

**INFORMED CONSENT FORM AND
AUTHORIZATION TO DISCLOSE PROTECTED HEALTH INFORMATION
FOR A RESEARCH STUDY**

Study Title: Phase II study with safety lead-in of lenvatinib, pembrolizumab, and weekly paclitaxel for recurrent endometrial, epithelial ovarian, fallopian tube and primary peritoneal cancer

Principal Investigator: Sarah Crafton, MD

Location: 4800 Friendship Ave
Pittsburgh, PA 15224

Phone: 412-578-1116 x 2 (24 hours)

Sponsor: Merck (Investigator Studies Program)

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with Allegheny Health Network. If you are an employee at Allegheny Health Network, your decision will not affect your employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

Key information about this study:

The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

There is an urgent need for new and improved treatment strategies for recurrent endometrial and ovarian cancer, and methods to identify which patients will benefit from these therapies.

Recently, pembrolizumab and lenvatinib have been approved for certain patients with recurrent endometrial cancer. In a previous study, we found that the combination of weekly paclitaxel with lenvatinib was active in patients with recurrent endometrial and ovarian cancer. While all 3 study drugs are FDA approved and the 2-drug combinations have been studied, the 3-drug combination

has not been studied yet. The investigators believe that the addition of pembrolizumab to weekly paclitaxel and lenvatinib (or weekly paclitaxel to pembrolizumab and lenvatinib) is highly effective and safe with manageable side effects in both recurrent endometrial and platinum resistant ovarian cancer. If you participate in this study you will receive paclitaxel (chemotherapy) intravenously (by vein) weekly, pembrolizumab (immunotherapy) intravenously every 3 weeks, and you will take 1-4 lenvatinib pills (targeted therapy) every day. We will also collect some extra blood and tissue samples for research. You will have imaging (CT scans) to monitor how the treatment is working for you. You will be able to continue treatment as long as you are benefitting from treatment and you are feeling well, however, you may decide to stop being in the study at any time. You will be closely monitored for side effects. The most likely side effects are changes in your blood counts, hair loss, high blood pressure, fatigue, diarrhea, nausea, skin problems, rash, thyroid dysfunction, shortness of breath, autoimmune reactions (abnormalities in liver, pancreas, kidney and lung function).

It is unknown at this time what other side effects could happen from combining the 3 drugs.

This project is being conducted by Dr. Floor Backes, MD, and is funded by Merck who is paying The Ohio State University Medical Center to perform this research.

In addition, one or more of the researchers from Allegheny Health Network has received compensation from the sponsor for consulting and advisory services. Dr. Thomas Krivak and Dr. Donna Kinzler, Co-Investigators at Allegheny Health Network (AHN), have both received speaking fees during the last 365 days from Merck, the study sponsor in collaboration with Ohio State. If you would like more information, please ask the researcher or the Allegheny Health Network Research Institute at 1-844-577-4621.

1. Why is this study being done?

While all 3 study drugs are FDA approved, and 2-drug combinations have been studied, the 3- drug combination has not been studied yet. The investigators believe that the addition of pembrolizumab to weekly paclitaxel and lenvatinib (or weekly paclitaxel to pembrolizumab and lenvatinib) is highly effective and safe with manageable side effects in both recurrent endometrial and platinum resistant ovarian cancer. The purpose of this trial is to study how well lenvatinib, pembrolizumab, and weekly paclitaxel work together in women who have recurrent endometrial cancer and/or recurrent platinum resistant ovarian, fallopian tube, and primary peritoneal cancer, and what kind of side effects patients may experience.

2. How many people will take part in this study?

We will enroll approximately 60 women at various sites.

3. What will happen if I take part in this study?

Before you begin the study:

You will need to sign this informed consent form.

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

1. History and physical examination will include blood pressure measurement and weight and pelvic examination to evaluate if there is tumor growing in your pelvis or vagina.
2. Blood tests to assess blood cell counts; liver, kidney and blood clotting function; blood mineral levels; thyroid function; CA-125 levels (marker in your blood to monitor your cancer if this has been a marker for you).
3. Urine test sample for urine protein level and a pregnancy test if you could become pregnant.
4. If you are able to become pregnant, a blood test will be done to make sure that you are not pregnant.
5. Electrocardiogram (EKG)
6. Tumor imaging will be obtained prior to treatment of your chest, abdomen and pelvis to determine where your tumor is located, and to determine the size of the tumor.
7. If your doctor has additional concerns that the study medication may not be safe for you, you may require additional tests to confirm you are a good candidate for the study (for example, if you have a history of significant and/or uncontrolled heart problems you may need an ultrasound of your heart).

