NCI Protocol #: 10240
Local Protocol #: OSU 19088
Protocol Version Date: August 17, 2022

Protocol Title: Phase II Study of XL184 (Cabozantinib) in Combination with Nivolumab and Ipilimumab (CaboNivoIpi) in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Whose Cancer Progressed After One Prior VEGFR-Targeted Therapy

Informed Consent Version Date: August 17, 2022

SUMMARY OF CHANGES – Informed Consent Document

I. NCI Initiated Changes, 08/17/2022

#	Page(s)	Comments
1.	All	• Updated Header Version Date to match the new protocol version date.

Research Study Informed Consent Document

Study Title for Participants: Testing the combination of XL184 (cabozantinib), nivolumab, and ipilimumab (CaboNivoIpi) in patients with advanced or metastatic (cancer that has spread) differentiated thyroid cancer for which radioiodine is no longer effective.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: "Protocol 10240, Phase II Study of XL184 (cabozantinib) in combination with Nivolumab and Ipilimumab (CaboNivoIpi) in Patients with Radioiodine-refractory Differentiated Thyroid Cancer whose Cancer Progressed after One Prior VEGFR-Targeted Therapy" (NCT # 03914300)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United State Department of Health and Human Services (HHS). We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

You are being asked to take part in this research study because you have differentiated thyroid cancer (DTC) that either stayed the same or did not get better (*e.g.*, did not respond) when you were given radioactive iodine and that worsened after treatment with a drug that targets a protein in our cells called the vascular endothelial growth factor receptor (VEGFR). This protein is needed to form blood vessels.

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 answer the following question:

Can we lower the chance of your thyroid cancer growing or spreading by combining XL184 (cabozantinib), nivolumab, and ipilimumab? We also would like to find out what good or bad effects the study drugs have on you.

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your DTC. The usual approach is defined as care most people get for DTC. We are also collecting blood samples in this study which can provide information on how XL184 affects the immune system.

What is the usual approach to my DTC?

The usual approach for patients with DTC that is no longer responding to radioactive iodine is treatment with more Food and Drug Administration (FDA)-approved chemotherapy such as Doxorubicin, Sorafenib, and Lenvatinib. There are no treatments that are proven to help patients with your health condition live longer.

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

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

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

If you decide to take part in this study, you will get the study drugs XL184 (cabozantinib), nivolumab, and ipilimumab until your disease gets worse or the side effects become too severe.

After you finish your study treatment, your doctor will continue to follow your condition and watch you for side effects. Six weeks after your last dose of study treatment, you will see your doctor for a checkup. After that, you doctor will contact you by phone every 3 months for 2 years.

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 study drugs. 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
- Rash
- Tiredness
- Vomiting
- Weight Loss

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

Benefits

XL184 (cabozantinib), ipilimumab, and nivolumab are medications that are approved by the FDA for use in other types of cancer, such as melanoma. Ipilimumab and nivolumab work by taking the brakes off your immune system which may allow your immune system to work against the tumor, but we do not know this for sure which is why we are doing this study.

It is unlikely that the combination of XL184 (cabozantinib), nivolumab, and ipilimumab will work in everyone with your cancer or help you live longer. This study will 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 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.

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), FDA, or study sponsor (NCI). 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 test the good and bad effects of the combination of study drugs XL184 (cabozantinib), nivolumab, and ipilimumab. The study doctors will also compare these effects to the effects seen with XL184 (cabozantinib) alone in a previous clinical trial. This combination could shrink your cancer, but it could also cause side effects, which are described in the risks section below.

XL184 (cabozantinib), nivolumab, and ipilimumab have each already been approved by the FDA to treat other cancers, but they have not been approved by the FDA to treat DTC and are therefore considered experimental.

There will be about 27 people taking part in this study.

What are the study groups?

In this study, you will get the study drugs XL184 (cabozantinib), nivolumab, and ipilimumab. You will also get levothyroxine, or T4, hormone therapy, which is a usual treatment used in patients with DTC who have received radioiodine and whose thyroid is not producing enough thyroid hormone.

