MC1541 / 15-005311

Phase 1b/2 Clinical Trial of Neoadjuvant Pembrolizumab Plus Concurrent Chemoradiotherapy With Weekly Carboplatin and Paclitaxel in Adult Patients With Resectable, Locally Advanced Adenocarcinoma of the Gastroesophageal Junction or Gastric Cardia

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MAYO CLINIC

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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC1541 Phase 1b/2 Clinical Trial of Neoadjuvant Pembrolizumab plus Concurrent Chemoradiotherapy with Weekly Carboplatin and Paclitaxel in Adult Patients with Resectable, Locally Advanced Adenocarcinoma of the Gastroesophageal Junction or Gastric Cardia

IRB#: 15-005311

Principal Investigator: Harry H. Yoon M.D. and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you get at Mayo Clinic now or in the future if you choose not to participate or discontinue your participation.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.

CONTACT INFORMATION

You can contact …	At …	If you have questions about …
Principal Investigator: Dr. Harry H Yoon **Arizona PI:** Dr. Daniel H. Ahn	**Phone:** (507) 284-2511 **Address:** Mayo Clinic 200 First St SW Rochester MN 55905 **Phone:** (480) 301-8000 **Address:** Mayo Clinic Hospital 5777 E Mayo Blvd Phoenix AZ 85054	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Mayo Clinic Institutional Review Board (IRB)	**Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681	▪ Rights of a research participant
Research Subject Advocate **(The RSA is independent of the Study Team)**	**Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu	▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information
Patient Account Services	**Toll Free:** (844) 217-9591	▪ Billing or insurance related to this research study

Other Information:

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.

1. Why are you being asked to take part in this research study?

You are being asked to take part in this research study because you have been diagnosed with cancer of the gastro-esophageal junction or the gastric cardia.

One standard treatment for your disease includes chemotherapy plus radiation followed by surgery. Another standard treatment includes chemotherapy without radiation followed by surgery. The treatment used in this study is chemotherapy with radiation followed by surgery.

The plan is have about 34 people take part in this study at Mayo Clinic.

2. Why is this research study being done?

In this study, we want to find out more about how effectively a new drug for cancer, called pembrolizumab, fights against your tumor when combined with chemotherapy and radiation. We also want to find out how safe and tolerable this combination is. Everyone in this study will receive pembrolizumab, which is experimental in the treatment of this cancer. This drug is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with melanoma or lung cancer. It is not approved by the FDA for other cancers. However, the FDA has allowed the use of this drug in this research study.

3. Information you should know

Who is Funding the Study?

Merck & Co. and Mayo Clinic are funding the study. Merck will pay Mayo Clinic to cover costs related to running the study.

4. How long will you be in this research study?

This study will last approximately three years. You will be in the study for as long as your cancer is responding to the treatment and you are not having side effects that cannot be managed.

5. What will happen to you while you are in this research study?

Before starting the study drug, you will participate in a screening period. The screening period will help the study doctor find out if you are eligible to enter the study. You will need to have the following exams, tests or procedures as part of your standard clinical care to find out if you can be in the study:

Prior to Registration

- Physical exam including complete medical history, height, weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood and urine tests
- Pregnancy test if you are a woman who is able to become pregnant
- Consultation with a radiation oncologist
- Consultation with surgeons
- Bronchoscopy
- Pulmonary function testing (PFT) to see how your lungs are working
- FDG-PET/CT of whole body
- CT scan of chest, abdomen and pelvis
- EGD with biopsy
- Endoscopic esophageal ultrasound
- Electrocardiogram (ECG) and Troponin T blood test to see how your heart is working

These exams, tests or procedures are part of regular clinical 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 decision will be up to the Principal Investigator.

You will also have the following required tests, which are part of the research study:

- Research blood tests (36 ml or about 2.5 tablespoons)
- Research tissue samples (taken during the biopsy)

Neoadjuvant treatment
If you are eligible for the study, you will start chemotherapy and radiation, plus pembrolizumab.

