ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A032001

MAIN-CAV: PHASE III RANDOMIZED TRIAL OF MAINTENANCE CABOZANTINIB AND AVELUMAB VS MAINTENANCE AVELUMAB AFTER FIRST-LINE PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH METASTATIC UROTHELIAL CANCER

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

The changes included in this update to A031801 have been made in response to the NCI Request for Rapid Protocol Amendment (RRA) from Dr. Rabih Said (rabih.said@nih.gov). This Action Letter is posted on the A031801 study page on the CTSU website. The revised CAEPR for cabozantinib with updated risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate the new risks, consistent with the NCI Model Consent Template instructions.

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.

Reconsent is required for patients consented on the study that are not yet receiving protocol treatment or currently on treatment with cabozantinib.

UPDATES TO THE PROTOCOL:

Section 9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events …

The AE Reporting table has been updated to the current version (effective date: August 30, 2024).

Section 9.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for XL184 (Cabozantinib s-malate, NSC 761968)

The CAEPR (Version 2.4, December 17, 2018) has been updated to Version 2.5, August 29, 2024 with the following changes:

- Added New Risk:
    - Less Likely: Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)
    - Rare but Serious: Endocrine disorders - Other (thyroid dysfunction)

- Deleted:
    - Also Reported on XL184 Trials but With Insufficient Evidence for Attribution: Aspiration.

UPDATES TO MODEL CONSENT:

Drug Risks

The "Possible Side Effects of Cabozantinib" table has been updated per CAEPR Version 2.5 with the following risk list changes:

- Added New Risk "In children or adolescents: may interfere with growth" in the Occasional Some May Be Serious table.

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: Testing the addition of the anti-cancer drug, cabozantinib, to the usual immunotherapy treatment, avelumab, in patients with metastatic urothelial cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol A032001, MAIN-CAV: Phase III randomized trial of maintenance cabozantinib and avelumab vs maintenance avelumab after first-line platinum-based chemotherapy in patients with metastatic urothelial cancer (NCT05092958)

Overview and Key Information

This study is being conducted by the Alliance for Clinical Trials in Oncology (Alliance), a national clinical research group supported by the National Cancer Institute (NCI). 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.

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 metastatic urothelial cancer.

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:

Can we prolong life for patients with metastatic urothelial cancer by adding a drug called cabozantinib to standard maintenance treatment avelumab?

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

What is the usual approach to my metastatic urothelial cancer?

The usual approach for patients who are not in a study is treatment with a kind of immunotherapy agent, avelumab, which is FDA approved for maintenance treatment for advanced urothelial cancer patients who do not progress after standard 1st-line platinum-based chemotherapy. Your doctor can explain which treatment may be best for you. The usual treatment 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 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 either get avelumab every 2 weeks for up to 2 years or avelumab every 2 weeks plus cabozantinib, which is a study drug targeting blood vessel formation, daily for up to 2 years.

After you finish treatment your doctor will continue to follow your condition for every 3 months for up to 5 years after you are registered to assess how you are doing.

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 avelumab plus cabozantinib may not be as good as avelumab alone at preventing your cancer from progressing or making you live longer.

There is also a risk that you could have side effects from avelumab plus cabozantinib. These side effects may be worse and may be different than you would get with the usual approach for you.

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

- Diarrhea, nausea, vomiting.
- Tiredness, taste changes, loss of appetite and weight loss.
- Redness, pain or peeling of palms and soles
- High blood pressure which may cause headaches, dizziness and blurred vision.

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

Benefits

There is evidence that the combination of cabozantinib and immunotherapy agents is effective in shrinking or stabilizing your type of cancer and delaying progression. It is not possible to know now if the combination of cabozantinib and avelumab will extend your life 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 or 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 Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor, The National Cancer Institute (NCI).

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 (avelumab) to using cabozantinib plus the usual treatment. The addition of cabozantinib to the usual treatment could shrink your cancer or prevent it from returning. 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 the combination of cabozantinib and avelumab makes patients live longer compared to the usual approach.
This treatment avelumab is already approved by the FDA for your cancer. The combination of avelumab and cabozantinib is not approved by the FDA for use in metastatic urothelial cancer.

There will be about 654 people taking part in this study.

What are the study groups?

This study has 2 study groups. You will be told which group you are in.

- **Group 1**

  If you are in this group, you will get the usual drug used to treat this type of cancer, avelumab. You will get this drug through a vein in the arm every 2 weeks for 24 months.

  There will be about 327 people in this group.