Treatment schedule: You will take XL184 (cabozantinib) tablets by mouth every day throughout the study. You should take XL184 (cabozantinib) at the same time each day, and you should take it on an empty stomach, which means you should not eat for 2 hours before and for 1 hour after. If you forget a dose, you may take it up to 12 hours after the usual time. Do not take the missed dose if it is less than 12 hours before you would take the next dose.

For the first 2 weeks, you will take only XL184 (cabozantinib). After that, you will get nivolumab through a vein in your arm once every two weeks and ipilimumab through a vein in your arm once every six weeks for 4 cycles. Each cycle will last 42 days (six weeks). You will receive ipilimumab for only the first four cycles (for a total of four doses). After the first four cycles, you will receive a larger dose of nivolumab through a vein in your arm once every four weeks. Each of these additional cycles will last 28 days (four weeks). You will continue to receive nivolumab and take XL184 (cabozantinib) tablets until your disease gets worse or the side effects become too severe. See the study calendar for more information.

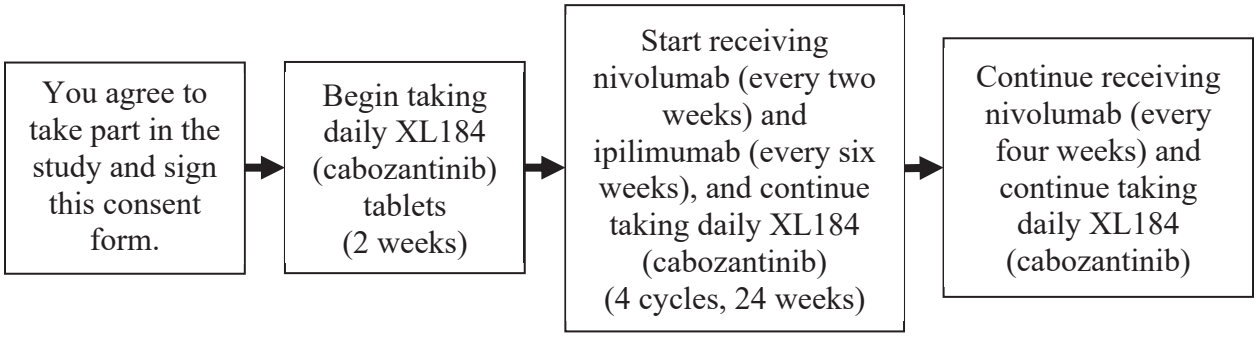
There is only one group in this study. All patients will receive the above study treatment. This study has two stages. Ten patients will be enrolled in the first stage. If the preliminary results from the first stage look promising, the study will move to the second stage in which an

additional 14 patients will be enrolled. Your doctor will tell you which stage of the study you are enrolled in.

If the study is in the second stage, you will need to provide blood samples for research studies on your tumor and immune system, and you will be asked to participate in optional studies. These optional studies will use tissue left over from your biopsy when you were diagnosed with cancer and will involve having one biopsy done before you begin receiving study drugs and another biopsy done after the first two cycles of treatment. These optional studies will be done to better understand how your cancer and your immune system responds to the study drugs. Please see the section "Optional studies that you can choose to take part in" for more information.

During the study, you will keep a medication diary. This helps you and the study team keep track of when you take your XL184 (cabozantinib) tablets. The study doctor will show you how to use this diary. Each time you visit the clinic, you must bring the diary, any remaining XL184 (cabozantinib) tablets, and the XL184 (cabozantinib) bottle.

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:

- Blood counts and blood tests done biweekly during the first cycle of treatment and at the beginning of each cycle thereafter.
- Electrocardiograms (EKGs) done at the start of each cycle to measure the activity of your heart.

- For Women: Pregnancy tests done at the start of each cycle.

This study will use genetic tests that may identify changes in the genes in your tumor's 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. If there are changes found that could cause health problems, then your study doctor will discuss your options with you. If the changes in your genes were inherited, the changes could also affect the health of your family members.