The side effects of pembrolizumab may cause delays and/or inability to receive standard treatment with radiation, chemotherapy, and/or surgery.

You will receive neoadjuvant treatment on this trial, which means part of your treatment is given before surgery to remove the cancer.

Most patients will receive chemotherapy with carboplatin and paclitaxel. All these drugs are given intravenously (IV) through a needle into a vein in your arm or through a port. For carboplatin and paclitaxel, you will need to come to the clinic once a week for infusions of these drugs for five weeks (Days 15, 22, 29, 36 and 43).

All patients will receive pembrolizumab. Pembrolizumab is also given by IV, but only on Days 1 and 22 during neoadjuvant treatment with carboplatin and paclitaxel.

You will also be receiving treatment with radiation during the neoadjuvant phase. Radiation is given every day, generally Monday-Friday, for a total of about five weeks.

During your neoadjuvant treatment, you will have the following tests and procedures. These exams are part of regular care for your cancer:

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests
- Electrocardiogram (ECG) and Troponin T blood test to see how your heart is working

You will also have the following, which are part of the research study:

- Research blood tests (20 ml or about 1.5 tablespoons)

Surgery
Once you complete neoadjuvant treatment and radiation, you will have a surgical evaluation as part of regular care for your cancer. If you are able to have surgery, it will be scheduled. You will have the following tests and procedures prior to surgery. These exams are part of regular care for your cancer:

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests
- Pregnancy test if you are a woman who is able to become pregnant

- Pulmonary function testing (PFT) to see how your lungs are working
- FDG-PET/CT of whole body
- Electrocardiogram (ECG) and Troponin T blood test to see how your heart is working

We will also draw some blood for research testing (20 ml or about 1.5 tablespoons).

At the time of your surgery, we will take a portion of your tumor tissue for research testing. (This testing is required for participation in this study.)

After your surgery, you will recover for a few weeks. Then, about four to seven weeks after your surgery, you will have the following tests and procedures (as part of regular care for your cancer):

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests
- CT scan of chest, abdomen and pelvis
- Electrocardiogram (ECG) and Troponin T blood test to see how your heart is working

Adjuvant Treatment
Once you have completed neoadjuvant treatment and surgery, you will be evaluated for whether your body is strong enough to start adjuvant treatment with pembrolizumab. During this stage, pembrolizumab is given once every three weeks. These three weeks are called a "cycle." You will receive up to six (6) cycles of adjuvant pembrolizumab. You will have the following tests and procedures once each cycle. These exams are part of regular care for your cancer:

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests
- CT scan of chest, abdomen and pelvis once every three months
- Electrocardiogram (ECG) and Troponin T blood test to see how your heart is working

Treatment discontinuation
When you stop treatment on this study, you will have the following tests and procedures if they have not been done recently. Your doctor will determine which ones are needed. These exams are part of regular care for your cancer:

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests
- CT scan of chest, abdomen and pelvis

We will also draw some blood for research testing (20 ml or about 1.5 tablespoons) at the time of treatment discontinuation or if the tumor comes back.

Safety Follow-up
About 30 days after your last treatment with pembrolizumab, you will have the following tests and procedures if they have not been done recently. Your doctor will determine which ones are needed. These exams are part of regular care for your cancer:

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests
- CT scan of chest, abdomen and pelvis

Follow-up visits
After you have finished all your treatment, you will have the following tests and procedures once every three months for the first year and then once every four months for two more years:

- Physical exam including weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood tests
- CT scan of chest, abdomen and pelvis once every three months starting from post-surgery scan for the first year; then once every four months for two more years

Optional Research Laboratory Tests:
If your cancer returns, and a biopsy of the recurrent tumor is collected, we would like to obtain a portion of the biopsy tissue for research testing. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand how to make this therapy more effective. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only, and you will not have to pay for them.

You can take part in the treatment portion of this study without taking part in these research laboratory tests.

If my cancer comes back and a biopsy is done, I agree to provide tissue sample(s) from my biopsy to Mayo Clinic for research testing planned as part of this study.

