Official Title: **Pembrolizumab, Radiotherapy, and Chemotherapy in Neoadjuvant Treatment of Malignant Esophago-gastric Diseases (PROCEED)**

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DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Pembrolizumab, Radiotherapy, and Chemotherapy in
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CONCISE SUMMARY

Patients who take part in this study have been diagnosed with cancer of the esophagus (the swallowing tube from the throat to the stomach) or have a diagnosis of gastric (stomach) cancer. The purpose of this study is to determine if adding pembrolizumab to standard treatment will improve how your cancer responds. Pembrolizumab is an investigational study drug that will be added to standard medical care. It is a type of immunotherapy that may help the immune system to attack cancer cells. The word "investigational" means the study drug is still being tested in research studies and is not approved by the U.S. Food and Drug Administration (FDA) for treatment of cancer of the esophagus or gastric cancer in combination with radiation.

Pembrolizumab is given intravenously (IV). The first dose of pembrolizumab is given 1-2 weeks before radiation and chemotherapy begins. Pembrolizumab is given 2 more times while you are receiving chemotherapy and radiation (CRT) for a total of 3 doses before surgery. If you have surgery, you may receive pembrolizumab after surgery for an additional 3 doses. You may receive a total of 6 doses during this study.

Pembrolizumab will be given in addition to standard therapy carboplatin and paclitaxel with radiation therapy. Patients will be evaluated at least weekly during radiation treatment. The purpose of this study is to determine if adding pembrolizumab to the standard treatment of chemotherapy and radiation will improve how your cancer responds. This study will also measure what effect (good and bad) the study drug pembrolizumab combined with carboplatin/paclitaxel and radiation therapy may have in treating your cancer, including changes in your tumor.

There are risks to this study drug that are described in this document. Some risks include inflammation of the lungs with shortness of breath and cough (called pneumonitis), inflammatory disease that affects multiple organs in the body and skin reactions (rash).

If you are interested in learning more about this study, please continue reading below.

You are being asked to take part in this research study because you have been diagnosed with cancer of the esophagus (the swallowing tube from the throat to the stomach) or you have a diagnosis of gastric (stomach) cancer. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are detailed below. Please tell the study doctor or study staff if you are taking part in another research study.

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Manisha Palta MD will conduct the study. The study was developed by Manisha Palta MD and is supported with funding from Merck & Co. Inc. A portion of the funds may reimburse part of Dr. Palta's and the research team's salaries.

WHO WILL BE MY DOCTOR ON THIS STUDY?

If you decide to participate, Dr. Palta or your regular Duke cancer doctor will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?

Cancer of the esophagus and gastric cancers are commonly treated with radiation therapy and chemotherapy. Radiation therapy is given Monday through Friday for about 6 weeks total. Following a rest period after radiation therapy and chemotherapy, subjects are restaged (response to treatment is measured) and subjects may then proceed to surgery. This is one of the standard treatment regimens often used with patients who have this cancer diagnosis.

On this study, an investigational study drug called pembrolizumab is added to standard medical care. The word investigational means the study drug is still being tested in research studies and is not approved by the U.S. Food and Drug Administration (FDA). The primary purpose of this research study is to determine if adding pembrolizumab to standard treatment will improve how your cancer responds. This study will also measure what effects (good and bad) the study drug pembrolizumab combined with carboplatin/paclitaxel and radiation therapy may have in treating your cancer, including changes in your tumor.

HOW DOES PEMBROLIZUMAB WORK?

Pembrolizumab works by blocking a specific protein in your body called PD-1. PD-1 is a protein that keeps the immune system from attacking cancer cells. In patients with cancer, pembrolizumab blocks this protein's function and may increase the immune system's ability to target and destroy cancer cells. Pembrolizumab is a type of immunotherapy.

Pembrolizumab has been studied in humans with many different types of cancer. Prior studies have evaluated the effects of the drug on these cancers, safety of pembrolizumab, as well as the levels of drug in the body. To date, these studies have increased our understanding of how to dose pembrolizumab in humans as well as identified common side effects of pembrolizumab. Pembrolizumab, (also called KEYTRUDA®), is approved by the FDA to treat other cancers, including certain types of skin cancers (melanoma, merkel cell), head and neck cancer, renal cell carcinoma and small cell lung cancer.

Research studies have tested pembrolizumab in subjects as a single drug with metastatic gastrointestinal cancers and in combination with carboplatin/paclitaxel in ovarian cancers. The effects that pembrolizumab will have in combination with standard medical care are unknown. Studies are ongoing to see what side effects (both good and bad) are associated with its use.

