Update #10

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A031704

PD-INHIBITOR (NIVOLUMAB) AND IPILIMUMAB FOLLOWED BY NIVOLUMAB VS. VEGF TKI CABOZANTINIB WITH NIVOLUMAB: A PHASE III TRIAL IN METASTATIC UNTREATED RENAL CELL CANCER [PDIGREE]

NCI-supplied agent(s): Nivolumab (NSC #748726), Ipilimumab (NSC #732442), and Cabozantinib (NSC #761968); IND #[redacted] IND holder: DCTD, NCI

ClinicalTrials.gov Identifier: NCT03793166

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

The changes included in this update to A031704 have been made in response to an RRA from Dr. Rabih Said (rabih.said@nih.gov). This Action Letter is posted on the A031704 study page on the CTSU website. Therefore, the model consent form has been revised to incorporate these new risks, consistent with the NCI Model Consent Template instructions. Additionally, a revised table for expedited AE reporting requirements has been added to the protocol. A revised CAEPR for Cabozantinib with new risks has been added to the protocol.

Because the CIRB is the IRB of record for this study, no recommended IRB level of review is provided by Alliance. This amendment must be implemented within 30 days after posting. Please refer to the amendment application and CIRB guidelines for further information.

Reconsent is required for participants who have not yet started treatment and anyone currently on treatment with cabozantinib.

Section 9.3.1 Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention

This section has been revised to include the updated AE Reporting Table. Additionally, the first four bullet points below the table have been removed as this information has been addressed in the updated AE Reporting Table.

Section 9.4 (Comprehensive Adverse Events and Potential Risks List (CAEPR) for Cabozantinib, (NSC #761968); IND #[redacted]

- 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 THE MODEL CONSENT:

What Possible Risks Can I Expect From Taking Part In This Study?

Based on the updated CAEPR described above, the following changes have been made to the NCI condensed risk profile for Cabozantinib:

- Added New Risk: Occasional: In children or adolescents: may interfere with growth

A replacement protocol document has been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

Research Study Informed Consent Document

Study Title for Participants: Immunotherapy with nivolumab and ipilimumab followed by nivolumab or nivolumab with cabozantinib for patients with advanced kidney cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol Alliance A031704, "PD-inhibitor (Nivolumab) and Ipilimumab followed by nivolumab vs. VEGF TKI cabozantinib with nivolumab: A Phase III Trial in metastatic untreated REnal Cell CancEr [PDIGREE]" (NCT03793166)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. 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 advanced or metastatic kidney 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 advanced kidney cancer, by adding a drug called cabozantinib to another treatment after receiving the standard treatment?

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

What is the usual approach to my advanced kidney cancer?

The usual approach for patients who are not in a study is treatment with drugs targeting blood vessel formation or immunotherapy, which allow the body's immune system to work against tumor cells. These are FDA-approved for advanced kidney cancer.

The investigational part of this study is the combination of nivolumab and cabozantinib that patients may be randomized to receive after ipilimumab and nivolumab.

Your doctor can explain which treatment may be best for you. Sometimes, combinations of these treatments are used. Your doctor can explain which treatment may be best for you. These treatments are proven to help patients with your type of kidney cancer live longer 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 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 receive treatment with ipilimumab and nivolumab every 3 weeks for 4 treatments (lasting about 12 weeks). Then, based on scan results, patients will be treated with either nivolumab or cabozantinib, or nivolumab and cabozantinib for up to 1 year. Treatment will be given until the disease worsens or the side effects become too severe.

After you finish treatment your doctor will continue to follow your condition by getting labs every 6 weeks and scans every 3 months until your disease worsens. Once the disease worsens the labs and scans are no longer required, and your doctor's office will check in with you once every 6 months for 5 years after you are registered to the trial to see 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 the study drugs may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the treatments (ipilimumab, nivolumab, and cabozantinib). 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
- Tiredness
- Weight loss, loss of appetite
- Changes in taste or voice
- Redness, pain or peeling of palms and soles
- High blood pressure, which may cause blurred vision

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

Benefits
If you agree to take part in this study, there may be direct medical benefit to you.

The combination of cabozantinib and nivolumab has been studied in smaller studies, and it is not possible to know now if adding cabozantinib to nivolumab 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. If you stop, you can decide if you want to keep letting the study doctor know how you are doing. This may mean slowly stopping the study drugs so that there is not a sudden unsafe change or risk to your health.

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). The study sponsor is the organization who oversees the study.

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

What is the purpose of this study?

The purpose of this study is to compare the usual treatment alone (treatment with ipilimumab and nivolumab followed by nivolumab alone) to the usual treatment with ipilimumab and nivolumab, followed by nivolumab with cabozantinib. The addition of cabozantinib to the usual treatment could shrink your cancer and prolong your life, but it may not. 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 adding cabozantinib to nivolumab can increase the percentage of patients alive at 3 years from 60% to 70%. You will have scans that will monitor the status of the cancer every 3 months.