If the exams, tests and procedures show that you can be in the study, and you choose to take part, you will proceed with the study.

You will need a biopsy of a tumor lesion prior to starting treatment.

During the study:

1. History and physical examination every 3 weeks on day 1 of every cycle which will include blood pressure measurement and may include pelvic examination.
2. Blood pressure measurements every time you come for chemotherapy (day 1, 8, 15 of every cycle) and you will keep a blood pressure log at home (daily measurement)
3. Electrocardiogram (EKG) cycle 2 day 1, cycle 4 day 1, and at the 30 day safety visit.
4. CT scan or MRI scan after the first 8 weeks and if your tumor is improving then you will have imaging studies approximately every 9 weeks (3 cycles). If your doctor suspects that your cancer is growing you will also get imaging studies.
5. Periodic blood testing for CA-125 level if you have ovarian cancer or if you have endometrial cancer and your CA-125 is initially elevated. CA-125 is a blood test that is generally performed for patients with your type of cancer to monitor the effectiveness of treatment.
6. Blood tests to assess blood cell counts prior to day 1, day 8, and day 15 of every cycle; liver and kidney function; blood mineral levels prior to day 1 of every cycle to make sure your body has recovered and it is safe to get chemotherapy. Your bloodwork will include thyroid function test every other cycle.

7. Blood pressure monitoring will occur immediately after the first treatment with lenvatinib and weekly when you come for treatment. If your blood pressure is high and need to start medications you may be asked to monitor your blood pressure every day. You can do this at home and provide the results to the study doctor or study nurse/coordinator.
8. Urine test prior to day 1 of every cycle.
9. Toxicity Assessments that involve asking you details about side effects of treatment will occur on day -15, -8, 1, 8, 15 of cycle 1, and day 1 of each cycle after that.
10. You will be strongly advised to avoid grapefruit, grapefruit juice, and herbal supplements with high risk of interaction with the CYP3A4 or CYP2C8 pathways, such as St. John's Wort, because substances like these may reduce the effectiveness of lenvatinib and/or paclitaxel that you will receive as your cancer treatment while on this study.
11. You are not allowed to take oral or intravenous steroids while on this study. Please check with your doctor before taking steroids.

Treatment

You will receive 3 study drugs.

Paclitaxel (chemotherapy) is given intravenously (by vein) weekly, pembrolizumab (immunotherapy) is given intravenously every 3 weeks, and you will take 1-4 lenvatinib pills (targeted therapy) every day. Throughout the study you will be monitored closely for side effects. After the first two cycles and then every 3 cycles (9 weeks) you will also get imaging to see how well the combination of these drugs work. You will have routine chemotherapy visits every 3 weeks (on day 1 of each 3-week cycle) with your gynecologic oncologist and intravenous chemotherapy therapy on day 1, day 8, and day 15. You will take chemotherapy pills (lenvatinib) daily by mouth starting cycle 1 day -15 and will continue every day for as long as you are on this treatment.

Your chemotherapy is given as an outpatient and your outpatient visit (including seeing your doctor) will take 2.5-3.5 hours. You can continue to be on this treatment as long as you are receiving benefit (cancer is shrinking or cancer is not growing and you are feeling well).

If you decide to stop taking this treatment, or your doctor decides to stop treatment because your cancer starts growing back, you will be monitored for side effects for 30 to 90 days after stopping treatment. You will have your normal cancer follow up visits. If your cancer has not come back or gotten worse and you have not started a new treatment, you will have (optional) CT scans to monitor your cancer approximately every 12 weeks for 1 year. You will not need to fill out any additional surveys or paperwork since all information will be collected from the medical records. If you continue follow up or treatment with a different doctor or hospital, we may contact you periodically (every 3-6 months) to see how you are doing.

