# Informed Consent Form

Perioperative Lenvatinib with Pembrolizumab in Patients with locally-advanced, non-metastatic Clear Cell Renal Cell Carcinoma

NCT Number: NCT04393350

Document IRB Approval Date: 1/29/2024

EMORY | WINSHIP CANCER INSTITUTE

A Cancer Center Designated by the National Cancer Institute

# You Are Being Asked to Be in a Research Study
# Concise Presentation of Key Concepts

You are being asked to be in a research study. A research study is designed to answer a scientific question. If you agree to be in the study, you will be one of 17 people who are being studied at Emory.

## Why is this study being done?

This study is being done to answer the question: will taking Lenvatinib in combination with Pembrolizumab be effective in treating kidney cancer before surgery? You are being asked to be in this research study because you have kidney cancer.

## Do you have to be in the study?

It is your decision to be part of this research study. You do not have to be in it. Your choice will not affect your access to medical care for your condition. Before you make your decision, you should take time to learn about the study.

## What do I have to do if I choose to participate in this study?

If you are eligible and want to be part of the study, you will receive 12 weeks of the study treatment (Lenvatinib and Pembrolizumab) followed by surgery and then 29 more weeks of Pembrolizumab alone (without Lenvatinib). You will be followed by the research team thereafter for as long as you consent to follow-up. The researchers will ask you to do or give the following: physical examinations (including height and weight), measurement of your vital signs, electrocardiograms (EKG or ECG) and echocardiograms or MUGA scans to test your heart function, collect blood and tumor samples, and body and brain scans (CT or MRI). Some of these procedures will be paid for by the study.

## How is this study going to help you?

If you are in the study, you will be helping the researchers answer the study question. The study results may be used to help others in the future.

## What are the risks or discomforts I should know about before making a decision?

The study will take time. The drug that is being tested may not work any better than regular care, and may even cause harm. All studies have some risks. Some risks are relatively small, like being bored or losing time. Some are more serious – for this study, these include: inflammation of the organs due to overactivity of your immune system, high elevation of blood pressure, damage to the kidney leading to the too much loss of protein in the urine, loss of privacy, and breach of confidentiality. A full list of expected risks, their frequency and severity are in the "What are the possible risks and discomforts?" section of this document.

**Alternatives to Joining This Study**

If you decide not to enter this study, there is care available to you outside of this research study. The study doctor will discuss these with you. You do not have to be in this study to be treated for your cancer.

**Costs**

You will have to pay for some of the study procedures, in particular those that are not covered by your medical insurance.

The study team can help you work out how much you might have to pay. There is more information in the cost section below.

**What Should I Do Next?**

Read this form, or have it read to you. Make sure the study doctor or study staff explains the study to you. Ask questions (e.g., about exact time commitment, about unfamiliar words, more details on specific procedures, etc). Make sure you understand which parts of these are research and which are standard care that you would have even if you did not join the study. Take time to consider this, and talk about it with your family and friends.

**Emory University and Saint Joseph's Hospital**
**Consent to be a Research Subject / HIPAA Authorization**

**Title:** Perioperative Lenvatinib with Pembrolizumab in Patients with locally-advanced, non-metastatic Clear Cell Renal Cell Carcinoma

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**Sponsor-Investigator:** Mehmet Asim Bilen, MD

**Study-Supporter:** Merck

## Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

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.

## What is the purpose of this study?

The purpose of this study is to determine the effectiveness of Lenvatinib in combination with Pembrolizumab before surgery and Pembrolizumab after surgery in kidney cancer.

Lenvatinib (also known as LENVIMA™, KISPLYX® and E7080) is approved in the US for use in the treatment of progressive or advanced thyroid cancer in adults when radioactive iodine treatment has not helped to stop the disease, It is also approved for the management of advanced kidney cancer in combination with another agent, as a single agent in unresectable hepatocellular carcinoma and combined with Pembrolizumab in the second-line treatment of metastatic endometrial cancer.

Lenvatinib is also being tested for the treatment of other types of cancer and in this setting is considered to be an investigational drug.

Lenvatinib belongs to a type of anti-cancer treatment known as receptor tyrosine kinase inhibitors (RTKIs). Tyrosine kinases are proteins involved in the growth of cells and the development of new blood vessels that supply them and can be present in high amounts in cancer cells. By blocking their action Lenvatinib may slow the rate at which the cancer cells grow and help to cut off the blood supply that feeds the cancer.

Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers including melanoma, small cell and non-small cell lung cancer, head and neck cancer, Hodgkin's lymphoma, bladder cancer, stomach and esophageal cancer, cervical and endometrial cancer, and hepatocellular carcinoma. In renal cell carcinoma, it is approved in combination with another agent for the first line treatment of advanced disease. It is not yet approved to treat locally advanced, non-metastatic kidney cancer.

Pembrolizumab works by blocking a receptor on the cell which allows the body's immune system to fight your cancer.

The two study drugs are thought to work by inhibiting two different possible ways in which a cancer cell can grow and spread. It is not known if giving the two study drugs at the same time will affect your cancer and survival the same as giving each of the drugs on its own, although we have evidence to suggest that the combination is effective in patients with metastatic kidney cancer.

Patients will be started on Lenvatinib 20 mg by mouth daily in combination with Pembrolizumab 200 mg intravenously for a total of four cycles, equating to 12 weeks of treatment as each cycle is 3 weeks in length. The dose of Lenvatinib you start with could be lowered or held if you experience serious side effects. You will then proceed to surgery (removal of the cancerous kidney). Then 1-3 months after the surgery, you will restart Pembrolizumab only (without Lenvatinib) and continue this for 13 cycles or 39 weeks.

The main purpose of this study is to first determine whether Lenvatinib combined with Pembrolizumab administered before surgery causes the size of your cancer to shrink. The secondary purposes of this study are to see how long any effect on your cancer lasts, how long you live, how surgery after the treatment goes and any side effects that you may experience during the study.

