ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A032002

PHASE II RANDOMIZED TRIAL OF IMMUNOTHERAPY VERSUS IMMUNOTHERAPY AND RADIATION THERAPY FOR PLATINUM INELIGIBLE/REFRACTORY METASTATIC UROTHELIAL CANCER (IMMORTAL)

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Pre-Activation
[X] Therapy / Dose Modifications / Study Calendar changes	[ ] Activation
[ ] Informed Consent changes	[ ] Closure
[ ] Scientific / Statistical Considerations changes	[ ] Suspension / temporary closure
[ ] Data Submission / Forms changes	[ ] Reactivation
[X] Editorial / Administrative changes	
[X] Other: Updated CTSU boilerplate language	

No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Cover Page
- The phone numbers and institution names have been removed from the co-chairs' contact information.
- Drs. [redacted] and [redacted] have replaced Dr. [redacted] as the new GU Committee Co-chairs. With this change, Dr. [redacted] Bladder Cancer [redacted] title has been removed.
- The Primary Statistician's email has been updated.

Protocol Contacts (Page 2)
- The institution name and phone number for the A032002 Nursing Contact have been removed.
- [redacted] has replaced [redacted] as the A032002 Pharmacy Contact.

Section 4.1 Investigator and Research Associate registration with CTEP
This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 4.2 Cancer Trials Support Unit registration procedures

This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 4.2.2 Protocol specific requirements for A032002 site registration

This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 4.4 Patient Registration Procedures

This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 6.1.2 (Medidata Rave)

This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 6.1.4 (Rave-CTEP-AERS integration)

This section has been completely removed as this study will no longer be using the Rave-CTEP-AERS system for reporting serious adverse events. Subsequent sections have been renumbered accordingly.

Section 6.3.1 TRIAD Access Requirements

The second bullet has been revised its entirety to align with current CTEP boilerplate language.

Section 8.2.1 General AE Management and Dose Modification Guidelines for Pembrolizumab (MK-3475)

In the "Table for Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions Associated with Pembrolizumab", item #3 under 'General Instructions' has been revised to the following: "Generally, when corticosteroids (prednisone) are used, investigators should begin a taper when the irAE is ≤Grade 1 and continue at least 4 weeks."

Section 9.1.1 CTEP-AERS integration

The section entitled "Rave-CTEP-AERS integration" has been completely removed as the trial is now IND exempt due to the change in drug from "atezolizumab" to "pembrolizumab." Subsequent sections have been renumbered accordingly.

Section 9.3 Expedited Adverse Event Reporting (Rave-CTEP-AERS)

- The section heading has been updated to the following as this study will no longer be using the Rave-CTEP-AERS system for reporting serious adverse events: "Expedited Adverse Event Reporting (~~Rave-~~CTEP-AERS)."

-This section has been completely updated as this study will no longer be using the Rave-CTEP-AERS system for reporting serious adverse events.

UPDATES TO THE MODEL CONSENT:

There have been no changes made to the model consent.

A replacement protocol document and model consent form have been issued

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ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

Research Study Informed Consent Document

Study Title for Participants: Immunotherapy with or without radiation therapy for metastatic urothelial cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Alliance A032002, "Phase II Randomized Trial of Immunotherapy Versus Immunotherapy and Radiation Therapy for Platinum Ineligible/Refractory Metastatic Urothelial Cancer (IMMORTAL) (NCT04936230)"

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.

We are asking you to take part in this research study because you have urothelial cancer that has spread and is either not responding to platinum chemotherapy or you are unable to have platinum 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 clinical trials and general cancer information.

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

Why is this study being done?

This study is being done to answer the following question:

Does adding radiation therapy to immunotherapy decrease the growth or spread of urothelial cancer?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your urothelial cancer. The usual approach is defined as care most people get for urothelial cancer.

What is the usual approach to my urothelial cancer?

The usual approach for patients who are not in a study is treatment with immunotherapy alone. The drug, pembrolizumab, is what is used as immunotherapy in this study. Pembrolizumab is FDA approved for patients who are ineligible to receive platinum containing chemotherapy or who have already received platinum containing chemotherapy. 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.

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 research 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 get either immunotherapy or immunotherapy plus radiation therapy. You will get immunotherapy until your disease gets worse or side effects become too severe.

After you start immunotherapy, you will have physical exams and imaging scans every 3 months. You will have blood and urine samples collected 6 weeks after agreeing to take part in this study and again at 3 months after beginning this study. Your doctor will continue to follow your condition for 3 years after initiation of immunotherapy and watch you for side effects.

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 immunotherapy plus radiation may not be better compared to immunotherapy alone at shrinking and controlling your cancer.

There is also a risk that you could have side effects from immunotherapy plus radiation. These side effects may be worse and may be different than you would get with the usual approach for you. These side effects depend on the portion of the body that receives radiation.