Blood samples: You will be asked to give extra blood samples (4 to 5 teaspoons) before your first treatment and before cycle 2, 3, 6, and at the time of cancer progression or stopping treatment. This blood test would not be needed for diagnosis but helps to study how your body and the treatment work to fight your cancer. No more than 12 teaspoons (58 mL) of blood will be collected at one time.

Tissue specimens: To better understand which patients are more likely to benefit from this treatment, we will be asking you to allow us to collect and store some tissue for research. You will need a research biopsy prior to starting treatment (in the 14 days before treatment). The tissue collected will not be needed for diagnostic purposes. If you have any other biopsies during or after the study, or have already existing specimens (from a previous surgery or biopsy) that are no longer needed for your care, we may study these as well. We will also ask for a biopsy if/when this treatment stops working to study why the treatment stopped working.

Clinical data: We are asking you to allow us to collect and store clinical data from your medical record for research. This includes data about your surgery and specimens collected, treatment plans, pathology and cytology reports, and genetic testing, if performed.

Medication diary:

You will be given a patient medication calendar to complete throughout the study. The patient medication calendar is a monthly calendar on which you are to record the number of tablet(s) of lenvatinib you take each day. You will need to bring the calendar with you to the doctor's office before each cycle, along with any unused study medications and empty medication containers.

Blood pressure Log:

You will be asked to check your blood pressures daily and to keep a log. Your study nurse and/or doctor will review your blood pressure log with you at your visits.

Study Calendar:

Schedule/Tests	Screening		Cycle 1					Cycle 2			Cycles 3+			EOT	Follow Up		
			Day -15	Day -8	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		30 day Safety	90 day Safety	Survival
Scheduling Window (Days)	-28 to -1	-14 to -1	± 1	± 1	± 3	± 1	± 1	± 3	± 1	± 1	± 3	± 3	± 3	± 7	± 7	± 7	± 7
Physical Exam/Provider Visit		X			X			X			X			X	X		
Vitals, weight, height, ECOG performance status		X	X	X	X	X	X	X	X	X	X	X	X		X		
Adverse Event Assessment		X	X		X			X			X			X	X	X	
Safety Labs for treatment		X		X	X	X	X	X	X	X	X	X	X		X		
CA-125		X			X			X			X				X		
Pregnancy Test (Urine or Serum β-HCG) as directed		X													X		
Echocardiogram/MUGA as directed	X																
Electrocardiogram		X															
Tumor Imaging (CT scans/MRIs)	X										X				X		
Pre-medications ¹			X	X	X	X	X	X	X	X	X	X	X				
Paclitaxel Administration ¹			X	X	X	X	X	X	X	X	X	X	X				
Lenvatinib Administration ¹			X	X	X	X	X	X	X	X	X	X	X				
Pembrolizumab Administration ¹					X			X			X						
Lenvatinib Dosing Diary			X		X			X			X						
Blood Pressure Monitoring		X	X	X	X	X	X	X	X	X	X	X	X				
Archival and Newly Obtained Tissue Collection ¹		X												X			
Research Labs			X					X			X			X			
Post-study anti-cancer therapies															X	X	X
Survival status															X	X	X

During the study you will not be allowed to take:

- Other chemotherapy or supplements that could treat cancer
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines and COVID-19 vaccine for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- It is strongly advised to avoid grapefruit or grapefruit juice and herbal supplements with high risk of interaction with certain enzymes (CYP3A4 or CYP2C8) that can change the absorption of the study drugs such as St. John's Wort while on study.
- Steroids unless your doctor approves this.
- Any other medications that can interfere or interact with the study treatments. These can make the cancer treatment work too much or too little resulting in side effects. Always check with your doctor if new medications are allowed (even if prescribed for a short duration)

4. How long will I be in the study?

At this time, it is expected that you will be in the study from the time you sign consent and you will be

continued to be followed on this study. You can continue to be on this treatment as long as you are receiving benefit (cancer is shrinking or cancer is not growing and you are feeling well).

If you experience confirmed disease progression or start a new anticancer therapy, you will move into the survival follow up phase, and may be contacted periodically by telephone.