**What is the Status of the Drugs Involved in this Study?**

Although both of the drugs being studied in this trial have been approved by the FDA for treatment of different types of cancer, the combination of Lenvatinib and Pembrolizumab together in treating kidney cancer before surgery has not yet been approved by the FDA and is considered experimental in this study.

**How Long Will I Be in the Study?**

If you agree to join this study, and you meet all of the study entry requirements, you will continue to receive Lenvatinib and Pembrolizumab until: 1) your cancer gets worse; 2) you have unacceptable side effects; 3) you decide that you no longer wish to take Lenvatinib and Pembrolizumab; 4) the study is stopped by the Sponsor or FDA for any reason; 5) you fail to follow instructions given by the

study doctor; or 6) the study doctor believes it is best for you to no longer be in the study. It is expected that you will receive both study drugs for a total of 4 cycles (12 weeks) prior to your kidney surgery and then 13 cycles (29 weeks) of Pembrolizumab alone after your surgery. The dose of Lenvatinib you start with could be lowered or held if you experience serious side effects. Also, you or your family will be contacted by telephone every 3 months after your last dose of Pembrolizumab to determine whether your cancer has gotten worse, what treatments you have received subsequently, and your survival status.

If you leave the study early, there are certain follow-up procedures that may be required. These tests are described in more detail under the section entitled “End of Study Visit”.

Please note that the 13 cycles (29 weeks) of Pembrolizumab administered after the kidney surgery was added as part of an amendment to the study protocol after data suggesting that 1 year of Pembrolizumab around the time of surgery improved survival for patients with localized kidney cancer undergoing removal of the kidney, just like you have. Patients who have completed combination pre-surgery therapy (Pembrolizumab and Lenvatinib) and underwent nephrectomy prior to the amendment will not receive adjuvant therapy. Those who are currently receiving treatment will be offered the option to receive adjuvant Pembrolizumab. All patients enrolled after the amendment including adjuvant Pembrolizumab will receive adjuvant Pembrolizumab if they enroll in the trial.

## What if I Decide Not to Take Part in this Study?

Taking part in this research study is voluntary. You may choose not to take part. If you do choose to be in the study, you may change your mind at any time. If you do not want to enter the study or decide to stop being in the study, your relationship with the study staff will not change, and there will be no penalty to you. You will not lose any benefits including health care services to which you are otherwise entitled.

## What Will Happen If I Agree to Take Part in this Study?

To find out if you can take part in this study, you will go through a screening process. In this process, you will be asked about your general health and your medical history. You will also be asked about medicines, prescriptions and any over-the-counter drugs and supplements you are taking right now or have taken within 28 days prior to the first dose of study drug.

## Screening and Baseline Tests and Procedures

Once all your questions have been answered and you feel comfortable that you understand what this study involves, you will need to sign this informed consent. The following tests and procedures to determine if you are eligible to take part in this study will be done. If any of these tests were performed prior to signing consent, as part of your routine care, and if they fall within the time allowed by the study, they may be used and need not be repeated. This evaluation process may take up to a maximum of 28 days prior to starting the study and will include the following:

- Medical History
- Record concomitant medications taken up to 30 days prior to treatment initiation
- Vitals [temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR)]
- Physical Examination, including height and weight

- Performance assessment
- Assessment of quality of life
- Collect blood samples for
  - Safety tests: thyroid function, blood counts, blood sugar, coagulation, pancreas, liver and kidney functions
  - Urine pregnancy test for women of childbearing potential at screening and within 72 hours of study drug
  - Inflammation test (C-reactive protein)
  - Urinalysis and urine protein to creatinine ratio to assess for any protein in your urine
- 12-lead ECG - An ECG records the rhythms and electrical activity of your heart. A number of electrodes (small, sticky patches) are stuck on your arms, legs and chest. The electrodes are connected to a machine that records the electrical signals of each heartbeat and monitors how your heart is working.
- Echocardiogram or MUGA (Multi Gated Acquisition Scan) - An echocardiogram is an ultrasound scan of the heart. Ultrasound is a very high frequency sound that you cannot hear, but it can be emitted and detected by special machines and is used to build up a detailed picture of the heart. You will be lying down on a bed and a small ultrasound instrument (with gel on it) will reflect pictures onto a screen of how your heart is pumping. This test gives good information about the structure and function of your heart. A MUGA scan is a nuclear medicine test used to evaluate the function of the heart ventricles (pumping chambers). The MUGA test involves the injection of a radioactive marker into the bloodstream. A scanner is then used to provide a movie-like image of the beating heart, which allows the doctor to determine the health of the heart's major pumping chambers.
- Radiologic imaging studies to evaluate tumor status. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, chest and abdomen/pelvis. CT stands for computed tomography. A CT scanner is used to take a series of X-rays of your body at slightly different angles. A computer puts these together to produce a very detailed picture of the inside of your body. Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to produce detailed pictures of the inside of your body. The pictures produced by the CT scans and the MRIs provide doctors with information to help them assess the extent of your cancer. CTs will be performed with oral and intravenous (IV) contrast; MRIs will be performed with IV contrast. This means that you may have to drink a special solution or receive a special dye by injection into a vein that will highlight areas of disease involvement more easily for a doctor who is reviewing your scans. These imaging studies will also be used for muscle and fat assessment.
- Fresh biopsy from kidney mass after the consent is signed and before the trial treatment is started for research will be obtained if a baseline biopsy has not already been done (with tissue accessible for testing). The biopsy will be used to confirmed diagnosis of kidney cancer and presence of clear cell component as well as for research. Because the development of cancer is complex, it is difficult to pre-specify all the genes that may be examined. However, all genes examined will have been thought to be important in your cancer and / or response to study treatment. The results are for research purposes only. The results of these tests will not be shared with you, any insurance company, your employer, your family, or any other doctor who is treating you or may treat you in the future. Information from these tests will not be entered into your medical record. Your personal information will be kept confidential to the extent required by applicable laws and regulations. The results of this research may help:

- Develop products or tests that may help patients do better on drugs or suffer fewer side effects from drugs. This genetic research may help the Sponsor to develop a unique and predictive test (like a diagnostic test) that can help identify which patients may respond best to treatment and which patients may be more at risk for bad side effects from treatments.
- Discover more about how the study drug may work, and to better understand why the study drug may work well in some patients but not others.
- Find more about what causes diseases and how to prevent and treat them. Many researchers use these samples to help develop new tests to diagnose diseases or develop new drugs to treat and possibly cure diseases.