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HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 38 people will take part in this study at Duke.

WHAT IS INVOLVED IN THE STUDY?
You must meet all study entry requirements in order to qualify for this study. Requirements will be reviewed with you by your study doctor and/or the study staff. Once you understand what is involved with participating in this study and all your questions have been answered you will be asked to sign and date this consent form to show that you want to take part in this research study.

If you participate in this study, pembrolizumab is given intravenously (IV) once every 3 weeks. The first dose of pembrolizumab is given 1-2 weeks before radiation and chemotherapy begins. Pembrolizumab is given 2 more times while you are receiving chemotherapy and radiation therapy (CRT) for a total of 3 doses before surgery. After CRT standard of care imaging scans are completed to measure the tumor response to study drug. If appropriate, you will then proceed to surgery. After about 4 weeks recovery time, pembrolizumab is given after surgery for an additional 3 doses. You will receive a total of 6 doses of pembrolizumab during the study.

If you decide to take part in the study, you may have additional clinic visits for blood work and assessments as you will be monitored closely for side effects. The study team will make every effort to plan study procedures around routine clinic visits to minimize extra visits for you. Participation in this study will involve a screening visit to determine whether you are eligible for the study. Some of the screening exams, tests and procedures are part of routine cancer care, and the results of those tests will be used to determine eligibility.

To makes sure you are eligible to participate in the study, the following assessments are necessary before you start study drug:

- You will have a complete physical exam including your height and weight.
- Complete review of your medical history.
- Your current medications will be reviewed.
- You will have your vital signs measured, which include blood pressure, heart rate, breathing rate, and temperature.
- The study team will assess your ability to perform daily activities (performance status).
- An Electrocardiogram (ECG) will be recorded; an ECG is a simple test that measures the rhythm of the heart. It may detect some abnormal conditions of the heart. The technician will put small “sticky” pads on your chest, arms and legs. These are attached to a machine that will record the heart’s electrical activity. This test is not painful and will only take a few minutes to complete.
- A urine sample is collected for routine analysis.

- The extent of your disease is assessed using Computerized Tomography (CT) or Positron Emission Tomography (PET) scans. All scans completed on this study are part of routine cancer care.
- Endoscopic ultrasound (EUS), a procedure to obtain high quality pictures of the tumor for staging may be completed for staging purposes. This procedure is part of routine cancer care and will not be repeated if previously completed.
- The doctors have assessed that surgery is possible to remove the tumor.
- You must inform your doctor/study nurse if you had a live vaccination in the last 30 days (live vaccines include measles, mumps, rubella, shingles)

Blood samples collected for the following routine tests:

- Complete blood count (test to measure red cells, white cells and platelets)
- Blood chemistry levels (to test your kidney and liver function)
- Blood to measure your blood clotting levels
- Pregnancy Test (women of childbearing potential only) - a sample of your blood is needed to complete this test. If you are pregnant, you cannot participate in this study.

Blood samples collected specifically for this research study include:

- Blood tests to check your endocrine function (Thyroid levels and Cortisol levels)
- Blood tests to check if you have Hepatitis B or C, viruses that may cause liver disease. If you are diagnosed with a reportable disease, the study team is obligated to report this according to state law requirements.
- For males, a testosterone level is measured
- For females, luteinizing hormone (LH) and follicle stimulating hormone (FSH) are measured
- Blood will be drawn to measure cells in your immune system that are active in fighting cancer. This research may help us to understand what factors lead to cancer or may tell us ways to improve the treatment of your cancer and potentially other cancers. The tests are called biomarkers; they look for specific genes or changes in genes that may be related to cancer. Biomarkers help to measure the body's possible response to study drug or to help explain how to improve the treatment of cancer. Analysis of these markers will help to understand why some subjects respond or experience side effects while others do not despite receiving the same treatment. The information obtained from this research may be used in the development of new therapies and diagnostic tests.
- In total, you will have about 3 tablespoons (45 mls) of blood drawn during the screening period. These baseline labs and blood biomarkers will be drawn no more than 14 days prior to your first dose of pembrolizumab.