If you decide to stop being in the study (for any reason) you will be followed for side effects (adverse events) for 30-90 days after you stop being in the study, and we will periodically (approximately every 3-6 months) check your records or may contact you to see how you are doing. If your cancer has not come back or gotten worse and you have not started a new treatment, you will have (optional) CT scans to monitor your cancer approximately every 12 weeks for 1 year. You will not need to make extra visits just for study follow up after stopping study medication and completing the 30 day safety visit. We will be able to obtain your information from your records. If you continue follow up or treatment with a different doctor or hospital we may contact you periodically (every 3-6 months) to see how you are doing. If your cancer goes away completely and you have no evidence of disease, you will continue follow up visits every 3-6 months.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with Allegheny Health Network.

Please note that according to FDA regulations, data collected about you up to the time of withdrawal remains part of the study data and may not be removed.

6. What risks, side effects, or discomforts can I expect from being in the study?

Physical Risks: When you have a test or procedure to remove tissue for your standard of care, your doctor will explain the risks at that time, and they may include discomfort, bleeding, bruising, and scarring. You may experience discomfort, bleeding or bruising associated with the blood draw and/or biopsy.

Privacy Risks: Every effort will be made to maintain your privacy, however this cannot be guaranteed. There is a risk in this project that someone other than researchers could get access to information we have stored about you. If that data suggested something serious about your health, it could be misused.

Research using your specimens may include mapping your DNA (whole genome sequencing). This information could identify you. Ask the study team if you have questions.

GINA: A federal law, called the Genetic Information Nondiscrimination Act (GINA), 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 from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions about your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this federal law. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under Ohio law, health insurance companies cannot ask about the results of a genetic test or use any information obtained from genetic testing to make decisions about providing coverage or benefits for health care services.

General/Unforeseeable:

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking lenvatinib, pembrolizumab and paclitaxel. In some cases, side effects can be serious in that they can be long lasting, may never go away, may result in hospitalization, or may be life threatening and possibly lead to death (fatal).

You should talk to your study doctor about any side effects that you have while taking part in the study.

What side effects could the study drugs cause?

Risks and side effects related to Paclitaxel (Taxol®) include:

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Paclitaxel, more than 20 may have:

- Low white blood cell counts – this may make you more open to infection
- Low platelet count - this may make you bruise more easily and bleed longer if injured
- Low red blood cell count which may cause tiredness, shortness of breath or fatigue
- Mild to severe allergic reaction which may be life-threatening with hives, wheezing (difficulty breathing) and change in blood pressure (low or high)
- Numbness and pain of the hands and feet that sometimes worsens with additional treatment and may not disappear after the drug is stopped. This may lead to difficulty walking, buttoning clothes, etc. (may be serious)
- Hair loss
- Muscle weakness and muscle loss
- Muscle and joint aches

- Nausea and/or vomiting
- Diarrhea
- Sores in the mouth or throat (that can lead to difficulty swallowing and dehydration)

OCCASSIONAL, SOME MAY BE SERIOUS

In 100 people receiving Paclitaxel, from 4 to 20 may have:

- Low blood pressure
- Irregular heartbeats
- Fever
- Fatigue, weakness
- Swelling, accumulation of fluid
- Elevation in liver function blood tests
- Confusion; mood changes
- Skin tissue irritation, swelling or discoloration around the injection site
- Skin tissue damage if some of the drug leaks from the vein while it is being given
- Changes in taste
- Rash

RARE, AND SERIOUS

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

- Elevation of serum creatinine in kidneys (damage to the kidneys which may be reversible or permanent damage)
- Inflammation of the colon, pancreas or lungs (may be serious)
- Liver failure
- Seizures
- A slowing of the heart rate (a slow pulse is not harmful; however, if you should develop any other irregularities in heart rate during treatment, an EKG and other tests may be required.)
- Heart attack
- Blood clots
- Blockage in the intestines
- Opening in the bowel wall

Risks and side effects related to Lenvatinib include:

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Lenvatinib, more than 20 may have:

- Low white blood cells or lymphocytes– this may increase the risk of infection
- Anemia (low red blood cell counts) which may cause tiredness, shortness of breath or fatigue and/or require blood transfusion
- Diarrhea, nausea, vomiting

- Fatigue
- Tiredness
- Loss of appetite
- Dehydration
- Change in hair color
- High blood pressure which may cause blurred vision
- Sores in mouth which may cause difficulty swallowing or dry mouth
- Pain or aches in muscles or joints or in abdomen
- Headache
- Redness, pain or peeling of palms and soles
- Protein in the urine
- Hoarse voice
- Blood clot in the lungs that can cause shortness of breath or fast heart rate