If it is determined that you are eligible to take part in the study you will be asked to return to the clinic the day before your scheduled start date (first day of receiving treatment) - this visit is called the Baseline Visit. If all the tests listed above were completed within the allowed timeframe from the baseline visit, some of the tests may not need to be repeated at the baseline visit.

**Treatment Schedule**

There are 3 sections of the treatment schedule including the neoadjuvant (pre-surgical) phase, the surgical phase, and the adjuvant (post-surgical) phase. In the neoadjuvant phase, you will receive 4 cycles (12 weeks) of treatment with Pembrolizumab and Lenvatinib. Pembrolizumab is administered every 3 weeks on Day 1 of each cycle while Lenvatinib is to be taken daily during the neoadjuvant/pre-surgical 4 cycles. During the surgical phase, you will have a post-neoadjuvant therapy safety visit and subsequently your kidney surgery. During the adjuvant phase, which will commence 4 to 12 weeks after your kidney surgery depending on your readiness after surgery, you will receive an additional 13 cycles (39 weeks) of Pembrolizumab (without any Lenvatinib).

## Neoadjuvant (pre-surgical) phase:

**Cycle 1, Day 1 / Baseline Visit (within 3 days of the first dose of study treatment)**

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, including weight
- Performance assessment
- Collect samples for
    - Blood counts, blood sugar, coagulation, pancreas, liver and kidney functions
    - Urine pregnancy test for women of childbearing potential within 72 hours of study drug
    - Inflammation test (C-reactive protein)
    - Urinalysis and urine protein to creatinine ratio

- Research blood sample (up to 60 mL) for biomarker analysis. A biomarker is a measurement that is used to evaluate health or make a diagnosis of disease. Your blood samples will be used to study cells, genes and proteins present in the liquid portion of the blood (serum). This study will attempt to find differences in the blood between patients and help us understand the cause of unintended side effects from the study treatment.
- Stool sample
- Lenvatinib will start to be taken by mouth
- First dose of Pembrolizumab administered into the vein of your arm
- 12-lead ECG
- Quality of life questionnaires and frailty assessment

**Cycle 1, Day 8 (± 3 days)**

- Record concomitant medications
- Vitals (temperature, HR, BP and RR) and height and weight
- Collect research blood sample (up to 60 mL)
- Lenvatinib taken by mouth (ongoing)

**Cycle 1, Day 8-15 (± 3 days)**

- Collect sample for liver function tests once during this time

**Cycle 2, Day 1 (± 3 days)**

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, including weight, pill diary and pill count
- Performance assessment
- Collect samples for:
    - Blood counts, blood sugar, coagulation, pancreas, liver and kidney functions
    - Urine pregnancy test for women of childbearing potential
    - Inflammation test (C-reactive protein)
    - Urinalysis and urine protein to creatinine ratio
    - Thyroid function test
- Research blood sample (up to 60 mL)
- Lenvatinib taken by mouth (ongoing)
- Second dose of Pembrolizumab administered into the vein of your arm
- 12-lead ECG

**Cycle 2, Day 29-36 (± 3 days)**

- Collect sample for liver function tests once during this time

**Cycle 3, Day 1 (± 3 days)**

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, including weight, pill diary and pill count
- Performance assessment
- Collect samples for:

  - Blood counts, blood sugar, coagulation, pancreas, liver and kidney functions
  - Urine pregnancy test for women of childbearing potential
  - Inflammation test (C-reactive protein)
  - Urinalysis and urine protein to creatinine ratio
  - Thyroid function test
- Research blood sample (up to 60 mL)
- Lenvatinib taken by mouth (ongoing)
- Third dose of Pembrolizumab administered into the vein of your arm
- 12-lead ECG
- Quality of life and frailty assessment

**Cycle 3, Day 50-57 (± 3 days)**

- Collect sample for liver function tests once during this time

**Cycle 4, Day 1 (± 3 days)**

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, including weight, pill diary and pill count
- Performance assessment
- Collect samples for:
  - Blood counts, blood sugar, coagulation, pancreas, liver and kidney functions
  - Urine pregnancy test for women of childbearing potential
  - Inflammation test (C-reactive protein)
  - Urinalysis and urine protein to creatinine ratio
  - Thyroid function test
- Research blood sample (up to 60 mL)
- Lenvatinib taken by mouth (ongoing)
- Fourth dose of Pembrolizumab administered into the vein of your arm
- 12-lead ECG

Note: Lenvatinib must be taken orally once daily with or without food at approximately the same time each day. If you miss a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

**<u>Surgical phase:</u>**

**Post- neoadjuvant treatment safety visit (within 7 days of last dose of Lenvatinib) after completion of cycle 4**

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, including weight, pill diary and pill count
- Performance assessment
- Quality of life questionnaires and frailty assessment

- Collect samples for:
  - Blood counts, blood sugar, coagulation, pancreas, liver and kidney functions
  - Inflammation test (C-reactive protein)
  - Urinalysis and urine protein to creatinine ratio
  - Thyroid function test
  - Urine pregnancy test for women of childbearing potential within 72 hours of study drug
- Research blood sample (up to 60 mL)
- Stool sample
- 12-lead ECG
- Radiologic imaging studies to evaluate tumor status. Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis (Those imaging studies can be done within 28 days after last study treatment dose and will also be used for muscle and fat assessment).