Some of the most common side effects that the study doctors know about are dependent on the irradiated area:

- Chest/Lungs
    - Fatigue
    - Cough
    - Reflux
    - Shortness of breath
- Abdomen
    - Fatigue
    - Nausea
    - Cramps
    - Diarrhea
- Pelvis
    - Fatigue
    - Cramps
    - Diarrhea
    - Frequent Urination
- Bone
    - Fatigue
    - Pain flare

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

Benefits

There is evidence that immunotherapy plus radiation is effective in shrinking or stabilizing your type of cancer. It is not possible to know now if this approach will extend your life or extend your time without disease compared to the usual approach. 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. This may mean slowly stopping the study drugs so that there is not a sudden unsafe change causing risk to your health. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

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.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (Alliance for Clinical Trials in Oncology). 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 alone to using radiation plus the usual treatment. The addition of radiation to the usual treatment could shrink your cancer. But, it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out 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 radiation stabilizes or decreases tumors of patients by 6 months compared to the usual approach.

There will be about 144 people taking part in this study.

What are the study groups?

This study has 2 study groups.

- **Group 1**

  If you are in this group, you will get the usual type of drug used to treat this type of cancer, pembrolizumab. You will get this drug through a vein in the arm once every 3 weeks.

  There will be about 72 people in this group.

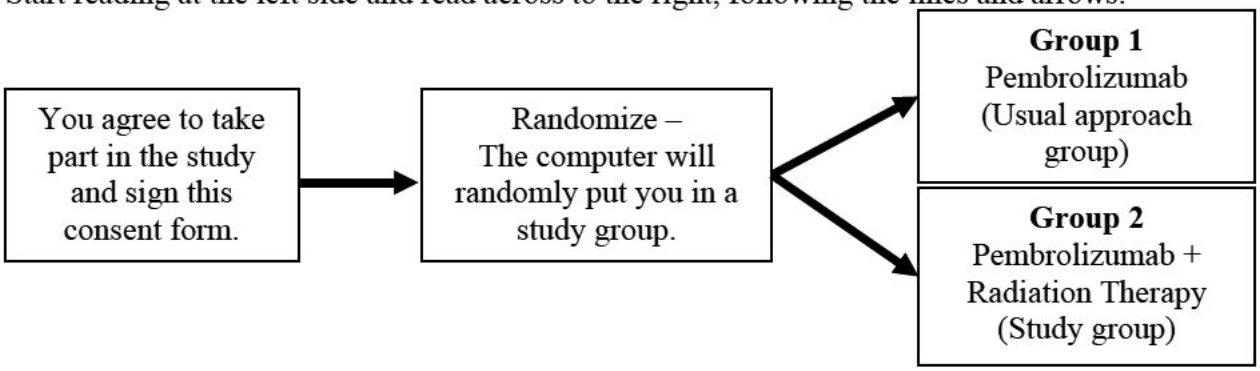
- **Group 2**

  If you are in this group, you will get radiation therapy plus the usual type of drug used to treat this type of cancer, pembrolizumab. You will get pembrolizumab through a vein in the arm once every 3 weeks. The radiation will be once a day, every other day for a total of 3 treatments. Multiple radiation treatment planning options exist for treating tumors with radiation therapy. These include 3-dimensional conformal radiation treatment, intensity-modulated radiation treatment, and stereotactic body radiation treatment. Your treating radiation oncologist will have the option to decide which treatment is in your best interest.

  There will be about 72 people in this group.

We will use a computer to assign you to one of the study groups. 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 a 50% chance of being in Group 1 or Group 2.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the 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.

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 immunotherapy plus radiation therapy may not be better than the usual approach at decreasing the growth or spread of urothelial cancer.

You also may have the following discomforts:

- 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 immunotherapy used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 4 months after you have completed the study.

Side Effect Risks

The immunotherapy and radiation therapy used in this study may affect how different parts of your body work 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 study if you receive radiation therapy.

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 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.

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 and Group 2 – Possible side effects of Pembrolizumab are listed in the tables below. This drug is part of the usual approach for treating this type of cancer.

Possible Side Effects for Pembrolizumab (MK-3475)
(CAEPR Version 2.7, December 13, 2022)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Pembrolizumab (MK-3475), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Pembrolizumab (MK-3475), from 4 to 20 may have:
• Nausea • Loss of appetite • Pain in back • Joint stiffness • Cough • Swelling and redness of the skin Pembrolizumab (MK-3475) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Anemia which may require blood transfusion • Pain in lymph nodes • Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness • 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
- 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
- Diarrhea
- Sores in the mouth which may cause difficulty swallowing
- Pain in belly
- Sores in the bowels
- Chills, fever
- 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
- Pain or swelling of the joints
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives

RARE, AND SERIOUS

In 100 people receiving Pembrolizumab (MK-3475), 3 or fewer may have:

- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss
- Swelling of the gall bladder
- Swelling of the spinal cord
- Feeling of "pins and needles" in arms and legs
  Redness, pain or peeling of palms and soles