Optional tissue biopsy collection before study regimen:

If you need to have an endoscopic ultrasound (EUS) for either staging or to dilate the esophagus before you start study drug, you may have an optional biopsy of your tumor before starting on study drug. A

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EUS procedure is completed by an Interventional Radiologist, Surgeon or other qualified doctor trained in this procedure. If a EUS is ordered by your doctor for staging or dilation, you will be asked to sign a consent form for the procedure by the staff carrying out the EUS. The additional biopsy to obtain tissue is for research purposes only and is optional. The biopsy will be used to understand more about your tumor, the characteristics of the tumor and the cancer cells in it or to potentially identify future biomarkers.

_____
Subject Initials Date **YES,** I consent to have the optional on-study biopsy

_____
Subject Initials Date **NO**, I do not consent to have the optional on-study biopsy

After completing the screening tests, your study team will check the results to determine whether you can continue in the study. If the screening evaluation confirms that, you are eligible to be enrolled in the study, you will be asked to return to the clinic to begin study drug.

Tissue Analysis:
Tissue already collected from your tumor and used to diagnose your cancer (archived tissue) will be analyzed for PDL-1 expression**.** The tissue will be studied to understand more about your disease and the characteristics of the tumor and the cancer cells to potentially identify biomarkers. Biomarkers are biological substances (DNA and RNA) that impact specific genes or changes in genes that may be related to cancer that can be measured for a variety of purposes related to medical treatment. This information is for research purposes only and the results are not shared with you.

You will be asked to sign a separate consent form called the Biospecimen Repository and Processing Core (BRPC) consent so that the tissue collected at diagnosis and while you are on study can be stored for future research studies.

By signing the BRPC consent form you are giving permission for the study team to collect a very small amount of tissue from biopsy tissue used to make your diagnosis of cancer. If you proceed to surgery, we will also collect tissue after surgery. All standard tests necessary for pathology results will be completed before any tissue is obtained for research purposes.

Study procedures and visits during study regimens:
Study drug regimens involve three different phases:

- Pembrolizumab combined with carboplatin, paclitaxel and radiation therapy before surgery
- Restaging scans followed by surgery (resection of the tumor)
- Pembrolizumab as a single drug after surgery

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The following tests and procedures are required during the study. Some of these tests and procedures may be part of regular medical care and you would have them whether or not you participate in this study. Some tests and procedures may be done just for the research study to determine the effectiveness of the study drug or to determine how the study drug is affecting your body.

The calendar below outlines the study procedures during study regimen:

Study calendar	Before radiation and chemotherapy	During radiation for 5 -6 weeks	After radiation and before surgery	Surgery	After surgery
Pembrolizumab	X (given once ~2 weeks before radiation starts)	X (given in week 1 and week 4)	No	No	X (once every 3 weeks for total of 3 doses)
Carboplatin	No	Given weekly	No	No	No
Paclitaxel	No	Given weekly	No	No	No
Physical assessments	X	Every week	X	X	X
Vital signs	X	Every week	X	X	X
Blood tests	X	Every week	X	X	X
Assess side effects	X	Every week	X	X	X
Scans	X	No	X	No	X
Research tissue collection	X (optional)	No	No	X	No
ECG	X (research)	No	Routine	Routine	No
Research blood	X	X	X	No	X (two times)

- Pembrolizumab is given intravenously (IV). The first dose is given within 14 days of starting radiation therapy. Pembrolizumab is repeated on weeks 1 and 4 of radiation therapy for a total of 3 doses before surgery. Pembrolizumab is given over 30 minutes.

- Carboplatin and paclitaxel are given IV once a week during radiation therapy. Carboplatin is given over 30 minutes. Paclitaxel is given over one hour.
- Pembrolizumab can be given on the same day as carboplatin/paclitaxel is given.
- All three drugs are given in the outpatient treatment room.
- You will be seen by medical oncology (doctor, nurse practitioner or physician assistant) before chemotherapy is given in the outpatient treatment center.
- Before radiation therapy starts, you will have a contrasted CT and/or PET scan completed in the radiation oncology department so that radiation treatment is precisely planned.
- Weekly bloodwork will be collected and reviewed. Bloodwork includes a complete blood count to check the numbers of the red and white cells and platelets and to assess liver and kidney function while on the study drug.
- On the weeks you are due to receive pembrolizumab, blood is collected to check your thyroid function.
- You will receive additional medication to help reduce nausea (upset stomach) during the study regimen. Your doctor will tell you about these medications and all medications given to relieve symptoms during the study regimen.
- You will be given an oral medication (steroid) to take 4 days starting the evening prior to chemotherapy infusion to help reduce sensitivity reactions
- On the days you receive chemotherapy, plan to spend at least 4-6 hours in the outpatient treatment center
- Radiation therapy is given Monday through Friday each week for 5-6 weeks, but the treatment start day can be at the discretion of the treating physician. You will receive 5 fractions (treatments) of radiation each week. Each fraction size will be 1.8 Gy (pronounced Gray, a standard unit of radiation measurement). The total dose of radiation will be 45 Gy over 5-6 weeks. During radiation, special imaging will be completed at regular intervals to ensure that the radiation dose is given exactly as planned by your doctor and the radiation team.
- Your radiation oncologist will see you weekly during radiation therapy. You will have a physical examination with vital signs.