OCCASSIONAL, SOME MAY BE SERIOUS

In 100 people receiving Lenvatinib, from 4 to 20 may have:

- Abnormal heartbeat
- Pain
- Constipation, heartburn
- Swelling of arms, legs
- Fever
- Weight loss
- Dizziness
- Changes in taste
- Cough, shortness of breath
- Internal bleeding which may cause coughing up blood, black tarry stool, or blood in vomit
- Bleeding from multiple sites including the nose
- Hair loss, rash, skin changes
- Changes in thyroid function which can cause tiredness, hair thinning, constipation, for which you may need to take medicines
- Slow wound healing
- Inflammation of the pancreas (pancreatitis)
- Inflammation of the gallbladder (cholecystitis)
- Low platelets - this may make you bruise more easily and bleed longer if injured
- Heart failure, heart attack which may cause shortness of breath, swelling of ankles, and tiredness
- Kidney damage
- Low blood pressure

Events of jaw bone damage, called osteonecrosis of the jaw (ONJ), have been observed with lenvatinib. Invasive dental procedures are an identified risk factor for the development of ONJ. We recommend you have an oral dental examination and appropriate preventive dentistry prior to

initiation of lenvatinib. You should continue periodic dental examinations and practice good oral hygiene during lenvatinib therapy. Avoid invasive dental procedures during lenvatinib treatment, if possible.

It is also possible that you may experience pain in your joints, back pain, musculoskeletal pain, or pain in your extremities (limbs).

RARE, AND SERIOUS

In 100 people receiving Lenvatinib 3 or fewer may have:

- Kidney problems which may require dialysis
- Blood clot or bleeding in organs which may cause confusion, paralysis, swelling, pain, or shortness of breath
- A tear or hole in internal organs (perforation) or connection between organs (fistula) that may require surgery and could lead to death
- A hole in the lung (pneumothorax) causing air around the lung and shortness of breath
- Liver damage which may cause yellowing of eyes and skin
- Change in the heart rhythm
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Blood in the urine

Possible Side Effects of MK-3475 (Pembrolizumab)

What is known about this study drug? Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers but may not be approved to treat your type of cancer. 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 side effects may be 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, SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), more than 20 and up to 100 may have:

- Itching of the skin
- Loose or watery stools
- Cough

COMMON, SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), from 5 to 20 may have:

- Pain in back

- Joint pain and stiffness
- Rash
- Fever
- Back pain
- Pain in belly
- Loss of skin color

MK-3475 (pembrolizumab) 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:

- Not enough thyroid hormone, so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatremia)

UNCOMMON, AND SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), 1 to 5 people

- Inflammation of the lungs, so you may feel short of breath and cough (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel 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 have 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 (colitis)
- 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 (Severe skin reactions, including Stevens-Johnson syndrome or toxic epidermal necrolysis)

RARE, SOME MAY BE SERIOUS OR LIFE THREATENING

In 100 people receiving MK-3475 (pembrolizumab), < 1 person may have:

- 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 (Guillain-Barré syndrome)

- Inflammation of the muscles, so you may feel weak or have pain in your muscles (myositis)
- 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 have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)
- 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, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- 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 (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, and bellyaches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- 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 (nephritis)
- 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 (myocarditis)
- 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 (thyroiditis)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- 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 (encephalitis)

- 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 (myelitis)
- Inflammation of blood vessels (vasculitis). Symptoms will depend on the particular blood vessels that are involved in the inflammatory process, for example; if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue.
- 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. 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.
- Inflammation of the protective sac surrounding your heart (pericarditis) which can cause sharp chest pain and shortness of breath (especially when lying flat), fever, and a fast or irregular heartbeat. In severe cases, your heart may have difficulty pumping blood throughout your body.

Additionally, 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 these side effects:

- *Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)*
- *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 (hemophagocytic lymphohistiocytosis)*
- *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 the 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).*

- *Diplopia, or double vision, has been reported, but it is uncertain if this is related to pembrolizumab at this time*

Other medications: There are certain medications and supplements that may interact with the study drug(s). You should not take any new medications or supplements without discussing it with your study doctor first.