☐ Yes ☐ No Please initial here: _____Date: _____

6. What are the possible risks or discomforts from being in this research study?

Risks and side effects of pembrolizumab (MK-3475)
The study doctors believe that the side effects listed below were caused by pembrolizumab.

Very common side effects (>10%) seen in people taking pembrolizumab include the following:

- Feeling tired
- Itching of the skin
- Rash
- Frequent or excessive bowel movements or diarrhea
- Fever
- Shortness of breath
- Decreased appetite
- Cough
- Nausea and vomiting
- Decreased in red blood cells that may result in feeling tired or short of breath
- Pain in joints
- Headache
- Back pain
- Swelling of the legs
- Muscle weakness or lack of energy
- Bowel movements occurring less often than usual (constipation)

Common side effects (1-10%) seen in people taking pembrolizumab include the following:

- Pain or cramping in a muscle or group of muscles
- Decreased release of thyroid hormone that may appear as feeling tired, weight gain, feeling cold easily, or bowel movements occurring less often than usual
- Abnormal laboratory result of liver test by blood that occasionally indicates liver failure, may have yellowing of the skin or whites of the eyes, fatigue, or leg swelling
- Feeling cold or sick
- Loss of skin color
- Pain or uncomfortable feeling in the belly
- Momentary feeling of whole body warmth possibly accompanied by sweating

- Sweating extensively while sleeping such that clothes and sheets are wet
- Feeling dizzy or unsteady when walking or standing
- Loss of weight
- Pain in the back, arms, or legs
- Weakness
- Decreased platelets that may cause a tendency to bruise easily or bleed easily
- Dry eyes
- Blurred or changed vision
- Dry mouth
- Feeling of pain, pins & needles, or burning, usually in the fingers or toes
- Inflammation of the lungs (pneumonitis)
- Change of blood cholesterol or triglyceride level
- Change of blood sugar or albumin level
- Change of blood electrolytes, e.g. sodium, potassium, or magnesium
- Loss of body fluid, may feel tired, confused, have a dry mouth, or feel thirsty
- Lung infection
- Fluid around the lung
- Blood clot developed in lung
- Inflammation of the large intestine (colon) that may lead to frequent or excessive watery bowel movements

Serious Adverse Events (*No event occurred in >2% of everyone treated*)
Please note that some of these events have been previously stated above, so some have occurred more frequently but with less severity. Serious adverse events seen in people taking pembrolizumab include:

- Trouble thinking clearly or confused easily
- Decreased white blood cells, red blood cells, and platelets - may have fever, feeling cold, infections, shortness of breath, feeling tired, a tendency to bruise easily, or a tendency to bleed easily
- Increased release of thyroid hormone which may cause anxiety, irritability, or trouble sleeping, weakness, trembling, sweating, feeling uncomfortable in warm weather, fast or uneven heartbeats, feeling tired, weight loss, and frequent or excessive bowel movements.
- Infection throughout the body by a fungus or bacteria or others that may result in fever, feeling tired, feeling cold, and not responding to most antibiotics. This is serious and can be life threatening.
- Inflammation of the lining around the heart which may cause sharp chest pain and/or a fever

- Inflammation of the pancreas
- Inflammation of the muscles that may result in weakness or pain in the muscles
- Inflammation of the kidneys causing them not to work as well, you may have swelling of the legs and possibly need dialysis
- Inflammation of the pituitary gland, which may manifest as headache, nausea, a sensation of the room spinning around you, changes in behavior, double vision, or weakness
- Change of blood pressure or body fluid level as a result of inflammation of the body status
- Failure of liver or lung function
- Damage of the peripheral nerves to cause weakness of muscle
- Cancer of the skin
- Severe infusion reaction, which may be life-threatening
- Severe skin reactions including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)
- Inflammation of the heart muscle which can cause shortness of breath or heart rhythm problems
- Myasthenic Syndrome (muscle weakness)
- Guillain-Barre Syndrome (damage to the nervous system (causing numbness and/or paralysis))
- Vogt-Koyanagi-Harada syndrome – an autoimmune disorder that affects tissues containing melanin such as eyes and skin and is usually found based on eye problems such as dry eye, eye swelling, eye pain, eye infection, blurred vision, and more
- Hemophagocytic lymphohistiocytosis -an abnormal immune response with activation of certain types of white blood cells (lymphocytes and macrophages) and the release of inflammatory proteins which then cause a variety of symptoms such as fevers, rash, anemia, enlarged lymph nodes, enlarged liver, enlarged spleen, and more
- Inflammation of the blood vessels (vasculitis) - – may cause fever, headache, weight loss, general aches and pains
- 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 are reported cases of fatal pneumonitis (Inflammation of the lungs) in patients who received pembrolizumab.