You and your family may want to know about any genetic test findings that may be important to your health. You may use this form to grant us permission in advance to give this information to your doctor. If a genetic test result about you seems to be medically important and you have granted us permission to contact you, the following steps will occur:

1. Researchers will compare your results against an up-to-date list of genetic changes known to affect health.
2. The research laboratory that performed the genetic test will contact your study doctor about the finding. The research laboratory, which will not have any identifying information about you, will provide your study doctor with a code number assigned to your genetic test sample.
3. Your study doctor will use the code number to identify you, and will then contact you about the medically important finding. Your study doctor may try to contact you several times.
4. You should have the genetic test repeated in a licensed clinical laboratory to confirm the results. This test must be paid for at your own expense.
5. If it is confirmed that there are changes found that could cause health problems, then your doctor will discuss your options with you. We strongly suggest that you also talk to a genetic counselor. Genetic counseling services must be paid for at your own expense.

It is more likely, however, that you will not be contacted by us about a medically important finding. Even if we do not contact you, it does not mean that your genes do not contain changes that are important to your health. Researchers are always learning about new and medically important changes in genes and some information may be learned in the future. Although new information may be learned later on, the researchers will only check your results against known genetic changes one time, and researchers will only decide to contact you about genetic test results at the time your DNA is initially sequenced. You will not be contacted or consented for any research done using your samples in the future, and you will not receive any reports or information about any medically important findings learned in the future. Also, sometimes the meaning of genetic test results can be uncertain, and we may not know for sure what the results mean for your future health. Sharing an uncertain genetic test result with you could offer little benefit, no benefit at all, or could even be harmful.

Results from genetic testing will not be a part of your medical records, unless the results are confirmed by additional testing that you agree to. See "Who will see my medical information?" for laws and risks in protecting your genetic information.

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:

If you are in Stage 2 of the study, you will need to provide blood samples for this study. Blood samples will be collected before you begin taking any study drugs, after you have been taking XL184 (cabozantinib) for two weeks but before you begin receiving nivolumab and ipilimumab, then after two cycles (twelve weeks) of treatment with XL184 (cabozantinib), nivolumab, and ipilimumab. If your disease gets worse during the study, another blood sample will be collected at that time. These blood samples will be used to test the effect of the study treatment on your immune cells. You will not receive the results of this testing.

If you are in Stage 2 of the study, there are also two optional studies that you may choose to take part in:

1. One optional study will involve using some of the tissue left over from a prior tumor biopsy when you were diagnosed with cancer or had surgery to remove your tumor.
2. Another optional study will include two biopsy collection procedures. This will involve taking small pieces of cancer tissue from your body and will be like the biopsy you had that helped diagnose your cancer.

See the "Optional Studies" section for more information. If you agree to take part in these studies, you may need to sign a separate consent form at the hospital or clinic where the biopsies are done.

A patient study calendar is attached at the end of this document. It shows how often these exams, tests, and procedures will be done.

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 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 study drugs 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 5 months (for women) or 7 months (for men) after you have completed the study.

Genetic Testing Risks

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.

Since this study is only testing tumor tissue, we will not know if a genetic change in your tumor is also in your normal tissue. If you want to find out if the change is in your normal tissue, then you will need to get other tests done outside of this study.

Genetic tests of normal tissue can reveal information about you and also about your relatives. Your doctor will talk with you about what testing your normal tissue may mean for you and your family. He or she also may suggest that you talk with a genetics counselor to learn more. You or your insurance plan would have to pay for any genetic tests and visits to a genetic counselor done outside of this study.

Blood Draw Risks

You may feel discomfort during some of the tests or procedures during this study or may experience some inconveniences. Some of the risks from drawing blood from your arm may include pain, bruising, lightheadedness, and rarely, infection.

Biopsy Risks

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, significant bleeding, or collapsing of the lung can occur. See the section about "Optional Studies" for more information.

Side Effect Risks

The drugs 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 drugs.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.

- Some side effects may make it hard for you to have children.
- 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.

