland Memorial Hospital.

How will your PHI be shared?
Because this is a research study, we will be unable to keep your PHI completely confidential. We may share your health information with people and groups involved in overseeing this research study including:

- The committee that checks the study data on an ongoing basis, to determine if the study should be stopped for any reason.
- The members of the local research team.
- The Institutional Review Board, Human Research Protection Program Office and the Compliance Office of the University of Texas Southwestern Medical Center, and other groups that oversee how research studies are carried out.
- The Research offices at the University of Texas Southwestern Medical Center and/or Parkland Health and Hospital System.
- The Food and Drug Administration (FDA) and other U.S. and international governmental regulatory agencies involved in overseeing drug or device research.
- Representatives of domestic and foreign governmental and regulatory agencies may be granted direct access to your health information for oversight, compliance activities, and determination of approval for new medicines, devices, or procedures.

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in the research study.

Parts of your PHI may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail or fax. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

How will your PHI be protected?
In an effort to protect your privacy, the study staff will use code numbers instead of your name, to identify your health information. Initials and numbers will be used on any photocopies of your study records, and other study materials containing health information that are sent outside of the University of Texas Southwestern Medical Center and/or Parkland Health and Hospital System for review or testing. If the results of this study are reported in medical journals or at meetings, you will not be identified.

Do you have to allow the use of your health information?

You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties but you will not be allowed to participate in the study.
After you enroll in this study, you may ask the researchers to stop using your health information at any time . However, you need to say this in writing and send your letter to Solomon Woldu, MD, 2001 Inwood Road, WCB3, 4th floor, Dallas, Texas 75390-9164. If you tell the researchers to stop using your health information, your participation in the study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?
The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study.

You will only have access to your PHI through the study staff until the conclusion of the study.

How long will your PHI be used?
By signing this form, you agree to let us use and disclose your health information for purposes of the study until two years beyond the end of the study. This permission to use your personal health information expires on the date noted above.

Contact Information – Who can you contact if you have questions, concerns, comments or complaints?

If you have questions now, feel free to ask us. If you have additional questions, concerns, comments or complaints later or you wish to report a problem which may be related to this study please contact the study team at 214-645-8787 during normal business hours or 214-645-8765 after hours and on weekends.

The University of Texas Southwestern Medical Center Human Research Protection Program (HRPP) oversees research on human subjects. HRPP and Institutional Review Board (IRB) representatives will answer any questions about your rights as a research subject, and take any concerns, comments or complaints you may wish to offer. You can contact the HRPP by calling the office at 214-648-3060.

Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research, sign this section. You will be given a copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE FOLLOWING STATEMENTS ARE TRUE:

- You have read (or been read) the information provided above.
- Your questions have been answered to your satisfaction about the research and about the collection, use and sharing of your protected health information.
- You have freely decided to participate in this research or you are voluntarily giving your consent for another person to participate in this study because you believe this person would want to take part if able to make the decision and you believe it is in this person's best interest.
- You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. Information in your medical record will be available to health care providers and authorized persons including your insurance company.
- You authorize the collection, use and sharing of your protected health information (another person's

protected health information) as described in this form.

Adult Signature Section

Printed Name of Participant	Signature of Participant	Date	Time AM PM
Printed Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date	Time AM PM

Printed Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date	Time

Witness / Interpreter Signature Section

Interpreter/witness (Interpreter signature required per hospital policies when physically present.)
I attest that I have interpreted the information in this consent form and it was explained to, and apparently understood by the subject or the subject's legal authorized representative, and that informed consent was freely given by the subject or the subject's legally authorized representative as indicated by their signature on the associated **short form**.

Printed Name of Interpreter	Signature of Interpreter	Date	Time AM PM

Witness Signature (required when interpreter is not physically present-e.g., Language Line is used):
By signing below:
I attest that the information in the consent form was accurately explained to, and apparently understood by the subject or the subject's legal authorized representative, and that informed consent was freely given by the subject or the subject's legally authorized representative as indicated by their signature on the associated **short form**.

Printed Name of witness	Signature of witness	Date	Time AM PM

Title of Study: Checkpoint Inhibitor and Radiation Therapy in Bulky, Node-positive Bladder Cancer (CIRTiN-BC)

Blind or Illiterate Signature Section *At the time of consent, also complete this section if consent is obtained from an individual who is unable to read and/or write but can otherwise communicate and/or comprehend English (e.g., blind, physically unable to write, etc.)*

Declaration of witness:
By signing below, I confirm I was present for the entire consent process. The method used for communication (e.g., verbal, written, etc.) with the subject was: _____ .

The specific means (e.g., verbal, written, etc.) by which the subject communicated agreement to participate was: _____.

			AM PM
Printed Name of Witness	Signature of Witness	Date	Time