A total of 6 cases of myocarditis (Inflammation of the heart muscle) have been reported in patients treated with pembrolizumab in clinical trials or in an expanded access program. There was 1 fatal case reported in a clinical trial.

We do not know all the side effects that may occur with pembrolizumab. The side effects of pembrolizumab may cause delays to your treatment with radiation and/or chemotherapy and may also delay your surgery.

Other less common side effects have been reported. The study doctor or staff can discuss these with you.

There may be other side effects or risks that are not known at this time.

Known potential adverse events from esophageal/gastric surgery or postoperative period (usually up to 60 days, but can be longer)

Common potential toxicities, >10%:

- Central nervous system: Pain. Pain at the wound site may be chronic.
- Endocrine & metabolic: Hyponatremia, hypomagnesemia, hypocalcemia, hypokalemia, abnormal glucose levels
- Gastrointestinal: Flatulence; cramping; bloating; nausea; vomiting; diarrhea; constipation; abdominal pain; trouble and/or pain with swallowing; delayed gastric emptying or other digestive dysfunction (e.g., dumping); reflux; decreased movement of the bowels (ileus) that could lead to complications that include but are not limited to small bowel dilatation, delay in conduit emptying, distension, pain, delay in reaching enteral nutrition goals, prolonged nasogastric tube requirement, wound complications, bacteremia (gut translocation), and abscess formation. Symptoms of dumping syndrome include nausea, diarrhea, weakness, sweating, dizziness or feeling faint.
- Hematologic: High white count, anemia, thrombocytopenia; deep venous thrombosis
- Cardiovascular: Abnormal heart rhythm which can cause irregular and/or forceful beating of the heart (palpitations, tachycardia), lightheadedness, fainting, and/or decreased blood pressure and be associated with EKG, cardiac imaging (including depressed ejection fraction), and/or biochemical abnormalities; edema of the extremities
- Respiratory, thoracic, or mediastinal: : Incomplete expansion of the lungs (atelectasis) with retention of secretions and shortness of breath that may require procedural intervention; pulmonary embolism; edema, effusion, shortness of breath, injury to diaphragm, lung damage, ventilator dependence or prolonged ventilation, respiratory failure, coughing, aspiration; laryngopharyngeal dysfunction including but not limited to issues with swallowing, airway protection, and speech.
- Nutrition: Poor nutritional status requiring enteral or parenteral feeding; poor appetite; weight loss
- Infection: pneumonia or thoracic, wound, urinary, intra-abdominal, bowel (e.g., c dif)
- Constitutional: Fatigue, fever

Less common potential toxicities, rare to 10%:

- Blood and lymphatic: Bleeding during or after the operation, which may require a blood transfusion; thrombosis with/without embolic event
- Respiratory, thoracic, or mediastinal: Laryngopharyngeal dysfunction including but not limited to issues with recurrent laryngeal nerve injury, voice/pharyngeal fatigue, vocal cord paralysis, sensory or motor dysfunction; thoracic dissection including but not limited to dissection of lymphatic, vascular, or other tissues and blood loss
- Cardiac: Myocardial infarction
- Other: A leak from the thoracic duct (a lymph vessel) that can be damaged during surgery, which could result in fluid around the lungs, shortness of breath, and loss of protein leading to malnutrition. Anastomotic leak which could result in fever, increased white cell count, and low blood pressure. Leaks could lead to increased fluid in the abdominal cavity. Fistula formation including but not limited to esophagus and tracheobronchial tree, or between bowel and other organs
- Gastrointestinal: esophageal/anastomotic stricture, fibrosis, or perforation; serious ileus or small bowel dilatation can lead to bacteremia, sepsis, perforation, peritoneal infection, abscess; bowel necrosis or ischemia
- Death