Diarrhea is a common side effect associated with XL184 (cabozantinib). You should notify your doctor immediately at the first sign of poorly formed or loose stools or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.

This study is looking at a new combination of study drugs. This 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 for XL184 (cabozantinib), nivolumab, and ipilimumab. 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 XL184 (Cabozantinib)
(Table Version Date: December 17, 2018)

COMMON, SOME MAY BE SERIOUS In 100 people receiving XL184, more than 20 and up to 100 may have:
• Diarrhea, nausea, or vomiting • Tiredness • Weight loss or loss of appetite • Changes in taste • Redness, pain, or peeling of palms and soles • High blood pressure which may cause headaches, dizziness, or blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving XL184, from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Constipation or heartburn • Dry mouth or skin

- Sores in mouth which may cause difficulty swallowing
- Swelling of arms or legs
- Infection
- Bruising or bleeding
- Dehydration
- Muscle weakness
- Dizziness or headache
- Cough or 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
- Hair loss or rash
- Change in hair color
- Blood clot which may cause swelling, pain, or shortness of breath

RARE, AND SERIOUS
In 100 people receiving XL184, 3 or fewer may have:

- A tear or hole in internal organs that may require surgery
- Non-healing surgical site
- Damage to the jaw bone which may cause loss of teeth
- Bleeding in the brain which may cause confusion
- Stroke which may cause paralysis or weakness
- Brain damage which may cause headaches, seizures, or blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Lung collapse

Possible Side Effects of Nivolumab
(Table Version Date: June 18, 2018)

PLEASE NOTE THE FOLLOWING IN REVIEWING THESE RISKS:
BMS-936558 (nivolumab) is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving BMS-936558 (nivolumab). In clinical trials, most immune-mediated side effects were reversible and managed by stopping BMS-936558 (nivolumab) temporarily, administration of corticosteroids, and supportive care.

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 urination; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving Nivolumab, 3 or fewer may have:

- 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 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, 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 Ipilimumab
(Table Version Date: March 29, 2019)

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.
- Problems 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 movements.
- 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; 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, vomiting, and can result in coma.
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: shortness of breath, or 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 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 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

Additional Drug Risks

The study drugs could interact with other drugs and food. Certain other drugs can change how your body processes XL184 (cabozantinib). This could change the effect of XL184 (cabozantinib), or it could change the side effects from XL184 (cabozantinib). XL184 (cabozantinib) may also change the effects of other drugs. Your study doctor will give you a wallet card that lists the study drugs you are taking. Share this information with your family members, caregivers, other health care providers, and pharmacists.

Rarely, there are problems getting enough supplies of the study drugs. 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. Tell your study doctor right away if you think that you have become pregnant during the study or within 5 months after your last dose of study drugs
For men: Do not father a baby while taking part in this study. Tell your study doctor right away if you think that your partner has become pregnant during the study or within 7 months after your last dose of study drugs.

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 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 nivolumab and ipilimumab ready and giving them to you.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- The EKG done at baseline.
- Genetic testing on the tissue left over from your biopsy when you were diagnosed with cancer.
- The blood draws for testing the effect of the study treatment on your immune cells.
- The biopsies in the optional study.

You or your insurance provider will not have to pay for the XL184 (cabozantinib), nivolumab, or ipilimumab while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to the study doctors, and they will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study or the study treatment now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.

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, 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 your 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 (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and you 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 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 the following studies.

Optional sample collections for known laboratory 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 are enrolled in Stage 2, and you choose to take part in these optional studies, researchers will collect some of the tissue left over from your biopsy when you were diagnosed with cancer or from the surgery you had to remove your cancer. This will be used to research how characteristics of your tumor and your immune cells affect how your cancer responds to the study drugs. You will also have two biopsy procedures done. One biopsy will be done before you begin taking any study drugs, and the second will be done after you have been receiving the study treatment for two cycles. These biopsies will take small pieces of cancer tissue from your body and will be like the biopsy you had that helped diagnose your cancer. You will only have the option of allowing researchers to collect these biopsies if you are enrolled in Stage 2 of the study.