Pembrolizumab (MK-3475) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body.
- Swelling and redness of the eye which may cause blurred vision with a chance of blindness
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin
- Damage to organs in the body when the body produces too many white cells
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.
- Swelling of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures and stiff neck
- 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.
- Swelling or tenderness of blood vessels

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Additional Drug Risks

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Possible Side Effects of Radiation Therapy

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, 20 to 100 may have:
• Reddening, tanning, or peeling of the skin • Mild pain • Hair loss • Tiredness • Diarrhea, nausea • Anemia, which may require transfusion • Infection, especially when white blood cell count is low

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, 4 to 20 may have:
• Thickening and numbness of the skin • Sores or ulcers on the skin or near the cancer location • Permanent hair loss • Bleeding from the skin • Sores in mouth which may cause difficulty swallowing

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• Damage to internal organs • Abnormal opening in internal organs which may cause pain and bleeding

What are my responsibilities in this study?

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

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research 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 5 months after your last dose of pembrolizumab

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 urothelial cancer. This includes:

- The costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- The costs of getting the immunotherapy ready and giving it to you.
- Your insurance co-pays and deductibles.
- The costs of radiation therapy.
- The costs of a biopsy if your physician deems it necessary.

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 have to pay for the immunotherapy 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 it works with to review research.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research.
- Imaging and Radiation Oncology Core (IROC).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly 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 and shared 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 if you agree 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.

Alliance for Clinical Trials in Oncology and Alliance Data Innovation Lab

The Alliance for Clinical Trials in Oncology and Alliance Data Innovation Lab, (a component of Alliance), are working on a special project called ICAREdata®. The goal of the ICAREdata® project is to develop ways to make it easier to provide health information that is necessary to answer research questions in future studies.

Only at selected sites participating in ICAREdata®, as a part of the main study your doctor will be collecting information about your health and your study treatments. This information is usually collected using a system that is separate from your hospital health record. The ICAREdata® study is being done to see if there is an easier, simpler way to collect your health information for research studies. The health information being collected by ICARE data® is limited to the same information that would usually be collected from your hospital health record when you participate in a research study. To do this, the study will also collect your health information pertaining to this clinical trial directly from your hospital or medical center's health records. The study may also compare these two ways of collecting your health information. The researchers will see if these two ways of reporting health information give the same result. This research may help to create a way to collect health information that is much faster and easier than how it is currently collected. If these two ways of collecting health information give the same result, then the easier ICAREdata methods can be used in future studies.

As part of this research study your health information pertaining to this clinical trial will be collected directly from your hospital health records. The information will be sent electronically in a secure record file to the Alliance Data Innovation Lab. This information will be compared to the information collected in the usual way for research as described above. Your health information will become a part of research data that is being used to improve data collection in people with cancer.

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

- All identifiers, such as your name, initials, and contact information will be removed from your health information. Your name will be replaced with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the rest of the information.
- Researchers outside of the Alliance Data Innovation Lab who study your information will not know who you are. They also must agree that they will not try to find out who you are.
- Your personal information will not be given to anyone unless it is required by law.
- If research results are published, your name and other personal information will not be used.

After identifiers have been removed, your information may be shared with other researchers (researchers who are not part of the Alliance Data Innovation Lab). Your health information will only be used for research in preventing, diagnosing, and treating cancer, or improving the health of people with cancer.

Where can I get more information?

You may visit the 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 the study 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 quality of life study

If you are an English speaker and choose to take part in this study, you will be asked to fill out a form with questions about your physical, functional and emotional well-being. Researchers will use this information to study how bladder cancer and bladder cancer treatments affects overall quality of life.

Since these forms are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

You will be asked to fill out these forms 5 times:

- ≤ 21 days prior to study enrollment
- 45 days after study enrollment
- 6 months after study enrollment
- 12 months after study enrollment
- 24 months after study enrollment

Together, these quality of life forms will take about 10 minutes to complete each time they are completed. The forms will ask about things like fatigue, pain, urinary symptoms, physical function, social wellbeing and emotional wellbeing. You don't have to answer any question that makes you feel uncomfortable.

Please circle your answer: I choose to take part in the quality of life study and will fill out these forms:

YES NO

Unknown future studies

If you choose to take part in this optional study, your tumor tissue from previous biopsy/surgery, urine and blood will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Alliance 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.

Right now, we don't know what research may be done in the future using your 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:

1. About 4 teaspoons of blood will be collected from a vein in your arm at 4 different times: at the beginning of the study, 6 weeks, and 3 months while you are receiving treatment, and if your cancer gets worse. Urine samples will also be collected at the same 4 time points. A sample of the tissue that was collected at the time of your biopsy or surgery when you were diagnosed with cancer will also be sent to the biobank.
2. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. 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.
4. 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 sample 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 sample 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, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the biobank know. Then, any sample that remains 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 for main trial*), at (*insert telephone number of study doctor for main trial*).

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

Samples for unknown future studies:

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

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

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