Any of the above postoperative complications can lead to prolonged hospitalization, permanent injury, or other complications including death

<u>Known Potential Adverse Events of Radiation Therapy</u>

Common (>20%)

- Inflammation of the esophagus
- Narrowing or scarring of the esophagus, which can cause problems with swallowing
- Fatigue
- Decrease in blood counts, which can cause infection, bleeding, and bruising
- Tanning and redness of the skin in the treatment area
- Nausea/vomiting

Occasional (4-20%)

- Growth of fibrous tissues underneath your skin
- Diarrhea
- Weight loss

Rare (1-3%)

- Inflammation of the muscle tissue of the heart
- Inflammation and/or scarring of the lung tissue or the lining around the lung
- Inflammation of the spinal cord
- Bleeding from the esophagus and stomach

Standard of Care Risks

Your doctor will discuss the risks of these tests and procedures, which are part of regular care for your cancer:

- Bronchoscopy
- Pulmonary function testing (PFT)
- FDG-PET/CT of whole body
- CT scan of chest, abdomen and pelvis
- EGD with biopsy
- Endoscopic esophageal ultrasound
- Electrocardiogram (ECG) and troponin T blood test
- Surgery to remove the cancer
- Chemotherapy with carboplatin and paclitaxel
- Risks of radiation therapy

Risks and Side Effects of Paclitaxel (see package insert for most current list)

Common known potential risks and side effects (happen >10% of the time):

- Skin becomes red and may feel hot (flushing)
- Heart rhythm abnormal as seen on electrocardiogram (ECG/EKG abnormal)
- Swelling in hands, lower legs and feet (edema)
- Decreased blood pressure (hypotension)
- Loss of hair (alopecia)
- Rash
- Feeling sick to your stomach, throwing up (nausea/vomiting)
- Loose stools (diarrhea)
- Swelling or sores in your mouth and throat or other parts of your body (mucositis, stomatitis)
- Belly pain (abdominal pain - reported with intraperitoneal paclitaxel)

- Lowered blood counts of white cells, which may increase your risk of infection (neutropenia, leukopenia) lowered counts of red cells, which may make you feel tired (anemia) lowered counts of platelets (thrombocytopenia) which may increase your risk of bleeding
- Elevated liver enzymes as seen on a blood test (alkaline phosphatase increased, AST increased)
- Injection site reaction redness, tenderness, skin discoloration, swelling (erythema)
- Numbness or tingling in your hands and feet (peripheral neuropathy)
- Pain and aching in your joints and muscles (arthralgia, myalgia)
- Weakness
- Kidney problems as seen on blood test (creatinine increased)
- Allergic or immune reaction can include many different symptoms such as rash, swelling in mouth and throat, trouble breathing (hypersensitivity reaction)
- Increased risk of infection

Less common known potential risks and side effects (happen 1% - 10% of the time):

- Abnormal heart rhythms – slow, fast, or irregular (bradycardia, tachycardia, rhythm abnormalities)
- High blood pressure (hypertension)
- Fainting (syncope)
- Blood clots (venous thrombosis)
- Nail changes (may discolor or fall out)
- High fever and low counts of white blood cells (febrile neutropenia)
- Abnormal liver blood tests (bilirubin increased)
- Trouble breathing (dyspnea)

Rare known potential risks and side effects (happen <1% of the time and limited to important or life-threatening):