What is involved in this optional sample collection?

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

1. **If you are enrolled in Stage 2 of the study:** Your study doctor, with your consent, will use some of the tissue left over from your biopsy when you were diagnosed with cancer or had or had surgery to remove your tumor. This is optional.
2. In addition, samples of tissue will be collected from optional extra biopsies. Two optional biopsy procedures will be performed: one before you begin receiving study therapy, and one on Cycle 3, Day 1, after you have been receiving study therapy for 14 weeks. For the biopsy procedure, the study doctor will use a needle to take pieces of your tumor. This process may be repeated several times in the same appointment in order to get enough tissue. If a biopsy is not possible or cannot be done safely before you begin the study drug, then your study doctor, with your consent, will need to use some of the tissue left over from your biopsy when you were diagnosed with cancer or had surgery to remove your tumor.
3. Researchers can only get samples from this tissue after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to 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, significant bleeding, or collapsing of the lung can occur.
- 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 for testing, 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.
- ^Each site may modify this section to quote correct dosimetry in accordance with its institutional policies and procedures. The following text and risk estimate is an example only.^

  Depending on the location of the biopsy, a CT guided biopsy may be performed. If your biopsy is CT guided, you will have one or more medical imaging studies which use radiation. The tests or treatments you will have include two CT guided biopsies. The radiation dose from this research is about 12 millisievert. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation.

Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. This research gives your body the equivalent of about 4 extra years' worth of this natural radiation. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may have received or will receive from other tests.

A possible health problem seen with radiation exposure is the development of a second cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research is low. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

How will information about me be kept private?

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

- 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. Only your study doctor and a few study researchers will have access to the master list linking the code numbers to names. The laboratories doing research with your samples will receive the following information only: your sample code number; your age, race/ethnicity, and gender; your type of cancer; any previous treatments you received for your cancer; and the treatment you will receive for this current study.
- Researchers who study your samples and information will not know who you are. They also must agree that they will not try to find out who you are. The researchers must be trained in the handling of private information. Any researcher who wants to study your stored samples and genetic information must apply and be approved to do so.
- Your personal information will not be given to anyone unless it is required by law.
- If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in these optional sample collections?

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 these optional sample collections?

There are no costs to you or your insurance for exams, tests, and procedures done for research purposes only. 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 these optional sample collections?

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 researchers know. Then, any sample that remains 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 need my tissue samples to be returned?

Tumor tissue can be returned if needed for medically necessary events or procedures to assure appropriate medical care, such as for DNA or RNA analysis. Specimens may also be retuned if tissue is needed to determine eligibility for enrollment in a research protocol or clinical trial. Every effort will be made to facilitate medically necessary events or procedures to assure appropriate medical care for a patient with a serious or life-threatening illness.

Tumor tissue samples and genetic material (DNA and RNA) that has already been given to or used by researchers cannot be returned. No samples will be returned for matters related to patients needing or wanting genetic testing to determine medically important risks.

What if I have questions about these optional sample collections?

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 for Stage 2:

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

YES NO NOT APPLICABLE

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 NOT APPLICABLE

This is the end of the section about optional studies.

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

Contact for Medically Important Genetic Test Results

I agree that my study doctor, or someone on the study team, may contact me and my doctor if the laboratory finds a possible genetic test result that may be important to the health of me and/or my family members.

YES NO

Before you join this study, you may wish to talk with family members to see if they would like to learn of any genetic test results that may be important to their health. You have the right to decide how to handle sharing this information with your family members. However, if you were to become unable to share this information with family members due to illness or injury, or if you were no longer alive, please select and sign one of the options below on releasing genetic information to family members. Only genetic test results that may be medically important to your family members would be released.

Select and sign ONE option from below:

(1) **You have my permission** to release my genetic test results to **any and all** family members involved, in the event that I am unable to or have not survived to grant permission myself.

Participant's signature _____

Date of signature _____

Witness's signature _____

Date of signature _____

(2) **You have my permission** to release my genetic test results or stored DNA **only** to the family members listed. Please write the name of the family member(s) in the space provided below.