<u>During the study at every clinic visit,</u>

- Your doctor will ask you about any side effects you may be experiencing, which may or may not be related to pembrolizumab.
- Research blood is collected five times: before the first dose of pembrolizumab, during week 3 of radiation, before surgery, before the 4th dose of pembrolizumab and at the final study visit (about 30 days after the 6th dose of pembrolizumab)

CT and PET scans:
If you take part in this study, you will have one or more CT scans and nuclear scans (PET scan) that use radiation. All scans performed while you are on study are standard of care; the results of these scans will be part of the information collected while you are on study.

The CT scan combines a series of X-ray views taken from many different angles to produce cross-sectional images of the bones and soft tissues inside your body.

A PET is a highly specialized imaging technique that uses short-lived radioactive substances (such as FDG a simple sugar labeled with a radioactive atom) to produce three-dimensional colored images of those substances functioning within the body. These images are called PET scans and the technique is termed PET scanning. PET scanning provides information about the body's chemistry not available through other procedures. Unlike CT or MRI (magnetic resonance imaging), techniques that look at anatomy or body form, PET studies metabolic activity or body function

Scans (CT and/or PET scans) are repeated about 4-8 weeks after radiation therapy and chemotherapy is completed. These are called restaging scans and are taken to measure how your cancer has responded to study drug. If the cancer is stable or improved, you will proceed to surgery. Surgery is a standard medical treatment. If the cancer has progressed through the study regimen, your doctor will discuss alternative treatment options with you.

After Surgery:
About 4 weeks (up to 12 weeks) after surgery and if you have recovered well enough to start study drug again, pembrolizumb will be given as a single investigational drug.

- Pembrolizumab is given IV once every 3 weeks for 3 doses (total) after surgery.
- A physical assessment by medical oncology (doctor, nurse practitioner or physician assistant) before each dose of pembrolizumab is given in the outpatient treatment center
- Bloodwork will be collected and reviewed. Bloodwork includes a complete blood count to check the numbers of the red and white cells and platelets, liver and kidney function and thyroid function during study regimen.

- **At each clinic visit, you will be asked to**:
  -Describe how you are feeling
  -Describe any problems you are having
  -Describe any side effects you are experiencing, which may or may not be related to pembrolizumab
  -Whether you have made any visits to other doctors or hospitals

A mandatory safety follow up visit will be scheduled about 30 days after the last dose of pembrolizumab is given if you have completed 6 cycles of the study drug. At the safety follow up visit, you will have:

- A full physical assessment
- Vital signs including weight
- Describe how you are feeling
- Describe any problems you are having

- Describe any side effects you are experiencing, which may or may not be related to pembrolizumab
- Research blood will be collected (In total, you will have about 5 1/2 tablespoons (80 mls) of blood drawn during the study regimen)

Once the safety follow up visit is concluded, your active participation on study is complete.
If you decide to withdraw or your doctor decides it is in your best interest to stop study drug, you will be asked to come back for the mandatory safety follow up study visit and to participate in the study follow-up.

If you discontinue study drug for any reason other than disease progression, you will be monitored for overall survival by viewing your medical records at routine clinic visits to find out how you are doing since receiving the study drug.

If you have confirmed disease progression or start, a new anticancer therapy you will be followed for survival status until withdrawal of consent, the end of the study or death whichever occurs first.
If you do not sign this consent form, you may continue to receive care, but not as a part of this study.

HOW LONG WILL I BE IN THIS STUDY?
How long you remain on study depends upon how you tolerate study drug. It may be necessary to delay receiving the study drug due to intolerable side effects. If this happens, study regimens may be held until your doctor determines you have recovered enough to complete the study regimen.

You will be in the study for about 9 months. It will begin at the time that you sign the consent document for the study and end at your final study visit, which will occur approximately 30 days after you have received the last dose of pembrolizumab.