- Severe immune system reaction that requires emergency medical response (anaphylaxis)
- Loss of control over muscles (ataxia)
- Heart problems which may be serious including heart attack, heart failure (atrial fibrillation, AV block, cardiac conduction abnormalities, CHF, MI, supraventricular tachycardia, ventricular tachycardia [asymptomatic])
- Back pain
- Having no energy, feeling tired and unwell (malaise)
- Infection in the eye (conjunctivitis)
- Loss of fluid in the body that may require hospitalization (dehydration)
- Liver problems or liver failure (hepatic encephalopathy, hepatic necrosis)

- Blocking of the small bowel or colon (intestinal obstruction, paralytic ileus)
- Hole in the wall of the small bowel or colon (intestinal perforation)
- Swelling and pain in small and large bowels (enterocolitis) which may be life threatening (neutropenic enterocolitis)
- Injury to the colon due to loss of blood flow (ischemic colitis)
- Infection in the veins (phlebitis)
- Rash on skin with bumps and pimples (maculopapular rash)
- Skin infection that feels hot and tender and may spread rapidly (cellulitis)
- Skin loss, hardening or sores especially if the drug leaks under the skin (exfoliation, fibrosis, induration, necrolysis, necrotic changes and ulceration following extravasation, extravasation recall)
- Flu-like symptoms with painful red or purplish rash that spreads and blisters (Stevens-Johnson syndrome)
- Life threatening skin reaction where skin swells, blisters and detaches – requires hospitalization (toxic epidermal necrolysis [TENS])
- Brain disease, damage or malfunction (neuroencephalopathy)
- Loss of hearing (ototoxicity)
- Swelling and inflammation of the pancreas (pancreatitis)
- Swelling of the lungs which may cause trouble breathing (interstitial pneumonia)
- Clot or blockage in the lung (pulmonary embolism)
- Fibrous growths in the lung tissue that make it hard to breathe (pulmonary fibrosis)
- Radiation recall – swelling and redness in areas of the body that have been previously treated with radiation
- Damage to the lungs from radiation treatment (radiation pneumonitis)
- Kidney problems, kidney failure (renal insufficiency)
- Seizures
- Eye problems such as blurred vision, double vision (visual disturbances)

Risks and Side Effects of Carboplatin (see package insert for most current list)

Likely Risks of Carboplatin

- Pain
- Decreased sodium levels in the blood (hyponatremia)
- Decreased magnesium levels in the blood (hypomagnesmia)
- Abnormally low calcium in the blood stream, that can result in muscle cramps, abdominal cramps, spasms (hypocalcemia)
- Low potassium levels in the blood (hypokalemia)
- Nausea

- Vomiting
- Stomach pain or abdominal pain
- Decreased production within the bone marrow that causes decreased production of red cells, white cells, or platelets (myelosuppression)
- Decreased white blood cells, which are the infection fighting cells, which could put you at risk for infection (leukopenia)
- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (anemia)
- A low number of white blood cells, which are the infection fighting cells, which could put you at risk for infection (neutropenia)
- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk of bleeding) (thrombocytopenia)
- Alkaline phosphatase increased
- Increased levels of liver enzymes in the blood that may be a sign of liver damage from disease or drugs (AST increased)
- Weakness
- Creatinine clearance decreased
- Increased concentration of nitrogen in the form of urea in the blood (BUN increase)

Less likely risks of Carboplatin

- Poison or toxin affecting the nerves or nervous tissue (neurotoxicity)
- Hair loss (alopecia)
- Difficulty passing stool (constipation)
- Loose stools (diarrhea)
- Mouth Sores (stomatitis)
- Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (mucositis)
- Change in taste sensation (dysgeusia)
- Bleeding (hemorrhagic complications)
- Elevation of a liver pigment (bilirubin) in the blood indicating liver problems
- Pain at the injection site
- Numbness, tingling, or inflammation of the nerves (usually in the hands and feet), which may be painful (peripheral neuropathy)
- Eye problems – blurring, double vision, floaters (visual disturbance)
- Hearing or balance problems (ototoxicity)
- Blood test showing kidney problems (creatinine increased)
- Infection
- Increased sensitivity to pain, touch, taste, (Hypersensitivity)

