Study Title for Participants: Testing the effectiveness of two immunotherapy drugs (nivolumab and ipilimumab) with one anti-cancer targeted drug (cabozantinib) for rare genitourinary tumors

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Alliance A031702, A phase II study of Ipilimumab, CabOzantinib, and NIvolumab in rare genitourinary Cancers (ICONIC) (NCT03866382)

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 a rare genitourinary (GU) tumor. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like 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.

Why is this study being done?

This study is being done to test the good and bad effects of the drugs called cabozantinib, nivolumab and ipilimumab, when given in combination. This combination of drugs may or may not shrink your cancer, but it could also cause side effects, which are described in the risks section below. The study doctors hope to learn if the study drugs will stabilize or shrink your cancer.

All these drugs, cabozantinib, nivolumab and ipilimumab have already been approved by the FDA to treat other cancers individually but not in combination.

There will be about 186 people taking part in this study.

What is the usual approach to my rare genitourinary cancer?

You are being asked to take part in this study because you have been diagnosed with advanced rare genitourinary cancer. Generally speaking, there is not standard treatment option for your cancer, and you may or may not have already been treated with platinum-based chemotherapy, immunotherapy and/or a targeted therapy, and your disease is now growing. People who are not in a study are usually treated with FDA approved anti-cancer drugs that are used for other types of cancer, which may have some benefit to treat your type of cancer. These other options are not yet FDA approved for your cancer.

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

If you decide not to take part in this study, you have other choices. For example:

- 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 but you may want to receive comfort care to help relieve your symptoms.

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

If you take part in this study, for the first 12 weeks, you will take cabozantinib by mouth, once a day AND you will receive nivolumab in your vein over about 30 minutes, once every 3 weeks, AND ipilimumab in your vein over about 90 minutes, once every 3 weeks.

After the first 12 weeks, you will continue cabozantinib by mouth, once a day AND you will receive nivolumab in your vein over about 30 minutes, once every 4 weeks. You may receive cabozantinib and nivolumab continuously until you have intolerable side effects or your scans show worsening disease based on criteria that the investigator has established.

In addition, if your disease improves as a result of treatment, and this continues for 2 years (24 months) on treatment, then we will stop treatment, and monitor your disease off treatment. After you finish taking the study drugs, your doctor will continue to watch you for side effects and follow your condition for 100 days. We will also contact you every 2 months after the first 100 days to get information on your survival status.

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 this combination therapy may not be as good as other treatment options that you may have for controlling your cancer.

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

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
- As a result of treatment, your immune system may attack normal organs and cause side effects in many parts of the body, resulting in shortness of breath, diarrhea, rash, hormonal and liver problems.

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

Benefits

This treatment may stabilize or shrink your type of cancer. It is unlikely that it will work in everyone with your cancer or help you live longer. This study may help the study doctors learn things that may help other people in the future.

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

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. This may mean slowly stopping the study drugs so that there is not a sudden unsafe change, risk to your health. If you

stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The 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 Alliance Cooperative Group / National Cancer Institute (NCI), Institutional Review Board (IRB), or Food and Drug Administration (FDA).

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?

This purpose of this study is to test the effectiveness of cabozantinib with nivolumab and ipilimumab in rare genitourinary cancers that have no standard treatment options.

The combination of these drugs are not currently approved by the Food and Drug Administration (FDA), a federal agency within the US that oversees the safety of drugs and medical devices. They are considered experimental, when used for treatment of rare GU cancers. This combination has been tested together in another study and has been proven to be safe with manageable expected toxicities. Therefore, the safe doses have been established for this combination that we plan to use in this study. The rare genitourinary cancers that can be enrolled in and treated on this study are:

- Rare advanced cancers of urinary tract (bladder, renal pelvises, ureters, and urethra), such as adenocarcinoma, urachal carcinoma, squamous cell carcinoma, plasmacytoid carcinoma, micropapillary carcinoma, sarcomatoid carcinoma, and previously treated small cell carcinoma.
- Rare advanced kidney cancers, such as sarcomatoid, medullary, chromophobe, and papillary carcinomas.
- Rare advanced cancers of testicles, such as Sertoli-Leydig cell tumors.
- Advanced, previously treated, small cell carcinoma of the prostate.
- Advanced, cancers of the penis.
- Other rare genitourinary cancers collectively referred to as rare histologies.

Cabozantinib is a drug that has been approved by the FDA, to treat medullary thyroid cancer. Ipilimumab has been approved by the FDA to treat melanoma and also in combination with nivolumab, to treat the most common type of kidney cancer, clear cell carcinoma. Nivolumab has been approved by FDA to treat melanoma, clear cell kidney cancer and to treat patients with locally advanced or metastatic urothelial carcinoma (the most common type of bladder cancer), who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy.