**Nephrectomy:**

- Preparation for kidney surgery will be done per standard of care
- Patients will undergo kidney surgery no earlier than 7 days after the last dose of Lenvatinib and research tissue will be obtained from surgical sample

**<u>Adjuvant (post-surgical) phase (4-12 weeks after kidney surgery)</u>**

**Cycle 5, Day 1 (± 3 days)**

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, including weight, pill diary and pill count
- Performance assessment
- Collect samples for:
  - Blood counts, blood sugar, coagulation, pancreas, liver and kidney functions
  - Urine pregnancy test for women of childbearing potential
  - Inflammation test (C-reactive protein)
  - Urinalysis and urine protein to creatinine ratio
  - Thyroid function test
- Research blood sample (up to 60 mL)
- Fifth dose of Pembrolizumab administered into the vein of your arm
- 12-lead ECG
- Quality of life and frailty assessment

**Cycle 6, Day 1 (± 3 days) through Cycle 17, Day 1 (± 3 days)**

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, including weight, pill diary and pill count
- Performance assessment

- Collect samples for:
  - Blood counts, blood sugar, coagulation, pancreas, liver and kidney functions
  - Urine pregnancy test for women of childbearing potential will be conducted every cycle
  - Inflammation test (C-reactive protein)
  - Urinalysis and urine protein to creatinine ratio
  - Thyroid function test
- Research blood sample (up to 60 mL)( only cycle 9 and 13)
- Stool sample will be collected during cycle 9 only during the adjuvant phase
- Pembrolizumab will be administered into the vein of your arm on day 1 of each cycle until completion of the adjuvant phase (13 cycles after surgery and 17 cycles total including the 4 prior to surgery)
- 12-lead ECG
- Quality of life and frailty assessment
- Radiologic imaging studies to evaluate tumor status will be repeated every 12 weeks while you are receiving adjuvant Pembrolizumab

Post-Treatment Phase/Post-adjuvant therapy safety visit (End of adjuvant phase, within 14 days after last cycle of Pembrolizumab)

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- History and physical exam, including weight, pill diary and pill count
- Performance assessment
- Collect samples for:
  - Blood counts, blood sugar, coagulation, pancreas, liver and kidney functions
  - Serum or urine pregnancy test for women of child bearing potential
  - Inflammation test (C-reactive protein)
  - Urinalysis and urine protein to creatinine ratio
  - Thyroid function test
- Research blood sample (up to 60 mL)
- Stool sample
- 12-lead ECG
- Radiologic imaging studies to evaluate tumor status. Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis (Those imaging studies can be done within 28 days after last study treatment dose and will also be used for muscle and fat assessment).
- Quality of life questionnaires and frailty assessment

**Long-Term Follow-Up Phase**

- After completing adjuvant therapy, patients will enter long term follow-up period and can be seen by medical oncology or urology team via clinic visit, chart review, or phone call to determine current status every 3 months (+/- 14 days) until disease recurrence or initiation of new anti-cancer therapy, whichever occurs first.

- Research blood sample (approximately 60 mL) will be collected after surgery
- Surveillance scan after surgery will be obtained per investigator based on routine clinical guidelines.

**How will my medicine be provided**?
The medicine that you will take will be dispensed by the pharmacy and delivered to the principal investigator or study team member. The principal investigator or health care providers on his/her research team will provide the medicine to you. If you have questions about the medicine, you should ask the principal investigator or study nurse. You may also call the pharmacy if you have questions about the medicine. The number for the pharmacy is included on your medicine package.

**Who owns my study information and samples?**
If you join this study, you will be donating your samples and study information. You will not receive any compensation if your samples or information are used to make a new product. If you withdraw from the study, data and samples that were already collected may be still be used for this study. Blood samples collection is mandatory, therefore there is no option to destroy samples.

**What Are My Responsibilities While I am in the Study?**
You must be honest and complete in giving your medical history. This history also includes any medicines that you have taken, or are taking now. It also includes any other clinical research studies that you have taken part in or are in now.

It is important that you follow the instructions of the study doctor and study team. It is important that you come to all of your scheduled study visits. It is also important that you follow the schedule when you take the study drug.

It is important that during the study, you tell the study doctor and/or the study team all changes in how you feel. You need to tell them even if you do not believe these changes are related to the study. This may include mental or emotional changes. You will be checked during the study for side effects. You will also be checked for other injuries or illnesses that may happen while you are in the study.

You cannot take certain medicines or live vaccines during the research study. This may include foods or supplements. Before taking any medicines besides the study drug or making changes to existing medicines, you must first ask the study doctor. These medicines may be ones that are ordered by a doctor. They also could be drugs like allergy medicines, cough and cold medicines and pain relievers. They may also be vitamins, herbs and minerals.

Only you, the study subject, can take the study drugs Lenvatinib and Pembrolizumab. All unused study drugs must be returned to the study doctor. This includes any empty drug containers.

**What are the possible risks and discomforts?**
In any research study, there may be side effects, complications, and/or injury that are both expected and unexpected. Such reactions, which may lead to serious injury or death, could occur through no fault of your own, the study staff, or the study sponsor.

**What are the possible side effects of receiving Lenvatinib?**

It is not possible to predict all of the risks and unwanted effects that might happen if you are given Lenvatinib either alone or in combination with other drugs. It is possible that new side effects not described here may occur in this study. The known side effects of Lenvatinib are listed below. Throughout the study, your study doctor will monitor your symptoms, blood pressure readings, and laboratory tests. If you develop any side effects your study doctor may need to temporarily stop and/or change the dose of your study drug, or to stop the study drug completely.

Like all medicines, this medicine can cause side effects, although not everybody will get all or even some of the side effects listed. The following side effects may happen with this medicine.