These treatments (ipilimumab and nivolumab combination treatment, and cabozantinib treatment alone) are already approved by the FDA for use in advanced kidney cancer which has not been previously treated, but the combination of all three drugs is not FDA approved. There will be up to 1175 people taking part in this study.

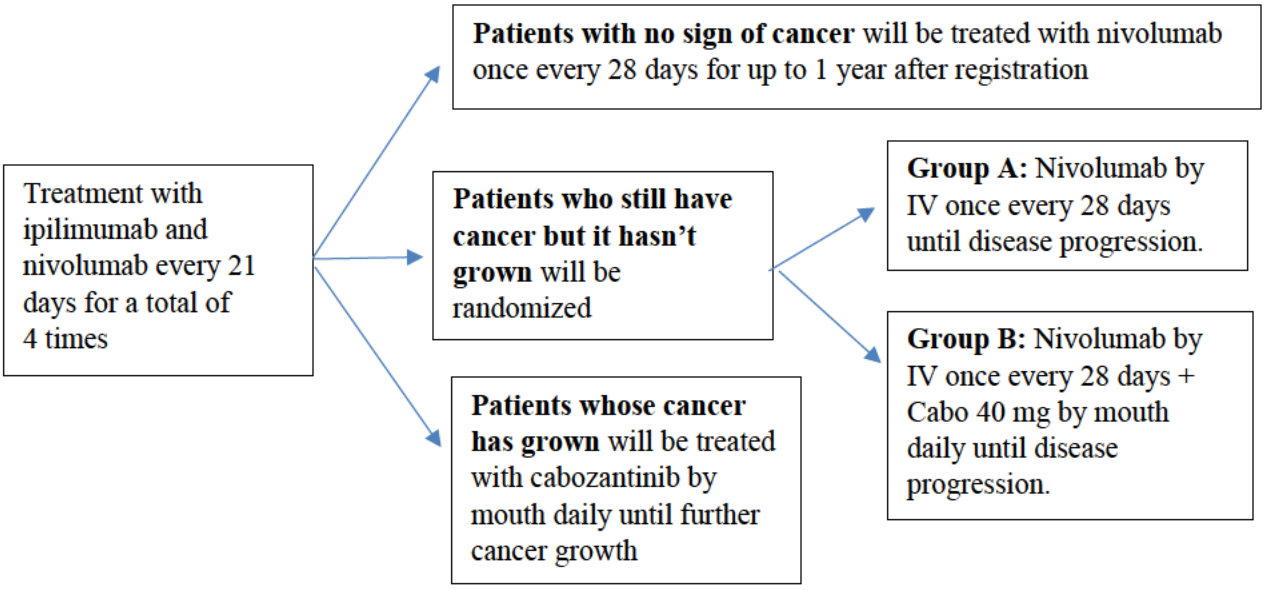
What are the study groups?

All patients who enroll on this study will first be treated with the combination immunotherapy of nivolumab and ipilimumab.

- Nivolumab is given through a vein, also called an intravenous (IV) infusion. It is given over about 30 minutes. For the first part of the study, nivolumab will be given every 21 days, up to 4 times (about 3 months).
- Ipilimumab is also given through a vein, and it usually takes about 30 minutes. There will be a minimum of 30 minutes between the end of when the nivolumab is given and the start of the ipilimumab. For this study, ipilimumab will be given the same as nivolumab, every 21 days, up to 4 doses (about 3 months).

Once you have completed the treatment with the nivolumab and ipilimumab you will have a scan and the further treatment you receive on this study will be determined by the results of the scan. You will fit into one of the categories below:

- **Patients who have no sign of cancer** on the scan will be treated with nivolumab (by IV) every 28 days for 1 year after you were first registered to the study
- **Patients whose scan still shows cancer but it hasn't grown**, will be treated with one of the following two groups:
  Group A: Patients will get nivolumab by IV every 4 weeks until your disease worsens or
  Group B: Patients will get nivolumab by IV every 4 weeks in combination with cabozantinib, which you will take by mouth daily, until your disease worsens.
  We will use a computer to assign you to one of the study groups above. 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, and it is not possible to switch to the other study group. There is a 50% chance that you will receive nivolumab and a 50% chance that you will receive nivolumab and cabozantinib.
- **Patients who scan shows that the cancer has grown** will be treated with cabozantinib, which is taken by mouth every day. You will continue to take the cabozantinib until a scan shows that the cancer has grown further.
  Cabozantinib needs to be taken on an empty stomach (do not eat 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 pill diary for you to record each time you take cabozantinib. Another way to find out what will happen to you during this study is to read the chart below. Start reading from 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.

The EKG done before treatment will 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 the EKG to carefully follow the effects of the study treatment, including preventing and managing side effects.

This study will use genetic tests that may identify changes in the genes in your DNA or 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. These tests will be done for research purposes only and will not be reported back to you.

There are several optional parts of the study, which will be described at the end of this consent form. You will be asked if you would like to take part in these optional additional studies. The optional studies include:

1) You will be asked to answer questions about how you are feeling. Researchers will use this information to learn more about how cancer and cancer treatment affects people.