Researchers would like to better understand the behavior of these rare cancers and to be able to predict who would respond to the treatment and who would not. Therefore, your study doctor will need to use some of the tissue left over from your biopsy when you were diagnosed with cancer. This sample is a required part of the study. If there is not enough tissue left over from your biopsy, your study doctor will need to do another biopsy to get this tissue, before starting the treatment. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer.

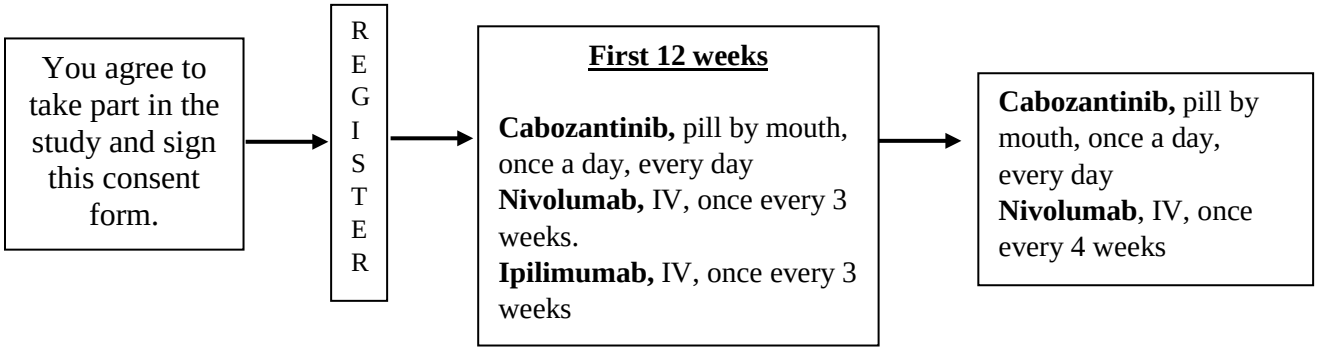
There will be up to 186 people taking part in this study.

What are the study groups?

This study has 9 different groups only based on the type of rare GU cancer that each patient has. Based on your type of cancer, you will be in one of these groups, but all 9 different groups including you, will get the same drugs (combination of cabozantinib, nivolumab and ipilimumab) and the same schedule.

Treatment schedule: For the first 12 weeks, you will take cabozantinib by mouth, once a day AND you will receive nivolumab in your vein over about 30 minutes, once every 3 weeks, AND ipilimumab in your vein over about 90 minutes, once every 3 weeks. After the first 12 weeks, you will continue cabozantinib by mouth, once a day AND you will receive nivolumab in your vein over about 30 minutes, once every 4 weeks. You may receive cabozantinib and nivolumab continuously until you have intolerable side effects, or your scan show worsening disease. In addition, if your disease improves as a result of treatment, and this continues for 2 years (24 months) on treatment, then we will stop treatment, and monitor your disease off treatment. See the study calendar for more information.

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.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

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

- If you are taking bisphosphonate medications, such as zoledronic acid, you will need a dental exam if you have not had one within the last two months.
- To monitor some of the side effects, your doctors may do electrocardiogram (ECG) and some blood work (labs) before starting your treatment and then at the beginning of each round of your treatment. These labs are prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT).
- You will be required to record when you take cabozantinib in a medication diary. The medication diary should be returned to your treating physician, along with any leftover pills that you did not take.

This study will use genetic tests that may identify changes in the genes in your DNA and your tumor DNA. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer.

Finding these changes would not affect your treatment in this study. However, they could affect your health in other ways. We do not plan to identify genetic changes that can affect your and your family's health risk, but if there are changes found that could cause health problems, then

your study doctor will discuss your options with you, such as additional confirmatory testing, and genetic counseling.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

- At the time of your enrollment, your doctors/their team will ask you a few questions to assess the level of your energy and functionality (Fatigue Assessment).
- Researches will need to use some of the tissue left over from your biopsy when you were diagnosed with cancer. This sample is a required part of the study. This specimen will be used for a review done by a central pathologist later. You will not get the results of this review.

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

General Risks

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your GU cancer at shrinking or stabilizing your 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 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 7 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.

Research Procedure Risks:

Blood Draw
Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

Radiation Risks
The CT or MRI scans that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the

sun and the environment. This type of radiation is called "background radiation". No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer.

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 drugs used to treat this type of cancer. 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 cabozantinib

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
- 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

Possible side effects of ipilimumab

Special precautions

Side effects of ipilimumab (MDX-010) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab (MDX-010) is used in combination with BMS-936558 (nivolumab). **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), more than 20 and up to 100 may have:

- Diarrhea, nausea
- Tiredness

Ipilimumab (MDX-010) 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:

- Skin: itching; rash, blisters including inside the mouth (can be severe); hives

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), from 4 to 20 may have:

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain
- Difficulty swallowing, eating
- Constipation, vomiting
- Weight loss, loss of appetite
- Fever
- Dehydration
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Low blood pressure which may cause feeling faint

Ipilimumab (MDX-010) 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:

- Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath
- 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

- 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.
- Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- 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.
- 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
- 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.