Although your active participation ends after the final study visit, by signing this consent form you are giving us permission to continue to follow you by viewing your medical records at routine clinic visits to find out how you are doing since receiving the study drug.

If your cancer progresses (worsens), your study doctor will discuss alternative cancer treatment options with you. Your doctor may discontinue the study drug at any time if your cancer has progressed, you experience intolerable or unacceptable side effects, your doctor determines that your safety is at risk, you become pregnant, or the study ends.

You can choose to stop participating at any time without giving a reason; withdrawing from the study will not result in any penalty or loss of any benefits to which you are entitled. If you decide to stop participating in the study, we encourage you to talk to your doctor first.

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Clinically relevant results of this research will be communicated with you by your treating physician at routine clinic visits. Feel free to ask your physician any questions that you may have regarding the results of this study.

WHAT ARE THE RISKS OF THE STUDY?
While participating in this study, you are at risk for side effects. Adding pembrolizumab to standard treatment may increase the number and/or severity of side effects. These side effects will vary from person to person therefore; you will be informed of the side effects that have occurred most frequently in study subjects who have taken pembrolizumab. Side effects are also called "adverse events". You will be told of any adverse events that are rare but serious and could be related to the study drug.
You should discuss the risks listed here with your doctor and study team, and you should ask about possible side effects that are not yet known.

Side effects may go away shortly after the study drugs are stopped, but in rare cases they may be serious, long lasting, and/or permanent, and may even cause death. If you experience any of the described symptoms or have any other problems, you must tell the appropriate study staff member or the study team.

Risks with Pembrolizumab

More likely seen in 20% of subjects receiving Pembrolizumab:

- Itching of the skin,
- Feeling tired, lack of energy,
- Lack of appetite (anorexia),
- Shortness of breath and cough

Likely side effects seen in 10% to 20% of subjects receiving pembrolizumab:

- Joint pain,
- Fever,
- Swelling of legs and/or feet,
- Weakness,
- Back pain,
- Rash,
- Low level of salt in the blood that may causing tiredness, confusion, headache, muscle cramps or stomach pain,
- Sick to your stomach (nausea and/or vomiting)
- Loose or watery stools (diarrhea)
- Infrequent or hard stools (constipation)
- Anemia, a decrease in number of blood cells that carry oxygen causing you to feel tired or short of breath

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Less common serious side effects seen in 1% to 4% of subjects receiving pembrolizumab:

- Inflammation of the lungs with shortness of breath and cough (called pneumonitis in rare cases this could cause death),
- Inflammatory disease that affects multiple organs in the body, but mostly the lungs and lymph gland (sarcoidosis)
- Inflammation of the bowels/gut causing severe stomach pain with loose or watery stools, or stools that are black, sticky with blood or mucus,
- Inflammation of the skin may cause widespread redness, itching peeling of the skin
- Inflammation of the liver that may cause poor appetite, tiredness, mild fever, muscle or joint aches, upset stomach and vomiting, bleeding and bruising more easily than normal, stomach pain, yellow eyes and skin, and dark urine.
- Inflammation of the kidney so you may pass less urine, have cloudy urine, have blood in your urine, low back pain
- Inflammation of the eye may cause redness of the eye, blurred vision, sensitive to light, eye pain or have headaches
- Inflammation of the pituitary gland (a gland in the brain), which may cause headaches, upset stomach, change in behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting.
- Inflammation of the brain that may cause headache, fever, joint and muscle aches and weakness, confusion, seizures, and loss of sensation/paralysis in the face or body (Encephalitis)
- Severe skin reaction that may cause blistering, tissue death and shedding or sloughing (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis)
- Inflammation of the heart muscle that may cause shortness of breath, chest pain, abnormal heartbeat (Myocarditis)
- Inflammation of the nerves that may cause pain, weakness or tingling in the hands and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness (disorder referred to as myasthenic syndrome)
- 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 the 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 pituitary gland may impact other hormone making glands (adrenals, thyroid or pancreas) in your body:

- Too little adrenal hormones causing tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and stomach pain, nausea, vomiting, diarrhea, fever, salt craving, rapid heart rate, and sometimes darkening of the skin like a suntan
- Too much thyroid hormone so you may feel anxious, angry, can't sleep, weak, tremble, increased sweating, weight loss, hair loss, tired, diarrhea
- Too little thyroid hormone so you may feel tired, gain weight, feel cold, voice gets deeper, hair loss, constipation
- Inflammation of the pancreas (that controls sugar levels) so that too much sugar in your blood, may need to urinate more often, loss weight, feel thirst, and may need regular insulin

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 right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

There may be risks with combining Pembrolizumab, Carboplatin, Paclitaxel, and radiation therapy that are not known.