2) Additional blood samples taken will be taken at different times during the study (while you are already getting blood taken for regular laboratory studies).

3) Submission of leftover tissue from your biopsy when you were first diagnosed with cancer, and biopsy tissue if your cancer comes back.

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 kidney 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.

Genetic Testing Risks

When you agree to be in this study you also agree to allow your tissue that was already collected to be sent to a lab to be tested for genetic changes. The genetic test used in this study will test your tumor for genetic changes. This change also may 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. You and your doctor will not know about the results of these tests.

Biopsy Risks

If there is not enough tissue when you register to the study you may be asked to consent to undergo a biopsy for this study. Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

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.
You will be provided with a clinical trial wallet card to indicate that you are participating in an NCI clinical trial. You should show this card to all your healthcare providers and keep the card with you at all times in case you go to the emergency room.

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 swelling, 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 swelling 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 (BMS-936558)

Special precautions Side effects of Nivolumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when Nivolumab 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 Nivolumab, more than 20 and up to 100 may have:
• Tiredness
OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Nivolumab, 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

Nivolumab 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 Nivolumab, 3 or fewer may have:

- Swelling of arms and legs which may cause a feeling of heaviness and tightness
- Dry eyes
- Sores in the mouth which may cause difficulty swallowing
- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss
- Swelling of the bowels

Nivolumab 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 Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.

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 • 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

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 7 months after your last dose of nivolumab.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for the costs of medical care you get as part of the study, just as if you would if you were getting the usual care for your advanced kidney 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.

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.

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. This includes:

- The genetic testing of the tissue.
- The biopsy at registration (if there is not tissue available)
- EKG prior to treatment

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 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 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

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 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*).

^Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here. ^

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 kidney 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

You will only participate in this part of the study if you continue onto the next part of study treatment after the nivolumab and ipilimumab. If you are an English, or Spanish speaker, you will be asked to fill out 3 forms. These forms will need to be filled out before starting the next part of the treatment (after treatment with nivolumab and ipilimumab), again after 6 and 12 months on study, and then every 6 months for up to 3 years after entering the next part of the stud, even if you stop treatment before that.y. These forms consist of questions related level of tiredness and general well-being. Each form will take about 15 minutes to complete. If you have any concerns or questions, please talk with your doctor or nurse right away. These forms are part of the research study to help researchers learn more about cancer treatment.

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 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

Blood: If you choose to take part in the optional blood study, researchers will collect blood for research on kidney cancer, and looking at the cells in your tumor tissue to look for genetic changes. The researchers will also look at whether or not they can predict which patients may respond better to chemotherapy and which will not.

Tissue at diagnosis: You may choose to allow your site to submit tissue left over from your biopsy when you were diagnosed with cancer. Your tumor sample will be tested by an outside laboratory to determine whether your cancer tumor has certain features that may help study doctors better understand kidney cancer. The researchers will also look at whether or not they

can predict which kidney patients may respond better to chemotherapy and which will not. The study doctors will look to see whether certain types of genes, proteins and certain types of white blood cells called lymphocytes are present within your tumor. Genomic (DNA/RNA) testing will be used to identify specific genetic changes related to cancer risk, how patients do, and treatments.
If there is no tissue leftover from when you are diagnosed with cancer you and your doctor may choose to get another biopsy for this study. The costs of the biopsy will be covered by the study. 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.

2) I agree to undergo a new biopsy if the amount of tissue at diagnosis is not enough for the studies described above.

   YES NO

Tissue if the cancer gets worse: If your cancer gets worse and you have another biopsy as part of usual care, we ask that you allow your doctor to submit any unused tissue to be studied the same way the "tissue at diagnosis" would be studied. This cost of this usual care biopsy will not be covered by the study.

You and your study doctor will not get the results of any tissue testing.

Unknown future studies

If you choose to take part in this optional study, any leftover blood and tissue will be 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. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use.

We don't know what research may be done in the future using your leftover blood and tissue samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- 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 in the blood and/or tissue studies, here is what will happen next:

1. **Blood:** About 2 tablespoons of blood will be collected from a vein in your arm. This will be collected up to 3 times: 1) before you start treatment, 2) after the initial treatment with ipilimumab and nivolumab and 3) in all patients at the end of treatment.
2. **Tissue:** The biopsy tissue, as discussed above, will be sent to the laboratory.
3. 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.
4. Researchers can only get samples from the biobank after their research has been approved by experts.
5. Researchers will not be given your name or contact information.
6. 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.
- If you are getting another biopsy before starting the treatment you doctor will explain to you the risks of this biopsy. Usually, common side effects of a biopsy are: small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur. Depending on the location of the biopsy and your health condition, the risks may vary and should be discussed with your doctor.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328.

How will information about me be kept private?

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

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

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

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

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

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

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

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

What if I have questions about this optional sample collection?

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

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

Samples for known future studies:

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

YES NO

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

YES NO

Samples for unknown future studies:

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

YES NO

Contact for Future Research

6) 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