RARE, AND SERIOUS

In 100 people receiving ipilimumab (MDX-010), 3 or fewer may have:

- Bleeding
- Blockage of the bowels which may cause constipation
- Fluid around heart
- Severe illness with multiorgan failure
- Confusion

Ipilimumab (MDX-010) 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:

- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck

Possible side effects of nivolumab

Special precautions

Side effects of BMS-936558 (nivolumab, MDX-1106) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when BMS-936558 (nivolumab, MDX-1106) is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving BMS-936558 (nivolumab, MDX-1106), more than 20 and up to 100 may have:

- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving BMS-936558 (nivolumab, MDX-1106), from 4 to 20 may have:

- Anemia which may require blood transfusion
- Swelling and redness of the eye
- Pain
- Diarrhea, nausea
- Dry mouth
- Fever
- Swelling and redness at the site of the medication injection
- Bruising, bleeding
- Pain or swelling of the joints
- Loss of appetite
- Reaction during or following a drug infusion which may cause fever, chills, rash

BMS-936558 (nivolumab, MDX-1106) 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:

- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- 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.
- Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- 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
- 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.

RARE, AND SERIOUS

In 100 people receiving BMS-936558 (nivolumab, MDX-1106), 3 or fewer may have:

- Dry eyes
- Sores in the mouth which may cause difficulty swallowing

BMS-936558 (nivolumab, MDX-1106) 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:

- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- 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.
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- 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
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 therapy, since the risk and severity of transplant-associated complications may be increased.

Nivolumab and ipilimumab can cause severe and life threatening immune-mediated side effects because these medications can turn on certain types of immune cells. These immune-mediated side effects may involve any organ system; however, the most common are inflammation of the intestines, the lungs, the liver and the skin and hormonal problems. If you experience any of the side effects listed in the tables above, it is important to let your study doctor know right away. Additionally, let your study doctor know of

any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Additional Drug Risks

The study drug could interact with other drugs and food. 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. You should not consume grapefruits, grapefruit juice, Seville oranges, or St. John's wort while on this study. 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.

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 the study drug 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 120 days 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 rare GU 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 nivolumab, ipilimumab and cabozantinib 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:

- EKG at screening

The NCI will supply ipilimumab, nivolumab, and cabozantinib at no charge while you take part in this study. Even though it probably won't happen, it is possible that the manufacturer may not continue to provide these medications to the NCI for some reason. If there is no treatment available at all, the study would close.

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. Contact information for your study doctor is listed on the consent cover page.

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.

No funds have been set aside to compensate you in the event of injury.

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 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:

- Montana Cancer Consortium
- The study sponsor and any company providing the study treatments now or in the future.
- The pharmaceutical companies providing the study drugs (Bristol Myers Squibb and Exelixis)
- The 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

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.

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

Where can I get more information?

You may visit the 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 information for your study doctor is listed on the consent cover page.

For questions about your rights while in this study, you may contact the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

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 rare GU cancers 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.

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 your tumor tissue and blood sample to better understand the changes that can happen in your tumor and blood as a result of treatment. The tumor tissue the researchers are collecting here is from the tissue left over from your biopsy when you were diagnosed with cancer. This will help the researchers to be understand the behaviors of your cancer, such understanding of why one tumor responds to treatment and the other one does not.

Unknown future studies

If you choose to take part in this optional study, your tumor samples will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Alliance for Clinical Trials in Oncology 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 tumor 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.
- Future research studies may include sequencing of all or part of your DNA called genomic sequencing. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes,

piece by piece. This is usually done to look for changes in your genome that may cause health problems.

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

What is involved in this optional sample collection?

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

1. Your doctors will collect blood samples for research purposes. They plan to collect about 3-4 table spoons at 3 different time points, which are before the start of your first treatment and then at the beginning of your second and third treatments.
2. Your sample 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 of a blood draw are a small amount of bleeding at the time of the procedure, bruising, and pain at the blood draw site.
- 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 in this optional biopsy.

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, who will let the biobank know. Contact information for your study doctor is listed on the consent cover page. 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. Contact information for your study doctor is listed on the consent cover page.

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:

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

YES NO

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to learn about results from these studies.

YES NO

Samples for unknown future studies:

I agree that my tissue and blood 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.

Signature:

This study has been explained to me, and I have been told what my enrollment in the study involves. I have read all pages of this consent and have had my questions answered to my satisfaction at this time. I consent to participate in this study and any additional studies where I circled 'yes'. I understand that by signing this form I have not given up any of my legal rights. I will be given a copy of this consent form. I may also request a copy of the protocol (full study plan).

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)