**Tell your study doctor straight away if you notice any of the following side effects because you may need urgent medical treatment as they are <u>serious and potentially life-threatening</u>:**

| **Lenvatinib**<br>**Serious Side Effects** | |
|---|---|
| **Common (may affect up to 1 in 10 people)** | **Uncommon ( may affect up to 1 in 100 people )** |
| • Stroke, mini-stroke or bleeding in the brain –may result in numbness or weakness on one side of the body<br>• Blood clot in the legs or lungs (pulmonary embolism) – may cause swelling of the calf associated with warmth or tenderness, sudden onset of shortness of breath, rapid breathing, tightening of chest or chest pain, cough or coughing up blood, rapid heart rate and a blue tinge to the lips<br>• Heart problems, heart palpitations or heart attack – may cause chest pain or pressure, pain in the arms, back, neck or jaw, shortness of breath, rapid or irregular heart rate, coughing, bluish colour to lips or fingers, feeling very tired<br>• Fistula formation or bowel perforation - abnormal connections between different organs in the body or between an organ and another part of the body such as the skin or windpipe, or formation of a hole in the wall of your gut which can cause severe abdominal pain.<br>• Bleeding inside the body particularly from the gut – may cause black, tarry, or bloody stools<br>• Dehydration and kidney failure – may result from diarrhea, feeling and being sick which are very common side effects<br>• Heart failure – a decreased pumping ability of the heart which may cause severe shortness of breath<br>• Liver damage or failure- may cause yellowing of the skin or eyes (jaundice), tiredness or sickness, loss of appetite, abdominal pain or high temperature. | • Posterior reversible encephalopathy syndrome (PRES) is a potentially fatal condition that may have the following symptoms: headache, confusion, convulsions and vision disturbance. An MRI scan may be required to diagnose this condition<br>• Pneumothorax – a leak of air from the lung into the chest so the lung cannot inflate. This may cause sudden chest pain or sudden shortness of breath. There may be a higher chance of this occurring if cancer has spread to the lungs or if treatment is for solid tumor cancers such as osteosarcoma or soft tissue sarcoma or in patients under the age of 25.<br>• Aortic dissection- tearing in the wall of the aorta (a large artery) which may cause severe pain in the back, |

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| • Hepatic encephalopathy – may result in confusion, drowsiness, poor concentration or loss of consciousness. | chest or abdomen and internal bleeding. |

Other side effects of Lenvatinib:

| **Other Side Effects – Some May be Serious** | | |
|---|---|---|
| **Very Common (affects more than 1 in 10 people and up to 8 in 10 people)** | **Common (may affect up to 1 in 10 people)** | **Uncommon (may affect up to 1 in 100 people)** |
| • high or low blood pressure<br>• loss of appetite or weight loss<br>• feeling sick and being sick, constipation, diarrhea, abdominal pain, indigestion<br>• feeling very tired or weak<br>• dry, sore, or inflamed mouth or throat<br>• high levels of protein in the urine<br>• hoarse voice<br>• headache<br>• hand-foot syndrome (redness, soreness and swelling of the skin on the hands and feet)<br>• joint pains<br><br>Everything above has a frequency of greater than or equal to 20% (i.e. more than 2 in 10 people and up to 8 in 10 people); everything below is 10-20% (i.e. more than 1 and up to 2 in 10 people)<br>• cough<br>• low level of platelets in the blood which may lead to bruising | • loss of body fluids (dehydration)<br>• dry skin, thickening and itching of the skin<br>• feeling bloated or having gas in the bowel<br>• feeling unwell<br>• inflammation of the gallbladder<br>• changes in blood test results for liver<br>• changes in blood test results for magnesium (low) – may increase the chance of having an abnormal heart rhythm<br>• changes in blood test results for kidney function<br>• changes in white blood cells ( low) which may increase risk of infections<br>• changes in blood test results (high) for lipase and amylase (enzymes involved in digestion)<br>• changes in blood test results for cholesterol (high) | • painful infection or irritation near the anus<br>• splenic infarction (severe pain in the upper left part of the belly (abdomen) which may be associated with fever, chills, nausea and vomiting)<br>• inflammation of the pancreas which may cause severe pain in the abdomen or back<br>• impaired healing - wounds may take longer to heal, including at the surgical site.<br>• Osteonecrosis (bone damage) of the jaw – may cause pain in the mouth, teeth, and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw |

| **Other Side Effects – Some May be Serious** | | |
|---|---|---|
| • musculoskeletal, muscle, limb or back pain<br>• swelling of the legs<br>• underactive thyroid and change in blood test result for thyroid stimulating hormone (high) - may result in fatigue, weakness, dry skin, hair loss, intolerance to cold<br>• rash<br>• feeling dizzy<br>• bleeding (most commonly nose bleeds, but may include bleeding from other sites such as blood in the urine, bruising, bleeding from the gums, coughing up blood)<br>• odd taste sensation<br>• trouble sleeping<br>• hair loss<br>• urinary infections (increased frequency in urination and pain in passing urine)<br>• changes in blood test results for potassium levels (low) and calcium levels (low) – may increase the chance of having an abnormal heart rhythm | | |

It is possible that you could have side effects of lenvatinib that are not described here, and you should contact the trial doctor or nurse if you have any of these or any other side effects during the trial.

Invasive dental procedures are an identified risk for the development of osteonecrosis of the jaw. A dental examination and appropriate preventive dentistry should be considered prior to starting

lenvatinib. Periodic dental examinations and oral hygiene are important while you take lenvatinib. If you have planned dental procedures, notify your dentist and oral surgeon that you are taking lenvatinib. Do not start medications without first discussing this with the trial doctor.

If any new information about lenvatinib is discovered during the course of the trial that may impact your safety or willingness to participate in the trial, you will be notified by the trial doctor.

**For pembrolizumab plus lenvatinib:**

**What side effects could the trial drug(s) cause?**
Researchers are studying the use of pembrolizumab together with lenvatinib to treat certain cancers. There is a limited amount of information about the risks of using these 2 drugs together. Previous research studied 354 patients who received pembrolizumab and lenvatinib together for an average of 11.9 months. Based on these patients, if you are taking pembrolizumab together with lenvatinib:

- You are still at risk for all of the side effects listed above for each of the drugs when taken alone.
- There were no NEW side effects when patients took these 2 drugs together. However, some of the side effects seen when patients took either drug alone were seen more often when patients took the 2 drugs together.