Risks of Paclitaxel and Carboplatin

In addition to the risks above, the following side effects are seen in subjects receiving Carboplatin/Paclitaxel:

More Common (10% or more)

- Hair loss (thinning or complete hair loss)
- Joint pains
- Loss of appetite which could cause weight loss

- Nausea and vomiting
- Tiredness (fatigue)
- Diarrhea
- Constipation
- Shortness of breath or difficulty breathing
- Mild to severe allergic reaction (drug hypersensitivity) which could be life-threatening with hives, wheezing and low blood pressure.

Less Common (less than 10%), but potentially serious

- Fever
- Blood clots
- Reduced white blood cells and fever
- Changes in the levels of some salts or chemicals in the blood (calcium; phosphorus, sodium and potassium)
- Changes in the nerves that can cause numbness, tingling, or pain in the hands and feet (peripheral neuropathy; and sensory peripheral neuropathy)
- Muscle pains
- Skin rashes (dermatitis)

Radiation Therapy Risks

More common (10% or greater)

- Diarrhea
- Fatigue (tired feeling)
- Loss of appetite with weight loss (weight loss can be significant)
- Lower blood counts, which can cause fatigue and increase the risk of infection and bleeding
- Nausea and vomiting
- Sore throat that could cause difficulty with swallowing (esophagitis)
- Skin changes, mild such as sunburn or suntan and loss of hair in the radiation treatment area
- Stomach pain and gastrointestinal discomfort

Less common (less than 10%), but potentially serious

- Changes in the liver and kidney function
- Decreased kidney function (in rare cases severe enough to need dialysis)
- Bleeding from the tumor in the area being treated (gastrointestinal bleeding)
- Bowel perforation (a hole in the bowel), which may be result in an abscess (collection of pus) or in rare cases, death
- Delayed wound healing after surgery
- Narrowing of the esophagus, causing difficulty with swallowing

- Shortness of breath with coughing (pneumonitis)
- Increased risk of developing heart disease

Your study doctor will be monitoring you for side effects throughout study regimen. It is important that you report side effects you experience to your study doctor right away, *even when you think these are not related to the study drug.* Your study doctor may give you other drugs to help with side effects. If you or your study doctor thinks that you cannot tolerate the side effects, the study drug may be stopped altogether and you will be withdrawn from the study.

Risk of Allergic Reaction

In addition, as with any medication, allergic reactions are a possibility. Signs of an allergic reaction include:

- Rash, hives, itching
- Having a hard time breathing
- Wheezing when you breathe
- Swelling around the face, mouth, lips, tongue, throat, or eyes
- Fast pulse
- Sweating
- Sudden drop in blood pressure causing dizziness and severe weakness

If you have any of the above allergic reactions at home, call your doctor right away or call for emergency medical help if the allergy is severe.

To minimize the risk of an allergic reaction, a steroid such as Dexamethasone may be given at the discretion of the treating physician. Common risks of Dexamethasone include increased appetite, possible weight gain, trouble sleeping, irritability, and increased blood sugar.

Many side effects go away shortly after the study drug is stopped, but in some cases side effects may be serious, long lasting, and/or permanent, and may even cause death. If you experience any of the described symptoms or have any other problems, you must tell the study team right away. Please ensure that all symptoms you experience while taking the study drugs are reported to the study team in a prompt manner. During the study, if new information (such as new side effects) is learned about the study regimen, you will be informed.

GENERAL RISKS OF TUMOR BIOPSY (optional)

This optional biopsy may be done with your permission and only if you require an EUS for staging or to dilate the esophagus. Possible known side effects for tumor biopsies include bleeding, bruising, infection, and discomfort or pain. Risks and side effects associated with a tumor biopsy depend on the type of biopsy done. There may also be risks associated with the use of general anesthesia or sedation,

including nausea, vomiting, blood vessel injury, nerve injury, allergy to drugs, aspiration (fluid going into the lungs), over sedation, brain damage, and death.

Reproductive Risks

The risks to an unborn human fetus or a nursing child from pembrolizumab in combination with carboplatin and paclitaxel are not known.

Women who are pregnant or nursing a child or men planning to father a child may not participate in this study. If you are of childbearing potential, you must agree to use birth control methods, which are considered to be highly effective to avoid pregnancy from screening through 4 months after the last dose of study drug.