Blood samples: Collection of treatment related and research related blood samples: Taking blood from your arm may sometimes cause pain/discomfort at the site where the blood is drawn, bruising, bleeding, occasional lightheadedness, redness, and/or swelling, and, rarely, faintness or infection.

Biopsies: Collection of research biopsies may cause pain or discomfort at the site and can cause damage to the tissue and surrounding tissues or organs.

For more information about risks and side effects, ask your study doctor.

Precautions will be taken to try to prevent side effects from occurring, and medicines are available to treat many side effects if they do occur. For example, you may develop signs of an allergic reaction during any given treatment with paclitaxel, pembrolizumab or lenvatinib, which could be severe or life threatening. The symptoms of the allergic reaction may include rash, sweating, swelling of the skin, itching, change in heart rate, difficulty breathing, low blood pressure and abdominal, back, arm or leg pain.

If these symptoms develop, you will be treated promptly with medications to control the allergic reaction. You may need to be put into the hospital if the allergic reaction becomes severe or life threatening. Before any treatment with paclitaxel, you will receive medications prior to each treatment to try to prevent an allergic reaction.

Surgery:

Although there are no planned major surgeries or procedures specified in this protocol after initiating chemotherapy, surgery may be indicated if you develop certain conditions such as a bowel obstruction, abscess or other infections, or symptomatic tumor recurrence. Since lenvatinib affects the way new blood vessels form, delayed, abnormal or incomplete healing may occur if you are taking this agent and you undergo surgery. Depending on type of wound healing complication, the recovery from these complications may take weeks to months and may require additional surgery. It is usually recommended that elective surgery be delayed in order for your body to clear this agent. However, this may not be possible based on your condition. Although little information is available to accurately determine the risk of wound complications from surgery once receiving chemotherapy and lenvatinib, it is generally considered increased above the risk assumed from surgery during chemotherapy alone. Your physician will inform you of these risks and the timing for intervention if necessary.

Reproductive Risks:

You should not become pregnant while on this study because the drug(s) in this study can affect an unborn baby. Women should not breastfeed while on this study. **It is important you understand that if you could become pregnant, you need to use birth control while on this study.** Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. You should notify your health care team immediately if you think you have become pregnant while participating in this study.

Imaging Risks:

The CT scans that you get in this study are a part of standard of care to monitor if your cancer has responded to treatment, will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

As part of the CT scans that you get in this study, you will get oral contrast to drink and iodine will be injected into your vein. Some people are allergic to iodine. Let your study doctor know if you have an allergy to iodine or seafood or if you have kidney problems.

7. What benefits can I expect from being in the study?

You may not directly benefit from participating in this study. You may potentially benefit from your cancer shrinking or disappearing because of the chemotherapy. However, no direct medical benefit can be guaranteed. No promise can be made concerning the study outcome because results from a clinical research study cannot be predicted. Researchers hope to improve current treatment options for patients, to better understand the potential side effects, and which patients benefit most from this treatment.

8. What other choices do I have if I do not take part in the study?

If you do not participate in the study you continue with regular clinical care with your doctor. You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Taking part in another research study, if one is available
- Receiving standard of care treatment
- Receiving comfort care, also called palliative care. This type of care may help to reduce the symptoms caused by cancer, but does not treat the cancer directly
- Receiving no treatment

9. What are the costs of taking part in this study?

All standard of care tests, procedures, or medications that may be necessary for the treatment of your medical condition will be billed to your insurance in the normal way. Paclitaxel is standard of care and will be billed to your insurance.

You will be responsible for co-payments, coinsurance, deductibles, or the full medical costs if your insurance does not cover the medical care. These costs are not covered by this research study. If you have any questions about treatment for which you may be responsible for paying, please discuss this with your physician or study staff and your insurance company.

Lenvatinib and pembrolizumab will be provided to you and not billed to you or your insurance company for this study. However, if you should need to take the study agent much longer than is usual, it is possible that the companies' supply of free agent could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

10. Will I be paid for taking part in this study?

There is no provision to provide financial compensation to you if you choose to participate in this research project.

If you agree to participate, your samples will be considered a gift to The Ohio State University. The university may sell or share your samples and personal information with others, such as private companies, government agencies, or other universities. The university will be paid if your samples and personal information are sold.