Below are the side effects that were seen more often when patients took the 2 drugs together (compared to taking either drug alone):

**VERY COMMON: Out of 100 people who receive pembrolizumab and lenvatinib together, 20 or more people may have the following:**
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools

**UNCOMMON: Out of 100 people who receive pembrolizumab and lenvatinib together, at least 1 but less than 5 people may have the following**:
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain

If any new information about the combination of lenvatinib with pembrolizumab is discovered during the course of the trial that may impact your safety or willingness to participate in the trial you will be notified by the trial doctor. It is possible that you could have side effects of the combination of lenvatinib with pembrolizumab that nobody knows about. You should get medical help and contact the trial doctor or nurse if you have any of these or any other side effects during the trial. It is

important to inform the trial doctor or nurse about any symptoms you experience, as they may be able to prescribe medications to treat these. Please tell them if you have any problems with your health or the way you feel during the trial, whether or not you think they are related to the trial drug.

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

**VERY COMMON**

**Out of 100 people who receive Pembrolizumab, 20 or more people may have the following:**
- Itching of the skin
- Loose or watery stools
- Cough

**COMMON**

**Out of 100 people who receive Pembrolizumab, at least 5 but less than 20 people may have the following:**
- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

**UNCOMMON**

**Out of 100 people who receive Pembrolizumab, at least 1 but less than 5 people may have the following:**
- Inflammation of the lungs so you may feel short of breath and cough.
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus

- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection.

**RARE**

**Out of 100 people who receive Pembrolizumab, less than 1 person may have the following:**

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis.
- Inflammation of the muscles so you may feel weak or have pain in the muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting.
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan.
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting.
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs

- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation
- Inflammation of the blood vessels
- The loss of fat tissue from your body or the redistribution of fat tissue to atypical areas of your body. This could be accompanied by metabolic abnormalities such as diabetes mellitus, high triglycerides or fat accumulation in the liver (leading to inflammation of the liver)
- Low levels of parathyroid hormone (a hormone made by 4 tiny glands in your neck) which may result in low blood calcium and cause muscle cramps or spasms; fatigue or weakness; numbness, tingling or burning in your fingertips, toes or lips (hypoparathyroidism)
- Inflammation of the stomach (gastritis). You may have pain in your belly, feel full, or sick to your stomach. You may also experience nausea, vomiting or loss of appetite.
- Low number of red blood cells (cells that carry oxygen) due to destruction of red blood cells (hemolytic anemia). You may feel weak, tired, lightheaded, short of breath, or have a fast heartbeat. You may also experience difficulty with physical exercise, pale or yellow skin, dark urine, or fever.
- Not enough pancreatic enzymes (proteins that break down food) that leads to poor digestion of food (exocrine pancreatic insufficiency). You may have bloating, gas, discomfort in your belly, diarrhea, abnormal stool that is oily, or weight loss.

In addition to the above, since Pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving Pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include join pain, stiffness and/or swelling.
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma.
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).
- Inflammation or swelling of the nerve fibers of the eye which send visual information from your eye to your brain. This health condition often has a sudden onset of vision loss, loss of color vision, pain when moving your eyes, and/or loss of peripheral vision. It may affect one or both eyes at the same time (optic neuritis).

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving Pembrolizumab. Sometimes this condition can lead to death.

**Risks to Pregnant Women**

If you are a woman and it is possible for you to become pregnant, a pregnancy test will be performed at study entry and you must confirm that you have not had unprotected sex within 30 days of entering the study. If it is possible for you to become pregnant, you must agree to use a highly effective method of birth control throughout the entire study period and for 120 days after the study drug is stopped. If an oral birth control is used, you must also use an additional barrier method. If you are using hormonal birth control, you must have been on a stable dose of the same product for at least 4 weeks before taking the study medication and you must continue to use the same birth control throughout the entire study period and for 120 days after study drug discontinuation. If you are currently abstinent, you must agree to use a double barrier method of birth control if you become sexually active during the study.

You will be exempt from these birth control requirements if you are unable to become pregnant i.e.:

- Women who have had a hysterectomy (uterus removed), bilateral oophorectomy (both ovaries removed), bilateral tubal ligation and documentation of the procedure at least one month before the start of the study.
- Postmenopausal women in the appropriate age group who had their last period more than one year before start of the study treatment.

If you are a man with a partner who is able to become pregnant, you must use an adequate birth control method and your partner must use a highly effective method of birth control, from at least the first day of your partner's last normal menstrual period, throughout the entire study period, and for 120 days after stopping the study drug. No sperm donation is allowed during the study period and for 120 days after study drug discontinuation.

**Birth control, pregnancy and breastfeeding**

- If you could become pregnant, use highly effective birth control while taking Lenvatinib and Pembrolizumab, and for at least four months after your last dose.
- Do not take Lenvatinib and Pembrolizumab if you are planning to become pregnant during the study. This is because it may seriously harm your baby.
- If you become pregnant while taking Lenvatinib and Pembrolizumab, tell your study doctor immediately. Information will be collected about the pregnancy and its outcome.
- Do not breastfeed if you are taking Lenvatinib and Pembrolizumab. This is because the medicine may seriously harm your baby.

**What are the other possible risks and discomforts other than medication side effects?**

Blood drawing: Local pain, bruising, bleeding, blood clot formation, and, in rare instances, an infection might occur in the area where blood is drawn. There is also the possibility of dizziness or fainting

while your blood is being drawn. [The decision to use a catheter (a thin tube) for blood collecting is made by the study staff. The study staff will explain the catheter to you if its use is necessary.]

ECG: The ECG (electrocardiogram) is a picture of the electrical action of the heart. During this procedure you will need to lie still for a few minutes so that electrodes can be attached to your chest. The electrodes may cause some discomfort when they are put on and taken off your skin. If you are a male and have any chest hair, it may need to be shaved off on the areas where the electrodes will be placed.