Participant's signature _____

Date of signature _____

Witness's signature _____

Date of signature _____

(3) **You do NOT have my permission** to release my genetic test results or stored DNA to any family members. I request that this information be kept private.

Participant's signature _____

Date of signature _____

Witness's signature _____

Date of signature _____

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 _____

Attachment A: Study Calendar for Protocol 10240 Consent Form

	Pre-study (≤30 days prior to registration)	Day -14 (two weeks before beginning nivolumab/ ipilimumab)	1 Cycle = 6 Weeks												1 Cycle = 4 Weeks	When your cancer gets worse	6 weeks after last dose of study drug	Long term follow-up
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycles 5+			
			Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1			
XL184 (cabozantinib) [A]		X----------X																
Nivolumab [B]			X	X	X	X	X	X	X	X	X	X	X	X	X			
Ipilimumab [C]			X			X			X			X						
Pre-study procedures including informed consent and demographics	X																	
Medical history, concurrent meds, height, weight, and general well-being	X	X	X	X	X	X			X			X			X	X	X	
Physical exam	X	X	X	X	X	X			X			X			X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood draws for general health status	X	X	X	X	X	X			X			X			X	X	X [J]	
Blood draws to study ability to form blood clots	X															X	X [J]	
Urine collection [D]	X	X	X	X		X			X			X			X	X	X [J]	
Pregnancy test [E]	X	X	X			X			X			X			X	X		
Electrocardiogram (EKG) [F]	X		X			X			X			X			X	X	X [J]	
Side effects assessment		X	X	X	X	X			X			X			X	X	X	

	Pre-study (≤30 days prior to registration)	Day -14 (two weeks before beginning nivolumab/ ipilimumab)	1 Cycle = 6 Weeks												1 Cycle = 4 Weeks	When your cancer gets worse	6 weeks after last dose of study drug	Long term follow-up
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycles 5+			
			Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1	Day 15	Day 29	Day 1			
Imaging studies to measure tumors [G]	X								X						X	X		
Optional archival tissue collection **Stage 2 only**	X																	
Blood draws for scientific study [H] **Stage 2 only**		X	X						X							X		
Optional Tumor Biopsy **Stage 2 only**		X							X									
Phone follow-up																		X [I]

A: XL184 (cabozantinib) will be given at 40 mg by mouth once daily starting two weeks before you begin receiving nivolumab and ipilimumab and continuing throughout the study treatment.

B: Nivolumab will be given at 240 mg through a vein in your arm on Days 1, 15, and 29 of each 6-week cycle for 4 cycles. After the first 4 cycles, it will be given at 480 mg through a vein in your arm on Day 1 of each 4-week cycle. It may be given 3 days before or after a scheduled dose.

C: Ipilimumab will be given at 1 mg/kg through a vein in your arm on Day 1 of Cycles 1-4 (for a total of four doses). It may be given 3 days before or after a scheduled dose.

D: Urine will not be collected during Day -14 to -1 if it was collected within seven days of Day -14.

E: A serum pregnancy test will be performed on women of childbearing potential at least seven days before study therapy begins. A serum or urine pregnancy test will also be performed on Day 1 of each cycle before treatment is given.

F: An EKG will be performed at baseline, on Day 1 of Cycles 1 to 5, and then every other cycle (every 8 weeks), at progression, and at 6 weeks after last dose of study drugs.

G: CT or MRI scans of the neck, chest, abdomen, and pelvis will be performed during pre-study and then every 12 weeks (*e.g.*, Day 1 of Cycles 3, 5, 8, 11, *etc.*). An imaging contrast agent may be given intravenously during CT or MRI scans. Some imaging scans will be repeated if clinically indicated.

H: Blood draws will occur throughout the study and at disease progression for scientific purposes.

I: We will check on how you are doing 6 weeks after last dose of study treatment, after which we will contact you every 12 weeks for 2 years.

J: Will be done if clinically indicated.