- Your samples and personal information may be used to make new products or technologies. You will not be paid if these new products or technologies are sold or make money.
- You cannot choose how your samples and personal information will be used. If you do not want to let others decide how your samples and personal information will be used, then you should not donate your samples.

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

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

No funds have been set aside by Allegheny Health Network or Allegheny Health Network Research Institute to pay you in case you are injured. You do not waive any of your legal rights to compensation, if any, by signing this form.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at anytime without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of research participants.

13. Will my de-identified information (and bio-specimens) be used or shared for future research?

Yes, it/they may be used or shared with other researchers without your additional informed consent.

By signing this consent you give permission for:

1. Some of your specimens that are not needed for diagnostic purposes, including tissue and blood, to be collected, stored, and used for research
2. Some of your specimens to be used for research to study changes in genetic material
3. Data from you and your medical record to be collected, stored and used for research
4. Your treating hospital or clinical team such as your study doctor or nurse/coordinator to contact you in the future to see how you are doing or ask if you are interested in hearing about other research projects.

14. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Data stored will consist of data that has been collected as part of your normal care and is part of your medical records. Any additional testing will be for research only and will not be shared with you.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

15. Authorization to Use and Disclose Individually Identifiable Health Information for a Research Study (HIPAA Authorization Statement)

Before you can take part in this research study, the Allegheny Health Network is required to obtain your authorization to use and/or disclose (release) your health information. This section describes to you how, and to whom, your health information will be used and/or disclosed (shared) while you are participating in this research study. It is important that you read this carefully. Allegheny Health Network and its researchers are required by law to protect your health information.

The following is a list of health information that will be used and/or disclosed:

- Name
- Date of birth
- Address
- Phone number
- Social Security Number
- Demographic information
- Physical exam, including height and weight
- Pelvic exam
- Full medical history
- Any questionnaires that you complete
- List of medications that you are taking, including over-the-counter supplements
- Vital signs
- EKG
- ECHO/MUGA results
- Blood and urine tests
- Tumor biopsy
- Pregnancy test, if applicable
- All imaging done that applies to this study, including tumor imaging
- Ultrasound, if necessary
- Diagnosis and treatment of a mental health condition
- Records about any study drug you received
- Toxicity assessments and side effects
- Records about phone calls made as part of this research
- Any research records created about you
- Any of your medical records that need to be accessed for the purpose of this study

The following is a list of entities that may use and/or disclose your health information as part of this study:

Internal Oversight

Those who oversee the study will have access to your health information, including the following:

- Allegheny Health Network (AHN)
- AHN Research Institute
- AHN Compliance Office
- Study Doctor and Study Staff

Governmental Oversight

Your health information may also be shared with government agencies that have oversight of the study or to whom access is required under the law:

- U.S. Department of Health and Human Services (HHS)
- U.S. Food and Drug Administration (FDA)
- Regulatory Agencies in other countries similar to the FDA

Others Outside Allegheny Health Network

The following persons and/or organizations outside of Allegheny Health Network may also use, disclose, and receive your health information in connection with this study:

- Sponsor (and companies owned/affiliated with sponsor): Merck, in collaboration with Ohio State, is the sponsor of this study. They will have access to your Protected Health Information (PHI).
- Study Monitor: A Medical Monitor provides medical expertise for trial oversight and safety concerns. The medical monitor will have access to your PHI.
- Independent data and safety monitoring board(s): A data monitoring committee – sometimes called a data and safety monitoring board – is an independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing. They will have access to your PHI.
- Institutional Review Board (IRB): An institutional review board, also known as an independent ethics committee, ethical review board, or research ethics board, is a type of committee that applies research ethics by reviewing the methods proposed for research to ensure that they are ethical. Ohio State University's IRB is the IRB for this study. They and their Office of Responsible Research Practices will have access to your PHI.
- Central Lab: Core laboratories collect, process, and analyze data from multi-center clinical studies through a single platform to prevent inter- and intra-variability by following standardized protocols. The central lab for this study is located at Ohio State University. They will have access to your PHI.
- If a patient is eligible for Medicare, federal law requires Merck and Ohio State to inform the Centers for Medicare & Medicaid Services (the agency responsible for the Medicare program) when they are going to pay for a patient injury. Merck and Ohio State may need to share information, such as your name, date of birth, sex, and Medicare ID number (if you have one), with the Centers for Medicare & Medicaid Services.
- Your insurance company will have access to your information if charges are billed to insurance.