Radiological Procedures: In order to find out if Lenvatinib combined with Pembrolizumab has an effect on your tumor, certain radiological procedures will be done as a part of this study. You may also undergo an ECHO or MUGA which will assist in evaluating potential side effects of Lenvatinib on your heart.

Radiation Risks: You will be exposed to radiation from nuclear medicine and CT scans. These procedures are necessary for your medical care and will occur even if you do not participate in this study. The radiation dose estimate that you will receive is equal to or less than the radiation exposure allowed to be received by a radiation worker for 2 years. The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. Although the risk from radiation is cumulative it is not expected to adversely affect your condition or treatment. The Emory University Radiation Safety Committee has reviewed and approved the use of radiation in this research study.

MRI Risks: MRI exams use powerful magnets to create images of the body. In addition to the possible reactions to contrast materials, you may feel claustrophobic while in the magnet, and will hear loud beeping or hammering noises. If you have tattoos or any metal items in your body such as implants, pacemakers, clips or shrapnel, we will do special screening to make sure your MRI scan is done safely.

Risk of Contrast Agents: Your CT or MRI procedure will require the use of a “contrast agent.” The contrast agent is a substance that helps the radiologist interpret the images. The contrast agent will be injected by either a hand-held needle or a machine that does the injection. Most contrast agents stay in your body for only a few minutes, but some of them can remain for a few hours or days without any harm to you or anyone near you. Contrast agents are generally quite safe, but any injection involves some risks. The injection could harm a nerve, artery or vein, or cause infection. The contrast agent could affect kidney function or cause an allergic reaction, though these outcomes are rare. The contrast agent could also leak from your veins a little causing swelling and discomfort, that is typically treated with ice packs.

Risk of Tumor Biopsy Procedure: This is a research procedure and would not be done if you were not participating in the study. Before the biopsy is done, you may receive pain relief medication and/or a numbing medication and/or a minor sedative to make you more comfortable. A doctor will then insert a needle into your tumor under the guidance of a CT scan to remove a sample. You may have pain, discomfort, infection or bruising where the biopsy tissue was obtained. You may feel faint or nauseous. This may happen during the biopsy or immediately after.

Risk of Becoming Ineligible for Surgery: Taking the study drug may delay and lower chances of having a successful surgery. It is possible that a) the tumor does not respond to the medications in the trial and tumor growth makes complete removal of the kidney and tumor less likely, b) the tumor does not respond to the medications in the trial and spreads to other organs in the body, which may make the cancer incurable, or c) you have side effects from the medications that make you ineligible for surgery.

Risk of Incidental Findings: Unanticipated clinically insignificant or potentially significant abnormalities may be detected from the proposed imaging or non-imaging test procedures proposed in this study. Such abnormalities will be communicated to you and to your health-care providers in a timely fashion. As for any abnormalities that are detected upon clinical diagnostic procedures, there is the risk of future potentially unnecessary additional diagnostic testing or therapeutic intervention, which can be associated with various complications.

**Will I benefit directly from the study?**
Taking part in this clinical study might not benefit you in any way. The study drugs may not help you. Your condition may get better, get worse or stay the same. However, your taking part may give more scientific information about the study drug and/or lung cancer.

**Will I be compensated for my time and effort?**
You will not be offered compensation for being in this study.

**What are my other options?**
If you decide not to enter this study, there is care available to you outside of this research study. The study doctor will discuss these with you. You do not have to be in this study to be treated for your cancer.

Taking part in this study, however, may make you unable to participate in some other research studies, if they exclude people who have taken certain treatments. You should discuss this with the researchers if you have concerns. You may wish to research other study options at websites like clinicaltrials.gov and ResearchMatch.org.

**How will you protect my private information that you collect in this study?**
Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Study records can be opened by court order. They also may be provided in response to a subpoena or a request for the production of documents.

**Storing and Sharing your Information**
De-identified data from this study (data that has been stripped of all information that can identify you), including your de-identified genetic information, may be placed into public databases where, in addition to having no direct identifiers, researchers will need to sign data use agreements before accessing the data. We will remove or code any personal information that could identify you before your information is shared. This will ensure that, by current scientific standards and known methods, it is extremely unlikely that anyone would be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Your data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, we may provide your deidentified data and/or specimens to other researchers. If we do, we will not include any information that could identify you. If your data or specimens are labeled with your study ID, we will not allow the other investigators to link that ID to your identifiable information.

**How is my Genetic Information Protected? What are the Risks?**
The Genetic Information Nondiscrimination Act (GINA) is a federal law that generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that GINA does **not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, and does not apply to employers with less than 15 employees.

In addition to GINA, the State of Georgia has laws that prohibit insurers from using genetic testing information for any non-treatment purpose. However, like GINA, this state law protection has exclusions: life insurance policies, disability income policies, accidental death or dismemberment policies, Medicare supplement policies, long-term care insurance policies, credit insurance policies, specified disease policies, hospital indemnity policies, blanket accident and sickness policies, franchise policies issued on an insurance policy written as a part of workers' compensation equivalent coverage, or other similar limited accident and sickness policies.

**Privilege**
In the State of Georgia, in some circumstances your genetic information has may have special legal protections called "privilege." This means that the information cannot be used as evidence in a court. By allowing us to use and disclose your genetic information for this research study along with other information about you that genetic information used in the research may no longer have that legal protection. Other protections described in this form will still apply. There are also other confidentiality protections for research data in general under Georgia state law.

**Medical Record**
If you have been an Emory and Saint Joseph's Hospital patient before, then you already have an Emory and Saint Joseph's Hospital medical record. If you have never been an Emory and Saint Joseph's Hospital patient, you do not have one. An Emory and Saint Joseph's Hospital medical record will be made for you if an Emory and Saint Joseph's Hospital provider or facility gives you any services or procedures for this study.