- **Group 2**

  If you are in this group, you will get a study drug called cabozantinib plus the usual drug used to treat this type of cancer, avelumab. The combination of the 2 drugs is considered investigational. You will get take cabozantinib as a single tablet you take by mouth every day for up to 24 months and avelumab through a vein in the arm over 60 minutes every 2 weeks for 24 months.

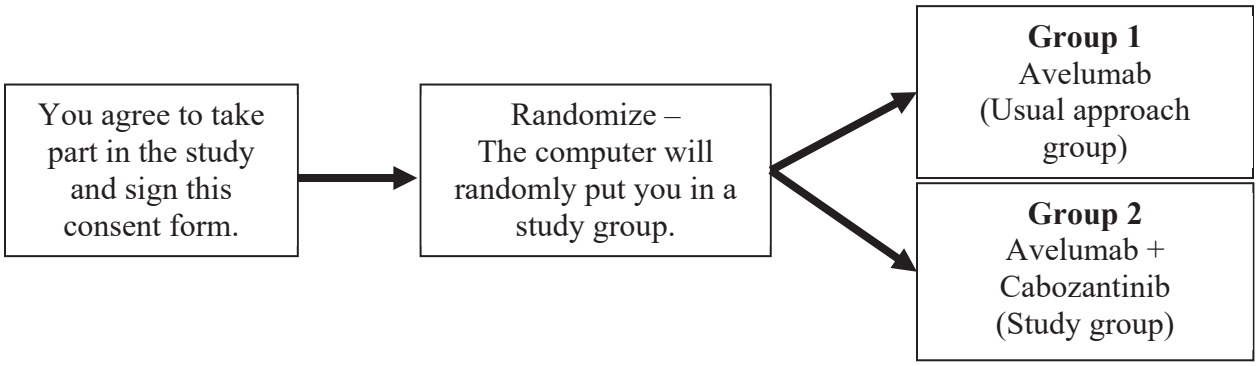
  Cabozantinib needs to be taken on an empty stomach (do not eat for at least 2 hours before and 1 hour after taking cabozantinib). Take with a full glass of water at the same

time each day. Do not crush or chew. You will be given a tablet diary for you to record each time you take cabozantinib.

There will be about 327 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 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.

If you speak English or Spanish and choose to take part in the quality of life study, you will be asked to answer questions about symptoms and side effects you may have during the study. Researchers will use this information to learn more about how cancer and cancer treatment affects people. This is an optional part of the study. There is more information about this part of the study at the end of the consent form. You will be asked if you would like to take part in this optional additional 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 cabozantinib plus avelumab may not be as good as the usual approach of avelumab alone at decreasing the growth or spread of urothelial cancer or preventing your cancer from coming back.

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 medications 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.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Side Effect Risks

The medications 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 medications.

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 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 drug 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.

Possible Side Effects of Avelumab
(CAEPR Version 2.1, June 27, 2023)

COMMON, SOME MAY BE SERIOUS In 100 people receiving avelumab, more than 20 and up to 100 may have:
• Nausea • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving avelumab, from 4 to 20 may have:
• Anemia which may require blood transfusion • Constipation, diarrhea, vomiting • Chills, fever • Swelling of the body • Infection • Reaction during or following a drug infusion which may cause fever, chills, rash, low blood pressure • Bruising, bleeding • Loss of appetite, weight loss • Dizziness, headache • Cough, shortness of breath • Dry skin • Acne, rash • High blood pressure which may cause headaches, dizziness, blurred vision Avelumab 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: • 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 [the term above is a clinical manifestation of lab values not previously listed on the risk list] • Damage to the pancreas which may cause belly pain and hospitalization

- Pain or swelling of the joints
- Problem of the muscle (myositis), which can cause muscle pain and severe muscle weakness sometimes with dark urine

RARE, AND SERIOUS
In 100 people receiving avelumab, 3 or fewer may have:

Avelumab 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 inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body
- Swelling and redness of the eye with a chance of blindness
- 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
- 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
- A condition with high blood sugar (diabetes) which leads to tiredness, frequent urination or excessive thirst which may require treatment with insulin
- Painful and enlarged lymph nodes
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement
- Inflammation of the brain (meningitis/encephalitis), 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
- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath
- Swelling and redness of the skin
- Skin: itching; rash, blisters including inside the mouth; loss of skin pigment

Possible Side Effects of Cabozantinib
(Table Version Date: August 29, 2024)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving XL184 (cabozantinib), more than 20 and up to 100 may have:

- Diarrhea, nausea, vomiting
- Tiredness
- Weight loss, loss of appetite
- Changes in taste
- Redness, pain or peeling of palms and soles
- High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving XL184 (cabozantinib), from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Constipation, heartburn • Dry mouth, skin • Sores in the mouth which may cause difficulty swallowing • Swelling of arms, legs • Infection • Bruising, bleeding • Dehydration • Muscle weakness • In children or adolescents: may interfere with growth • Dizziness, headache • Cough, shortness of breath • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine • Bleeding from multiple sites including the nose • Changes in voice • Hair loss, rash • Change in hair color • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving XL184 (cabozantinib), 3 or fewer may have:
• A tear or hole in internal organs that may require surgery • Non-healing surgical site • Damage to the jawbone which may cause loss of teeth • Bleeding in the brain which may cause confusion • Stroke which may cause paralysis, weakness • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Lung collapse

The combination of cabozantinib and immunotherapy could cause diarrhea, fatigue, liver toxicity, rash, musculoskeletal pain, decreased appetite, nausea, altered taste, abdominal pain, cough, and upper respiratory tract infection.

Additional Drug Risks

The study drug could interact with other drugs and foods. You should not eat grapefruit or Seville oranges, drink grapefruit juice or use St. John's wort while on this study and receiving cabozantinib. Taking or eating these items can raise cabozantinib levels to unsafe levels in your body. Your study doctor will give you a drug information handout and wallet card that lists these

possible interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.

For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

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

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.
- Write down in your medication diary when you take cabozantinib at home.

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 4 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 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 standard treatment avelumab ready and giving it to you.
- 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 and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- The genetic testing of the tissue.

The NCI will supply cabozantinib at no charge while you take part in this study.

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 providing the study treatments now or in the future.
- The pharmaceutical company providing the study drug (Exelixis)
- 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

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.

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.

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.

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.

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 metastatic urothelial 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 choose to take part in this study, you will be asked to fill out 3 forms with questions about your physical functional, emotional, and social well-being. If you have bladder cancer you will be asked to complete an additional questionnaire to evaluate urinary symptoms. Researchers will use this information to learn more about how cancer and cancer treatments affects people.

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 6 times during the study. This includes:

- before starting treatment
- at 3, 6, 12, 18, and 24 months after you are registered to the study.

The forms will take approximately 15 minutes for non-bladder cancer patients to complete and approximately 15-20 minutes for bladder cancer patients to complete as they have an additional questionnaire. The forms will ask about things like fatigue, pain, fatigue, insomnia, urinary function, bowel symptoms, and overall quality of life. You do not have to answer any question that makes you feel uncomfortable.

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

   YES NO

Optional analysis of radiologic images collected during the study and/or storage for possible future studies

As a part of your treatment monitoring, you will have scans at the regular timepoints that will be used in medical care. Your doctor will use the scan you had before you started treatment and all the scans while you are on treatment to study whether the treatment is working or not.

Besides using scans to study how your cancer responds, researchers are also trying to learn how to look at specific features from scans and applying algorithms to try to see whether certain items on scans can help them understand how well a patient will respond to therapy, and if there is any relationship of features seen on the scans which may increase side effects or effects on quality of life.

Researchers will use the collected scans that will already be done as standard care to help them study the role of imaging in cancer.

If you agree to participate in the imaging study, you will NOT be required to do additional scans. Scans already collected will be used for this study.

2) Please circle your answer: I agree to the study of my scans for the study mentioned above.

YES NO

Optional sample collections for known laboratory studies and/or 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.

Known future studies

If you choose to take part in this optional study, researchers will collect blood and leftover tumor tissue from previous surgery or biopsies for research on why some cancer patients respond to some treatments better than the others.

If there is no tissue leftover from when you were diagnosed with cancer, you and your doctor may choose to get another biopsy for this study if clinically indicated. You will be asked to consent to allow for collection of additional tumor tissue. Your study doctor will tell you if this is needed. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer. If you agree to get the biopsy, you may need

to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done. If you choose not to do the biopsy you may still enter this trial.

Unknown future studies

If you choose to take part in this optional study, your tumor tissue from previous biopsy/surgery, urine, stool 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 4-5 tablespoons of blood will be collected from a vein in your arm at three different times: at the beginning of the study, on the first day of Cycle 2, and if your cancer gets worse or when you stop the study treatment. A sample from the tumor that was collected at the time of your previous biopsy or surgery when you were diagnosed with cancer will be also be collected. Urine samples will be also collected at the same 3

time points. Researchers would also like to collect stool samples at 2 different timepoints: at the beginning of the study and if your cancer gets worse or when you stop the study treatment. A sample of the tumor tissue will also be collected.

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.

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 known future studies:

3) I agree that my tissue and blood samples and related health information may be used for the laboratory studies described above.

YES NO

Samples for unknown future studies:

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

YES NO

I agree that my tissue, blood, and urine 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