In order to participate in this study, you must agree to share your health information with the persons and organizations listed above. If these persons or organizations that you authorize to receive and/or use protected health information, are not health plans, covered health care providers or health care clearinghouses subject to federal health information privacy laws, they may further disclose the protected health information and it may no longer be protected by the federal health information privacy laws.

Expiration of Authorization

This authorization will not expire unless you revoke it in writing. You may revoke or end this authorization by writing to the Principal Investigator:

Sarah Crafton, MD
 4800 Friendship Ave
 Pittsburgh, PA 15224

If you revoke your authorization, you will also be removed from the study. Revoking your authorization only affects the use and sharing of your health information after the written request is received. Any health information obtained prior to receiving the written request may be used to maintain the integrity of the study.

Authorization

By signing this document (authorization), you authorize that your health information can be used and/or disclosed as described.

Your access to your protected health information created or obtained by Allegheny Health Network in the course of the research (that includes treatment) may be temporarily suspended for as long as the research is in progress. By signing this document, you are agreeing to the denial of access to your protected health information, created for the research, while you are participating in this research study. Your access to your protected health information will be reinstated upon completion of the research.

If you choose to not sign this document, you will not be permitted to participate in this research study.

I. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

II. Who can answer questions about the study?

For questions, concerns, or complaints about the study, or if you feel you have been harmed as a result of study participation, you may contact Dr. Floor Backes at 614-366-9084.

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact Privacy Officer, Suite E2140, 600 Ackerman Road, Columbus, OH 43202, 614-293-4477.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact Dr. Floor Backes or at 614-366-9084.

If you have any questions or concerns regarding Allegheny Health Network Research Institute, please contact 1-844-577-4621.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form.

Your signature below indicates your permission to take part in this research and to the use and disclosure of your protected health information. You will receive a copy of this signed document:

 Signature of Subject

 Date

 Printed Name of Subject

 Time – include AM/PM

 Signature of Witness to Signature

 Date

 Printed Name of Witness to Signature

 Time – include AM/PM

Investigator/Research Staff

I have explained the research to the participant before requesting the signature(s) above. A copy of this form has been given to the participant.

 Signature of Physician Investigator/Qualified Practitioner

 Date

 Printed Name of Physician Investigator/Qualified Practitioner

 Time – include AM/PM

Consent – (Signature Block for Adult Unable to Consent)

Your signature below indicates your permission for the subject named below to take part in this research and to the use and disclosure of this person’s protected health information. You will receive a copy of this signed document:

Printed Name of Subject	Date
Signature of Surrogate Decision Maker or Legally Authorized Representative	Time – include AM/PM
Printed Name of Surrogate Decision Maker or Legally Authorized Representative	Relationship to Subject
Signature of Witness to Surrogate or Legally Authorized Representative Signature	Date
Printed Name of Person Witnessing Surrogate or Legally Authorized Representative Signature	Time – include AM/PM

Assent

- ☐ Obtained
- ☐ Not obtained because the capability of the subject is so limited that the subject cannot reasonably be consulted.

CONSENT & AUTHORIZATION

The Ohio State University
IRB Study ID: MOD00000720
IRB Effective Date: 6/20/2025

IRB Protocol Number: 20172
Version: 7.1 (06/05/2025)

My signature indicates that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, that consent was freely given by the subject and the subject signed this consent document.

Check box ONLY if the witness is an “impartial” witness - an individual (greater than 18 years of age) with no affiliations to the patient (e.g. not a relative) and/or to the research study (e.g. not a study coordinator). An “impartial” witness is only required when a “short form” consent form is used or the subject is unable to read the consent form and the written informed consent document is read and comprehended by the subject or the subject’s legally authorized representative and oral consent is given by either the subject or the subject’s legally authorized representative.

Signature of Witness to Consent Process

Date

Printed Name of Witness to Consent Process

Time – include AM/PM

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. A copy of this form has been given to the participant or his/her representative.

Signature of Physician Investigator/Qualified Practitioner

Date

Printed Name of Physician Investigator/Qualified Practitioner

Time – include AM/PM