You must confirm that, to the best of your knowledge, you are not now pregnant, and that you do not intend to become pregnant. If there is any possibility that you may become pregnant during the study, the study doctor will discuss appropriate birth control measures with you. If you suspect that you have become pregnant during the study, you must notify the study doctor immediately and you have to stop study drugs immediately. You will not be able to continue in the study if you become pregnant. If you become pregnant, the study doctor will ask to follow the pregnancy outcome and follow up through first well-baby visit to monitor you and your child's safety.

Female

If you are a woman of childbearing potential, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), this must be negative before you can continue in this study. If sexually active, you must agree to use appropriate contraceptive measures for the duration of the study and for 4 months afterwards. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study doctor immediately. Your study doctor will talk with you about appropriate contraception for you and your partner

Male

Your participation in this research may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for **4** months afterward. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs,

you will need to report it to the study doctor, and she should promptly notify her doctor. Your study doctor will talk with you about appropriate contraception for you and your partner.

If you father a child during your participation in the study, you must notify the study team Immediately. If your partner becomes pregnant, your study team will ask to follow the pregnancy until the first well-baby visit to monitor your partner's and your child's safety. In that case your partner will be asked to consent to the following of the pregnancy by signing a separate consent form.

ADDITIONAL RISKS RELATED TO STUDY PROCEDURES:

Risks of Radiation associated with scans:
The radiation you receive from the CT scans and PET scans that may be ordered is the same, as you would receive for general care of your cancer. During CT and/or PET scans, you will receive a contrast agent through a vein in your arm. The contrast agent improves the quality of the scan image and helps the doctors see the tumor and tumor response more clearly. There is a risk of an allergic reaction to the contrast agent in some people, especially those with prior allergies to iodine. Allergic reactions can be mild or severe and can be life threatening. Signs of a mild allergic reaction include a feeling of warmth, nausea, and vomiting. More severe allergic reactions include severe vomiting, hives, a drop in blood pressure, and swelling.

The radiation exposure from these tests is very small compared to that from the radiation therapy, and will not add significantly to your risk.

Risks of Drawing Blood:
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

ECG Risks:
Possible side effects from the patches that are placed on your skin when the ECG is performed could be a rash or minor irritation of the skin.

Risks of Communicable Disease Testing:
As part of this study, you will be tested for the hepatitis B and C virus, which causes hepatitis. You will be informed of the results of the tests whether they are positive or negative. If the test results indicate, you are infected with hepatitis B and/or C you will receive additional counseling about the significance of your care and possible risks to other people. We are required to report all positive results to the North Carolina Division of Public Health. The test results are confidential to the extent permissible under the law. If you do not want to be tested for hepatitis B and C, then you should not agree to participate in this study.

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Drug and Food Interactions:
For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be direct medical benefit to you. This regimen may improve your disease outcome. We hope the information learned from this study will benefit patients with this type of cancer in the future.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?
There may be other treatment options available to you including receiving standard therapies. You should speak to your doctor about all of your treatment options and the associated risks and benefits, before deciding to participate in this study. Possible alternatives include:

- Receiving standard treatment with chemotherapy and radiation only
- Taking part in another study
- Receiving palliative care (or comfort care), it does not treat the cancer directly but instead tries to improve how you feel and to relieve symptoms.
- You could choose not to have any treatment at this time. If you choose this option, you may reconsider at any time, and this decision will in no way affect the regular care that you receive.

Please talk to your doctor about these and perhaps other options.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, Dr. Palta and her study team will report the results of your study-related laboratory tests and scans to Merck &Co. These could include laboratory tests such as your blood counts and tests to measure the function of your liver and kidneys, ECGs, and CT and or PET scans. Some of these blood, urine and x-ray studies will be done as part of your regular care. Dr. Palta will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record and may be reported to Merck & Co. Inc. Results of tests and studies done solely for this

research study and not as part of your regular care will not be included in your medical record. Your research records may be reviewed in order to meet federal or state regulations.

Reviewers may include Merck & Co. Inc, the Food and Drug Administration, representatives of the National Cancer Institute, Duke Cancer Institute, Duke University Office of Audit, Risk, and Compliance, the Office for Human Research Protection (OHRP) and the Duke University Health System Institutional Review Board. If your research record is reviewed by any of these groups, they may also need to review your entire medical record.