Rare but serious risks of Carboplatin

- Severe allergic reaction (anaphylaxis) can include potentially deadly anaphylactic shock
- Loss of appetite, not feeling hungry (anorexia)
- Narrowing of the bronchioles (breathing tubes in the lungs) which can make it difficult to breath (bronchospasm)
- Cardiac failure
- Lack of oxygen to the brain caused by either bleeding in the brain or blood clot. Also called a stroke (cerebrovascular accident)
- Blood Clot (embolism)
- Redness of the skin (erythema)
- Fever
- A disorder that usually occurs when an infection in the digestive system produces toxic substances that destroy red blood cells (Hemolytic uremic syndrome, [HUS]) HUS often affects the kidneys
- Hyper/hypotension (high/low blood pressure)
- Weakness, feeling tired, unwell (malaise)
- Damage to the skin from leakage of fluid out of the vein which may cause pain, reddening, or irritation on the surrounding tissue (extravasation)
- Damage to the kidneys (Nephrotoxicity)
- Itching (pruritus)
- Rash
- Secondary malignancies such as leukemia, lymphoma
- Dark red, raised, itchy bumps or hives (urticaria)
- Vision loss

Radiation Risk

You will be exposed to radiation from the FDG PET/CT and CT scans required for your care. The amount of radiation has a low risk of harmful effects.

Blood draws

The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

Pregnancy and Birth Control

It is not known if the study drugs may affect an unborn or nursing baby or if the study drugs have an effect on sperm. Chemotherapy can cause harm to an unborn child. If you are pregnant, trying to become pregnant or breast-feeding, you may not be in the study. The study doctor will perform a blood or urine pregnancy test before the start of and during the study, if you are able to have a baby.

For Persons Able to Become Pregnant
If you are sexually active and able to become pregnant, you must agree to use **one** of the birth control methods listed below:

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

OR

You must agree to use **two** of the methods listed below:

- Hormonal methods, such as birth control pills, patches, injections, or vaginal ring
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- For women who have never given birth to a child the following options are also allowed in combination with another method:
    - Cervical cap with spermicide
    - Contraceptive sponge

You must use birth control for the entire study and for at least 120 days after your last dose of pembrolizumab.

If you miss a period, or think you might be pregnant during the study, you must tell the Principal Investigator immediately. The Principal Investigator may ask for your permission to collect information about the outcome of your pregnancy and your newborn.

For Persons Able to Father a Child
If you are sexually active, and able to father a child, you must agree to use **one** of the birth control methods listed below:

- Vasectomy
- Intrauterine device (IUD) used by female partner
- Contraceptive rod implanted into the skin of female partner

OR

You must agree to use **two** of the methods listed below:

- Hormonal methods, such as birth control pills, patches, injections, or vaginal ring used by female partner
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)

You must use birth control for the entire study and for at least 120 days after your last dose of pembrolizumab.

If your partner thinks she might have become pregnant while you are in the study or for 30 days after your last dose of pembrolizumab, you must tell the Principal Investigator immediately. The Principal Investigator may ask for your partner's permission to collect information about the outcome of her pregnancy and her newborn. You won't have to stop taking the study drug or stop taking part in the study if your partner becomes pregnant.

Other Risks
Many side effects go away shortly after the pembrolizumab is stopped, but in some cases side effects can be serious, long lasting, or may never go away There may be a risk of death. Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

7. Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time:

- if it is in your best interest,
- if you don't follow the study procedures,
- if the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

8. What if you are injured from your participation in this research study?

Where to get help:
If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries:
Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance.

9. What are the possible benefits from being in this research study?

This study may not make your health better. However, it may help other cancer patients in the future.

10. What alternative do you have if you choose not to participate in this research study?

You don't have to be in this study to receive treatment for your condition. Your other choices may include:

- Treatment for your cancer without being on a study
- Treatment on a different research study
- No treatment

Talk to the Principal Investigator or your doctor if you have any questions about any of these treatments or procedures.