Copies of the consent form/HIPAA authorization that you sign will be put in any Emory and Saint Joseph's Hospital medical record you have now or any time during the study.

Emory and Saint Joseph's Hospital may create study information about you that can help with your care. For example, the results of study tests or procedures. These study results will be put in your Emory and Saint Joseph's Hospital medical record. Anyone who has access to your medical records will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA privacy rule. State and federal laws may not protect the research information from disclosure.

The results of some study tests and procedures will be used only for research purposes and will *not* be placed in your medical record. For this study, those items include: results on the correlative blood samples and results on the analysis of tumor biopsy specimens.

Tests and procedures done at non-Emory and Saint Joseph's Hospital places may not become part of your Emory and Saint Joseph's Hospital medical record. Also, if you decide to be in this study, it is up to you to let your other health providers know.

**In Case of Injury**

If you believe you have become ill or injured from this research, you should contact Dr. Bilen at telephone number [redacted]. You should also let any health care provider who treats you know that you are in a research study.

If you get ill or injured from being in the study, Emory and Saint Joseph's will help you to get medical treatment. Neither Emory, Saint Joseph's nor the sponsor will pay for your medical treatment. Your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurance does not pay, then you will have to pay these costs.

Emory, Saint Joseph's and the sponsor have not, however, set aside any money to pay you if you are injured as a result of being in this study or to pay for this medical treatment. For Emory and Saint Joseph's, the only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory or Saint Joseph's employee. "Negligence" is the failure to follow a standard duty of care. You do not give up any legal rights you may have by being in this study, including any right to bring a claim for negligence.

**Costs**

The study sponsor will pay for certain items and services that you may receive if you take part in this study.

Lenvatinib and Pembrolizumab will be free of charge.

You will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for your regular medical care. If you have insurance, Emory and Saint Joseph's Hospital will submit claims to your insurance for items and services that the sponsor does not cover. Emory and Saint Joseph's Hospital will send in only those claims for items and services that it reasonably believes your insurance will pay and that the sponsor has not paid.

The actual amount that you have to pay depends on whether or not you have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if you are in a study. How much you will have to pay for any co-payments, deductibles or co-insurance depends on your plan. Emory and Saint Joseph's Hospital and the sponsor will not pay for these costs.

It is a good idea to contact your insurance provider and tell them you want to be in this research study. Ask them what they will pay for and what they will not pay for. You can also ask the study team for help in figuring out what you will have to pay.

If you do not have insurance, Emory and Saint Joseph's Hospital will review your case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if you have to pay any costs for taking part in the study and what those costs will be.

**Withdrawal from the Study**

You have the right to leave a study at any time without penalty.

For your safety, however, you should consider the study doctor's advice about how to go off the study treatment. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

**Will the Information Collected from the Tumor Tissue, Blood Samples and Scans be Kept Confidential?**

While you are in this study, you will have blood (serum/plasma) and biopsy samples collected to be used for the current study analysis, including re-running study tests, if necessary, and storing samples for future research. Blood samples collection is mandatory, therefore there is no option to destroy samples. The purpose of storing these samples is to make them available to scientists who are trying to develop new tests, treatments, and ways to prevent diseases. We hope that these samples and images will provide information that will help researchers in the future. The samples will be labeled with an identification code. Your samples and images will never be labeled with your name and will remain separate from the files linked to your name.

Successful research using the samples or other parts of the samples could result in a commercial or therapeutic product with significant value, such as a product for the medical treatment or diagnosis of cancer or other disorders. You will not share in any financial benefits of these uses.

Your samples will only be used for research and will not be sold. These samples may be utilized by Emory and Saint Joseph's Hospital for further or additional analyses to answer scientific or medical questions, but if your samples or images are given to other researchers (other than Emory and Saint Joseph's Hospital) your samples would only be given to researchers who have had their research reviewed by an Institutional Review Board (IRB), which is a committee that protects the rights and privacy of study subjects.

## Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study in which you may choose to participate.

**PHI that Will be Used/Disclosed:**
The PHI that we will use or share for the main research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

**Purposes for Which Your PHI Will be Used/Disclosed:**
We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information.

**Use and Disclosure of Your Information That is Required by Law**:
We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults. We will also comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

**Authorization to Use PHI is Required to Participate**:
By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form. If you do not sign this form, you may still receive non-research related treatment.

**People Who will Use/Disclose Your PHI:**
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory and Saint Joseph's Hospital may use and disclose your PHI to get payment for study related treatment and to run normal business operations.

- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory and Saint Joseph's Hospital offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Compliance Offices, and the Emory Office for Clinical Research.
    - Government agencies that regulate the research including: Food and Drug Administration.
    - Public health agencies.
    - Research monitors and reviewer.
    - Accreditation agencies.
    - Study-Supporter: Merck
- Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your PHI may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

**Expiration of Your Authorization**
Your PHI will be used until this research study ends.

**Revoking Your Authorization**
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at:

Mehmet Asim Bilen, MD
Winship Cancer Institute, Emory University
1365-C Clifton Road NE
Atlanta, GA 30322

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the study.

**Other Items You Should Know about Your Privacy**
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally

will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

**Contact Information**

Contact Dr. Bilen at [redacted]

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at [redacted] or irb@emory.edu:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

## Consent and Authorization

***TO BE FILLED OUT BY SUBJECT ONLY***

Please **print** your name, **sign**, and **date** below if you agree to be in this research study, and any optional studies you initialed above. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the signed form to keep.

_____
**Name of Subject**

| _____ | _____ | ____:____ am / pm |
|---|---|---|
| **Signature of Subject (18 or older and able to consent)** | **Date** | **Time (please circle)** |

***TO BE FILLED OUT BY STUDY TEAM ONLY***

_____
**Name of Person Conducting Informed Consent Discussion**

| _____ | _____ | ____:____ am / pm |
|---|---|---|
| **Signature of Person Conducting Informed Consent Discussion** | **Date** | **Time (please circle)** |