The information and results obtained from your participation in this study will be retained in your research record for six years after the study ends. At that time, either the research information not already in your medical record will be destroyed or information identifying you will be removed from the study results at DUHS. Any research information in your medical record will be kept indefinitely. This information may be further disclosed to, Merck &Co. Inc. If disclosed by the Merck & Co. Inc, the information is no longer covered by the federal privacy regulations. If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by the federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS?

You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. No all services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out of pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays that with a Medicare Advantage plan. Please discuss the costs of the study with Dr. Palta. At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

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You or your insurance company will not be billed for tests and studies that are not a part of your routine standard of care, such as the research ECG, and some blood tests (thyroid function tests, hormone level tests) as people who are not part of the study do not usually have them performed. The optional biopsy procedure to obtain research tissue is billed to the study; however the EUS procedure for dilatation would be billed to insurance as standard medical care.

You or your insurance provider will be responsible for all costs related to your medical care, including the drugs used in this study. Standard medical care that you receive under this study will be billed to your insurer and/or you in the ordinary manner. You may wish to contact your insurance representative to discuss this further before making your decision about participating in the study. In order to make sure that tests and studies done solely for research purposes are charged correctly, we will carefully monitor your Duke Hospital and Clinic charges as long as you are participating in this study. These tests and studies are not a part of routine care, and people who are not part of the study do not usually have them performed. Merck &Co. will provide commercially available Pembrolizumab free of charge for use in this study. Please ask Dr. Palta if you would like to know more about which tests and studies are being done solely for research purposes.

WHAT ABOUT COMPENSATION?
You will not be paid for your participation in this study.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., your Duke physicians or the study supporter Merck Sharp& Dohme, Corp., to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Palta [redacted]

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
Participation in this study is voluntary. You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you decide to withdraw, we ask that you contact Dr. Palta in writing and let her know that you are withdrawing from the study.

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[redacted] [redacted]

Dr. Palta may ask you to return for a checkup if she thinks that stopping the drug suddenly may harm you. Dr. Palta may also ask you to complete the tests that would ordinarily occur when a person completes the study.

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. If this occurs, you will be notified and your study doctor will discuss other options with you.
We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Withdrawal of samples:
If you agree to allow your tissue and blood to be kept for future research, you are free to change your mind at any time. We ask that you contact Dr. Palta in writing and let her know you are withdrawing your permission for your tissue and blood to be used for future research. At that time, we will ask you to indicate in writing if you want the unused tissue and blood destroyed or if your samples (having all identifying information removed that would link the sample to you) could be used for other research.

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.

Your samples and data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.

The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples other than what is described in this consent form.

WHAT HAPPENS TO MY SAMPLES?
Genetic Testing
The genetic studies described are for research purposes only. Therefore, you will receive no results from this study except as described below. It is not the purpose of this study to look for or provide you with any medical information or diagnoses relating to your present condition or any other disease or illness. The research tests are not being used as diagnostic tests for any disease or illness. Your participation in this study is not a substitute for your regular medical care or checkups.

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Genes are molecules found within almost every cell in your body. These molecules create a blueprint or master plan of what your body looks like and how it functions. They may play an important role in how your body handles drugs. As part of this study, the genes in your blood and tumor samples may be analyzed. Part of this research may also be to help identify genetic changes in cancer cells that are different than your normal genes and may explain why these cells are cancerous as well as how the immune system might be able to recognize these cells. Therefore, some of the blood sample may be used for genetic testing.

Through this research, we may find that you have an abnormal gene or gene product (RNA or protein) which indicates a risk for developing a disease at some time in the future. It is also possible that the research results may indirectly provide unexpected personal information about you or your family (such as ethnic/racial background or an unknown genetic relationship between family members). Please talk with your study doctor if you have any questions or concerns about the genetic testing being done in this research study. She may also refer you to a genetic counselor for further information.

Potential Risks and the Genetic Information Non-Discrimination Act (GINA):
There is a potential risk of loss of confidentiality. Every effort will be made to protect your confidential information, but this cannot be guaranteed. The genetic information obtained as a result of your participation in this research will not be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location at DUHS, accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law.

The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:
- Health insurance companies and group plans may not request genetic information from this research;
- Health insurance companies and group 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 when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Manisha Palta at [redacted]

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For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form.

_____
Printed name of Subject

_____ _____ _____
Signature of Subject Date Time

_____
Printed name of Person Obtaining Consent

_____ _____ _____
Signature of Person Obtaining Consent Date Time