11. What tests or procedures will you need to pay for if you take part in this research study?

The study drug will be given to you at no cost; however, you may need to pay for the administration of the study drug during the neoadjuvant portion of treatment. You and/or your insurance might also have to pay for other drugs or treatments given to help control side effects. You and/or your insurance will need to pay for all tests and procedures needed for your clinical care, including copayments and deductibles.

The following tests/procedures are being done for research purposes only and the costs will be covered by this study:

- Additional EGD and biopsy if tissue from your original EGD biopsy is inadequate or does not arrive in a timely manner; and if you agree to undergo the additional procedure
- Research testing on blood samples
- Research testing on tissue samples
- Adjuvant treatment with pembrolizumab given in the Clinical Research and Trials Unit (CRTU) at Mayo Clinic Hospital in Rochester, MN.

Before you take part in this study, you should call your insurer to find out if the cost of these tests and/or procedures will be covered. You will have to pay for any costs not covered by your insurance.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the Contact Information section of this form.

12. Will you be paid for taking part in this research study?

You won't be paid for taking part in this study.

13. What will happen to your samples?

Submission of blood and tissue samples is required to take part in this study. These samples will be collected prior to starting the study, during therapy, at the time of surgery to remove the cancer, and at the end of your treatment on this study. We will also collect a blood sample if your cancer comes back.

In addition, we would like to keep your sample for future research that is not described in this consent form. You can still take part in this current study even if you don't want your sample used for such future research. If you agree to give your sample, it will be the property of Mayo Clinic.

Other researchers at Mayo Clinic who aren't involved with this study may ask to use your sample for future research. Researchers at other institutions may also ask for a part of your sample for future studies. Your sample will be sent to researchers in a coded format, which protects your identity.

Some future studies may examine your DNA, which is the genetic information you inherited from your parents (genetic testing). The Principal Investigator may contact you if there are findings which may be useful for your health care. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

Please read the following statements and mark your choices:

1. I permit my sample to be stored and used in future research of cancer at Mayo Clinic:

   ☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my sample to be stored and used in future research at Mayo Clinic to learn about, prevent, or treat any other health problems:

   ☐ Yes ☐ No Please initial here: _____Date: _____

3. I permit Mayo Clinic to give my sample to researchers at other institutions:

   ☐ Yes ☐ No Please initial here: _____Date: _____

There is a very small chance that some commercial value may result from the use of your donated sample. If that happens, you won't be offered a share in any profits.

You may request to have your sample destroyed by writing to the Principal Investigator. The address is found in the "Contact Information" section of this consent form.

Because we cannot predict how your sample will be used in the future, we cannot promise that samples can be retrieved and destroyed.

14. How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study. Various methods are used to safeguard confidentiality. Some or all of the following may be used in this study: assigning a specific code or registration number to each participant's data and samples, research materials stored in locked areas, password protected data stored on a computer. This code will be used if your study information is sent outside of Mayo Clinic. The groups or individuals who receive your coded information will use it only for the purposes described in this consent form. If the results of the research are made public, information that identifies you will not be used.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission.

Health information may be collected about you from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Why will this information be used and/or given to others?

- To do the research.
- To report the results.
- To see if the research was done correctly.

Who may use or share your health information?

- Mayo Clinic research staff involved in this study.

With whom may your health information be shared?

- The Mayo Clinic Institutional Review Board that oversees the research
- Other Mayo Clinic physicians involved in your clinical care
- Researchers involved in this study at other institutions
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research
- The sponsor(s) of this study and the people or groups it hires to help perform this research
- A group that oversees the data (study information) and safety of this research

In addition, individuals involved in study oversight and not employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you. However, the individuals will not be allowed to record, print, or copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with Mayo Clinic.

You can cancel your permission to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate at: researchsubjectadvocate@mayo.edu.

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission lasts forever, unless you cancel it.

ENROLLMENT AND PERMISSION SIGNATURES:

Your signature documents your permission to take part in this research.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature