GI18-333 / 19-010617

Phase 2 Study Of Novel SEQUEnced Immunotherapy (Pembrolizumab) With Anti-angiogenesis And Chemotherapy In Advanced Gastric And GastroesophageaL Junction (GEJ) Adenocarcinoma (SEQUEL)

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MAYO CLINIC

Name and Clinic Number
Protocol #: GI18-333

Approval Date: **May 15, 2026**
Not to be used after: **December 9, 2026**

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: HCRN GI18-333: Phase 2 study of novel SEQUEnced immunotherapy (pembrolizumab) with anti-angiogenesis and chemotherapy in advanced gastric and gastroesophageaL junction (GEJ) adenocarcinoma (SEQUEL) **(Cohort 1)**

IRB#: 19-010617

Principal Investigator: Dr. Harry Yoon and Colleagues

Key Study Information

This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. **Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision.** You should not sign this form if you have any questions that have not been answered.	
It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits or rights you would normally have if you choose not to take part.
Research Purpose	The purpose of this research is to see if giving pembrolizumab helps anticancer therapy (specifically ramucirumab and paclitaxel) work better, compared to giving ramucirumab and paclitaxel without pembrolizumab. An additional question addressed by the study is whether giving pembrolizumab at the same time as ramucirumab and paclitaxel is better than pembrolizumab alone followed by ramucirumab and paclitaxel alone. You have been asked to take part in this research because you have cancer in or near your stomach that is advanced.

What's Involved	Study participation involves Induction Immunotherapy with pembrolizumab. Pembrolizumab will be given on Day 1 of each 21 day Cycle (every 3 weeks) as an intravenous infusion (IV) over 30 minutes. You will continue to receive pembrolizumab as long as your disease is responding. For Combination treatment you will receive Arm A study treatment. Arm A patients will get ramucirumab and paclitaxel for 2 cycles then pembrolizumab followed by ramucirumab and paclitaxel. Arm B patients previously enrolled will have the option of moving to Arm A study treatment or remaining on Arm B study treatment. You will need to have what is called a "Screening Visit", during which exams, tests, or procedures will be performed to find out if you can participate in this study. Most of these exams, tests, or procedures are part of your regular cancer care and will be billed to you or your insurance company. If you have had some of the tests done recently, they may not need to be repeated. You will have doctor visits, blood tests, urine tests, radiology imaging, electrocardiogram (ECG), and we may use your tissue from the biopsy you would normally receive for your care.
Key Information	Participation may result in the following: • Spend more time in the hospital or doctor's office. • Be asked sensitive or private questions about things you normally do not discuss. • May not be able to take part in future studies. **Very Common side effects seen in patients treated with pembrolizumab include the following:** • Itching of the skin • Loose or watery stools • Cough **Common side effects in people taking Ramucirumab** • Fever • Swelling in the arms, legs, hands, or feet • Infusion-related reactions. **Possible Side Effects of Paclitaxel** • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

	• Infection, especially when white blood cell count is low • Bruising, bleeding You will not be paid for participating in this study.
Learn More	If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.

Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

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 either a printed or electronic copy of this form to keep. A copy of this form will be put in your medical record.

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.

Contact Information

If you have questions about …	You can contact …
▪ Study tests and procedures ▪ Materials you receive ▪ Research-related appointments ▪ Research-related concern or complaint ▪ Research-related injuries or emergencies ▪ Withdrawing from the research study	**Principal Investigator** Dr. Harry Yoon (Rochester) **Phone:** (507) 284-2511 **Institution Name and Address:** Mayo Clinic 200 First St SW Rochester, MN 55905
▪ Rights of a research participant	**Mayo Clinic Institutional Review Board (IRB)** **Toll-Free:** (866) 273-4681
▪ Rights of a research participant ▪ Any research-related concern or complaint ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study	**Research Participant Advocate (RPA)** **(The RPA is independent of the Study Team)** **Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** ResearchParticipantAdvocate@mayo.edu
▪ Billing or insurance related to this research study	**Patient Account Services** **Toll-Free:** (844) 217-9591

Other Information:
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.

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

We are asking you to take part in this research study because you have cancer in or near your stomach that is advanced.

Why is this research study being done?

This study is being done to see if giving pembrolizumab helps anticancer therapy (specifically ramucirumab and paclitaxel) work better, compared to giving ramucirumab and paclitaxel without pembrolizumab. An additional question addressed by the study is whether giving pembrolizumab at the same time as ramucirumab and paclitaxel is better than pembrolizumab alone followed by ramucirumab and paclitaxel alone.

What is the usual approach to my cancer?
There is no single standard treatment for front-line (first) treatment of this type of cancer. Chemotherapy is used, with nivolumab or pembrolizumab for some patients, but the disease often returns despite treatment.

Second-line (second) treatment many times includes ramucirumab and paclitaxel chemotherapy or other chemotherapy regimens. Chemotherapy kills cancer cells and also damages normal healthy cells.

Ramucirumab is a monoclonal antibody that targets cancer cells and leaves healthy cells alone. Ramucirumab works by finding and attaching with the vascular endothelial growth factor receptor-2 (VEGFR-2) and blocks the activation of VEGF. When there is too much VEGF, it can help the cancer grow and spread to other places in the body. Ramucirumab can stop VEGF from becoming active and control or slow down tumor growth by decreasing the blood supply to the tumor.

Pembrolizumab is a monoclonal antibody that blocks the programmed cell death protein 1 (PD-1) pathway. PD-1 can help cancer cells hide from the immune system and grow. Pembrolizumab attaches to PD-1 and blocks it so that the immune system can identify cancer cells and work to destroy them.

Paclitaxel is a type of chemotherapy called a taxane. Paclitaxel kills rapidly dividing cells which include both cancer cells and normal cells.

There will be about 18 people taking part in Cohort 1 this study.

Information you should know

Who is Funding the Study?
The cancer centers conducting this study are part of a network called the Hoosier Cancer Research Network. Harry H. Yoon MD MHS is the sponsor-investigator (the physician in charge) of this research study. He works at the Mayo Clinic. Merck, the company supplying pembrolizumab for this study, has provided a grant to fund this study.

Information Regarding Conflict of Interest:
Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her responsibilities for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study.

How long will you be in this research study?

If you decide to take part in this study, you will first receive pembrolizumab alone as part of Induction treatment (first treatment). You will continue to receive the pembrolizumab as long as your disease responds and if your disease starts to become active (progress) you will move on to the Combination treatment part of the study.

For Combination treatment you will receive to Arm A treatment. Arm A patients will get ramucirumab and paclitaxel for 2 cycles then pembrolizumab followed by ramucirumab and paclitaxel. Arm B patients previously enrolled will have the option of moving to Arm A study treatment or remaining on Arm B study treatment. There is an equal chance (50:50) that you will receive either Arm A or Arm B. Our approach is intended to maximize the synergy (increase the ability for the medications to work together) between prior immunotherapy and ramucirumab/paclitaxel.

You will continue Combination treatment as long as your disease responds (i.e., does not worsen).

After you finish your treatment, your doctor and study team will watch you for side effects. They will check in on you approximately every 2-3 months for 2 years after treatment.

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

You will need to have the following exams, tests, or procedures to find out if you can be part of the study. Most of these exams, tests, or procedures are part of your regular cancer care and will be billed to you or your insurance company. If you have had some of the tests done recently, they may not need to be repeated. Your doctor will talk to you about what testing is required to participate in the study. Some tests or procedures will be performed just for this research study. They will be paid for by the study and are marked below.

"Screening" tests are done before any study treatment and the results will help the study doctor see if you are eligible for this study. The tests and procedures outlined below may not have to be completed in one day but if so, you can take breaks in between testing.

Before you begin the Induction Immunotherapy part of the study, you will need to have the following screening procedures:

- You will have a chance to review the consent form with your study doctor and ask any questions you might have. Before any testing can be done, you will need to sign the informed consent.
- You will have a medical history done where the study doctor will ask you questions about your health including your cancer and if you are having any side effects now. If you've had prior PD-L1 or genetic testing, researchers would like to have those results. If you do not have PD-L1 results available, the testing will be ordered as part of your standard of care. You will also be asked about all medications you are taking.
- A physical examination including vital signs (temperature, heart rate, blood pressure, weight, height, and oxygen saturation) will be performed. You will also be asked if you are having trouble with your usual activities such as bathing, getting dressed, going to the store, or working (ECOG performance status).
- ECG/EKG also called an electrocardiogram. It shows the electrical activity of you heart and how it's working.
- You will have the following tests done as a part of your standard disease care:
  - About 1½ teaspoons of blood to check how your bone marrow, liver, and kidneys are functioning. These tests are called a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel
  - About 1 teaspoon of blood to check how your thyroid gland is working. These tests are called TSH, freeT3 and T4

- About ½ teaspoon of blood to check a marker for your type of cancer. This is called CEA
- About ½ teaspoon of blood to check albumin and lactate dehydrogenase (LDH)
- FOR WOMEN OF CHILD-BEARING POTENTIAL (WOCBP) About ½ teaspoon of blood or urine will be sent for a pregnancy test
- Urine test to see if there is too much protein, sugar or blood in your urine and to check your creatinine levels

- Radiology Imaging: you will have a CT scan of your chest, abdomen and pelvis as part of your standard of care disease assessment
- Tissue will be requested specifically for research purposes. More information about correlative samples is provided at the end of this consent.
  - Researchers will request samples of tissue stored from a previous biopsy or surgery (archival). If you do not have archival tissue available, you will be asked to undergo a research biopsy. If you do not have archival tissue available and you are not able to undergo a research biopsy, you are not eligible for this study.

All eligible participants will receive Induction Immunotherapy with pembrolizumab. Pembrolizumab will be given on Day 1 of each 21-day Cycle (every 3 weeks) as an intravenous infusion (IV) over 30 minutes. You will continue to receive pembrolizumab as long as your disease is responding. If your disease becomes active (progresses) you will move on to Combination Immunotherapy treatment on Arm A. You will receive three medications: (1) ramucirumab IV over 60 minutes, (2) paclitaxel IV over 60 minutes and (3) pembrolizumab IV over 30 minutes.

The first two cycles are each 28 days long and you will receive two medications: (1) ramucirumab on Days 1 and 15 and (2) paclitaxel on Days 1, 8 and 15. Subsequent cycles are 49 days long and you will receive three medications: (1) pembrolizumab on Day 1, (2) ramucirumab on Days 22 and 36 and (3) paclitaxel on Days 22, 29 and 36. You will continue this combination as long as your disease is responding to the treatment.

If you were previously randomized to Arm B, you will have the option of moving to Arm A study treatment or remaining on Arm B study treatment.

In addition, to enable short chemo holidays, Day 1 of study treatment can be delayed by up to 2 weeks if you meet a certain criteria and you and your doctor decide it is in your best interest to delay the study treatment. In order to do this, you must talk with your doctor at least 6 weeks in advance of that cycle.

After you finish study treatment, the research staff will continue to monitor you for side effects and follow your condition about every 2-3 months for about 2 years after you stop treatment. This may mean a phone call or email to you or your local physician.

What exams, tests, and procedures are involved in this study?
Day 1 of each Induction Immunotherapy Cycle

- A physical examination including vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following blood tests done
  - About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel
  - About ½ teaspoon of blood to check CEA and albumin
  - Cycle 1 Day 1 only: About ½ teaspoon of blood to check LDH
  - Every 2-3 cycles starting with Cycle 3: About 1 teaspoon of blood to check TSH, freeT3 and T4
  - C1D1, C4D1, C7D1 then every 3rd cycle about ½ a teaspoon of blood may be collected for troponin and creatine kinase. These tests can give information about how your heart is functioning.
- PRIOR TO C3D1 THEN EVERY 3 CYCLES: Radiology Imaging: you will have a CT scan of your chest, abdomen and pelvis as part of your disease assessment
- PRIOR TO C1D1 Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
  - Researchers will collect about 12 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

Safety Visit after Induction Immunotherapy (Day 30 after last dose of Pembrolizumab)
If you stop study treatment during Induction Immunotherapy and do not continue to the Combination Immunotherapy you will have a safety visit. Listed below is what will be included in this visit.

- A physical examination including vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following tests done
  - About 1½ teaspoons of blood may be collected to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel
  - About 1 teaspoon of blood will be collected to check CEA and albumin. Troponin, creatine kinase and thyroid testing may also be performed.
  - Urine test to see if there is too much protein, sugar or blood in your urine.
- Tissue will be requested if you are having a standard of care biopsy.
  - Researchers will request a tissue sample if you are having a standard of care biopsy. This is called a correlative sample and it is required if a standard of care biopsy is performed.

- Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
  - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

After your Day 30 safety visit, if you do not proceed to the combination therapy, the research staff will continue to watch you for side effects and follow your condition about every 3 months for about 2 years after you stop treatment. This may mean a phone call or email to you or your local physician.

Prior to starting Combination Immunotherapy treatment

- A physical examination including vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following tests done
  - About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel
  - About 1 teaspoon of blood to check TSH, freeT3 and T4
  - About ½ teaspoon of blood to check CEA, albumin, and LDH
  - Urine test to see if there is too much protein, sugar or blood in your urine and to check your creatinine levels
- Radiology Imaging: you will have a CT scan of your chest, abdomen and pelvis as part of your disease assessment
- Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
  - If this was not done after completion of induction immunotherapy, researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.
- Tissue will be requested if you are having a standard of care biopsy.
  - Researchers will request a tissue sample if you are having a standard of care biopsy. This is called a correlative sample and it is required if a standard of care biopsy is performed.

ARM A: Day 1 of each Combination Immunotherapy Cycle

- A physical examination including vital signs and ECOG performance status.
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following tests done
  - About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel including magnesium

- C3D1 then Day 1 of each cycle about 1 teaspoon of blood to check TSH, freeT3 and T4
- About ½ teaspoon of blood to check CEA and albumin
- Cycle 1 Day 1 only: about ½ teaspoon of blood to check LDH
- C1D1, C3D1, then Day 1 of each cycle about ½ teaspoon of blood may be collected to check troponin and creatinine kinase.
- C1D1, C3D1, then every other cycle: Urine test to see if there is too much protein, sugar or blood in your urine and to check your creatinine levels

- Radiology Imaging: you will have a CT scan of your chest, abdomen and pelvis as part of your disease assessment. These scans will occur before every cycle starting with Cycle 3 for about 9 months; then disease assessment will occur about every 3½ months.
- PRIOR TO C3D1: Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
  - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.
- Tissue will be requested if you are having a standard of care biopsy.
  - Researchers will request a tissue sample if you are having a standard of care biopsy. This is called a correlative sample and it is required if a standard of care biopsy is performed.

ARM A: Days 8 and 15 of each Combination Immunotherapy Cycle

- You will be asked if you are having any side effects and what medications you are taking
- Vital signs and ECOG performance status
- You will have the following blood tests done
  - About 1 teaspoon of blood to check a complete blood cell count (CBC) with differential
- PRIOR TO C1D8: Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
  - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

ARM A: Days 22, 29 AND 36 of each Combination Immunotherapy, Cycle 3 and subsequent

- Cycle 3 and Cycle 4; DAY 22: A physical examination
- Vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are

taking
- You will have the following blood tests done
    - About 1 teaspoon of blood to check a complete blood cell count (CBC) with differential and platelets
    - DAY 22: About 1 teaspoon to check a Chemistry Panel including magnesium
    - DAY 22: About ½ teaspoon of blood to check CEA and albumin

Safety Visit after Combination Immunotherapy (Day 30 after last dose of study treatment)
If you stop study treatment during Combination Immunotherapy and are not going to receive additional therapy, you will have a safety visit about 30 days after your last dose of study treatment. Listed below is what will be included in this visit.
- A physical examination including vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following tests done
    - About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel including magnesium
    - About ½ teaspoon of blood to check CEA and albumin
    - About ½ teaspoon of blood may be collected to check troponin and creatine kinase. Thyroid testing may also be performed
- Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
    - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

After your Day 30 safety visit, the research staff will continue to monitor you for side effects and follow your condition about every 3 months for about 2 years after you stop treatment. This may mean a phone call or email to you or your local physician.

Patients that were previously randomized to ARM B will have the option of moving to Arm A study treatment as described above or remaining on Arm B treatment as described below:

ARM B: Day 1 of each Combination Immunotherapy Cycle
- A physical examination including vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following tests done
    - About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel including magnesium

- C2D1 then Day 1 of each Cycle about 1 teaspoon of blood to check TSH, freeT3 and T4
- About ½ teaspoon of blood to check CEA and albumin
- CYCLE 1 DAY 1 about ½ teaspoon of blood to check LDH
- About ½ teaspoon of blood may be collected to check troponin and creatinine kinase.
- Urine test to see if there is too much protein, sugar or blood in your urine.

- Radiology Imaging: you will have a CT scan of your chest, abdomen and pelvis as part of your disease assessment. These scans will occur before every cycle starting with Cycle 3 for about 9 months; then disease assessment will occur about every 3½ months.
- PRIOR TO C2D1: Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
  - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.
- Tissue will be requested if you are having a standard of care biopsy.
  - Researchers will request a tissue sample if you are having a standard of care biopsy. This is called a correlative sample and it is required if a standard of care biopsy is performed.

ARM B: Days 8 and 15 of each Combination Immunotherapy Cycle

- Vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following blood tests done
  - About 1 teaspoons of blood to check a complete blood cell count (CBC) with differential
- PRIOR TO C1D8: BLOOD will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
  - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent

ARM B: Days 22, 29, 36 and 43 of each Combination Immunotherapy Cycle

- Cycle 1, Cycle 2 and Cycle 3; DAY 22 : A physical examination
- Vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following blood tests done
  - About 1 teaspoon of blood to check a complete blood cell count (CBC) with

differential and platelets
- DAY 22, 29, and 43: About 1 teaspoon to for a Chemistry Panel including magnesium
- DAY 29: About ½ teaspoon of blood to check CEA and albumin
- DAY 29: Urine test to see if there is too much protein, sugar, or blood in your urine and to check your creatinine levels

Safety Visit after Combination Immunotherapy (Day 30 after last dose of study treatment)
If you stop study treatment during Combination Immunotherapy and are not going to receive additional therapy, you will have a safety visit about 30 days after your last dose of study treatment. Listed below is what will be included in this visit.

- A physical examination including vital signs and ECOG performance status
- You will have the following tests done
- About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel including magnesium
- About ½ teaspoon of blood to check CEA
- About ½ teaspoon of blood may be collected to check troponin and creatinine kinase.
- Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
- Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

After your Day 30 safety visit, the research staff will continue to monitor you for side effects and follow your condition about every 3 months for about 2 years after you stop treatment. This may mean a phone call or email to you or your local physician.

<u>Required Samples</u>
The samples below are required to participate in this study because the research done on them is an important part of the study.

Required Correlative Blood Draw
Whenever possible blood will be collected at a time when blood is being obtained for other tests your doctor has ordered. Risks of blood collection are described above.

If you've had prior PD-L1 or other genetic testing, researchers would like a copy of those results for entry into the database for this study. If available, these results are required.

You will have about 2 teaspoons of blood drawn for germline DNA testing at the following time points: (1) prior to treatment Cycle 1 Day 1 (C1D1).

Germline variations or "mutations" are present at birth and are in all your cells. These variations are passed on to future generations.

Someone who inherits a germline variation will have that variation in all the cells of his or her body (since it was present at conception). Germline variations may not cause any problems, may cause disease, or may produce beneficial genetic diversity.

You will also have about 10 teaspoons of blood drawn for peripheral blood mononuclear cells (PBMCs) and plasma at the following time points: (1) prior to C1D1 pembrolizumab monotherapy, (2) prior to Combination Therapy or end of treatment for those that do not move on to combination therapy, (3) 1 week after start of Combination Therapy, (4) 8 weeks after Combination Therapy and (5) End of treatment.

These samples will be used to look at PD-L1 which is a protein in your blood that affects the way your immune system responds to cancer. There will also be analysis of immune cells to see how they change during throughout study treatment.

You may not get health benefits from any of these studies, but they are an important part of the research. The results will not be added to your medical records and you or your study doctor will not know the results. The results of this testing would only be used for research as described above and not to guide your medical care.

Required Correlative Tissue Collection/Biopsy
A sample of tissue from a previous biopsy or surgery (archival) will be requested after you are registered to the trial. If you do not have archival tissue available and are having a biopsy that is considered standard of care, part of this tissue will be requested and is required if a standard of care biopsy is being performed. If archival tissue is not available and you do not have a standard of care biopsy scheduled, you will be asked to have an additional research biopsy that will not be considered part of your routine clinical care.

In addition, during treatment on the study if you have a standard of care biopsy, a part of the tissue is required for correlative analysis. The risks of a biopsy have been described above. This sample will be used to look at microsatellite instability (MSI) and tumor mutational burden (TMB), as well as other immune markers. A high MSI means that the DNA repair mechanisms in the tumor cells are faulty, and as a result, they can acquire a significant number of mutations that can make them easily recognizable by the immune system, potentially making these tumors good candidates for immunotherapy. TMB measures the number of mutations within a tumor. These tests together could help determine people that will respond to immunotherapy treatment.

PD-L1 and other immune markers which may or may not have been previously tested in some form, will also be analyzed with the hope that this information can someday help other people going through this type of cancer treatment.

You may not get health benefits from any of these studies, but they are an important part of the research. The results may not be added to your medical records and you or your study doctor will not know the results. The results of this testing would only be used for research as described above and not to guide your medical care.

Special Considerations
Because we need to understand how the study treatment affects the cancer and your body, we are requesting one additional item as a condition of participation in this study. **Please note: Responding "No" to will prevent you from taking part in this study**.

Please check the appropriate boxes and initial and date below:

We ask that you be willing to enrollment in a parallel biopsy protocol entitled: "Exploration of tumor biology in patients with metastatic esophageal and gastric cancer (biorepository protocol for prospective tissue collection)". A separate consent form will be provided for the parallel protocol that will detail the requirements for participation.

I understand and agree with this request:

☐ Yes ☐ No Please initial here: _____Date: _____

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

If you choose to take part in this study, there is a risk that the approach being studied may not be as good as the usual approach to treating your cancer. There is also a risk that you could have side effects from the study medication(s). These side effects may be worse and may be different than you would get with the usual approach for your cancer.
Some of the most common side effects that the study doctors know about are:

- Ramucirumab- increased risk of bleeding such as nose bleeds. Reaction to the infusion.
- Paclitaxel- hair loss, nausea and vomiting, numbness and tingling in your hands or feet (neuropathy) and joint and muscle pain, and low neutrophil count (type of white blood cell).
- Pembrolizumab- fatigue, cough, rash with itching and decreased appetite

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

Participation may also result in the following:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

Genetic Testing Risks

This study will use genetic tests that may identify changes in the genes in your blood. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer.

Some of the samples will be used for research tests that will include genetic studies and testing. The intent is not to give participants (or his/her medical providers) the results of any testing done for research purposes; however, incidental germline (heritable) mutations may be identified of which a participant may or may not already be aware. In the case that an incidental genetic finding is identified, the sponsor-investigator of this project will be notified. The possible decisions for handling incidental findings may include notification of the participant (and provider); recommendation for genetic counseling, which may or may not include genetic testing (e.g., if the finding was not done in a CLIA certified laboratory); or, neither. In general, a member of the participant's treating team will be given the information to help with notification. In all cases, the current policy of the treating institution and local/participating site IRB, as applicable, will be followed and any additional approvals that may be required prior to participant notification will be secured in advance.

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

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

All health insurance companies and group health plans must follow this law.

Be aware that this new Federal law doesn't protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

The study treatment may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

Tell the study doctor if you notice or feel anything different. The study doctor may be able to treat some side effects or adjust the study drug(s) to try to reduce side effects.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

The sections below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Side Effects of Pembrolizumab

Pembrolizumab works by helping your immune system to fight your cancer. However, Pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects that may become serious or life-threatening, and in some cases, may lead to death and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Very Common side effects seen in ≥20% of patients treated with pembrolizumab include the following:

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

Common side effects seen in ≥5% to < 20% of patients treated with pembrolizumab include the following:

- Anemia- decrease in red blood cells which carry oxygen throughout your body. This may cause fatigue (extreme tiredness), dizziness or shortness of breath
- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach
- Decreased appetite
- Headache
- Dizziness

Uncommon side effects seen in ≥1% to < 5% of patients treated with pembrolizumab include the following:

- Inflammation of the lungs (pneumonitis) so you may feel short of breath and cough. Sometimes this might lead to death
- Thyroid hormone imbalance so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism).
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut (colitis), which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. These severe conditions can sometimes lead to death. Severe skin reactions, including Stevens-Johnson syndrome or toxic epidural necrolysis.
- Lung infection (pneumonia)

- Low white count and low neutrophil count (certain type of white blood cell) which can increase your risk for infection
- Low platelet count (thrombocytopenia) which can increase your risk of bleeding

Rare side effects seen in < 1% of patients treated with pembrolizumab include the following:

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

- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis).
- Inflammation of 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)
- Autoimmune thrombocytopenic purpura- low platelet count caused by the immune system destroying platelets and leading to bleeding tendencies
- Inflammation of the stomach (gastritis). You may have pain in your belly, feel full, or sick to your stomach. You may also experience nausea, vomiting or loss of appetite.
- Low number of red blood cells (cells that carry oxygen) due to destruction of red blood cells (hemolytic anemia). You may feel weak, tired, lightheaded, short of breath, or have a fast heartbeat. You may also experience difficulty with exercise, pale or yellow skin, dark urine, or fever.
- Not enough pancreatic enzymes (proteins that break down food) that leads to poor digestion of food (exocrine pancreatic insufficiency). You may have bloating, gas, discomfort in your belly, diarrhea, abnormal stool that is oily, or weight loss.
- Inflammation of the protective sac surrounding your heart (pericarditis) which can cause sharp chest pain and shortness of breath (especially when lying flat), fever, and a fast or irregular heartbeat. In severe cases, your heart may have difficulty pumping blood throughout your body.

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

- 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 coma (Haemophagocytic lymphohistiocytosis- HLH)
- Vogt-Koyanagi-Harada syndrome (VKH) chronic inflammation of melanocytes, which are specialized cells that produce a pigment called melanin. Melanin gives skin, hair, and eyes their color. Symptoms may include headache, neck stiffness, dizziness, inner ear problems, inflammation of multiple parts of the eye, detached retina, loss of skin color (pigment), and hair loss.
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).
- Inflammation or swelling of the nerve fibers of the eye which send visual information from your eye to your brain. This health condition often has a sudden onset of vision loss, loss of color vision, pain when moving your eyes, and/or loss of peripheral vision. It may affect one or both eyes at the same time (optic neuritis).
- Myocarditis-myositis-myasthenia gravis overlap syndrome which is when the body's immune system attacks its own heart muscle (myocarditis), skeletal muscles (myositis), and the nerves that control muscles (myasthenia gravis) all at once. This may cause you to experience chest pain, swelling of the legs, fast or irregular heartbeat, dizziness, fainting, weakness, pain in your muscles, tiredness, drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, and difficulty breathing.
- If you have had a tissue transplant (for example, a corneal transplant in your eye), you may experience rejection of the transplanted tissue. Your doctor should tell you what signs and symptoms you should report depending on the type of tissue transplant that you had.

Please note that the side effects of pembrolizumab such as gastritis, hemolytic anemia and exocrine pancreatic insufficiency may be delayed, late onset or long-term.

Possible Side Effects of Ramucirumab

Tell your doctor about all drugs and supplements you take while participating in this study. Tell your doctor if you take vitamin E, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen (Advil, Motrin), and naproxen (Aleve, Naprosyn), warfarin (Coumadin), ticlopidine (Ticlid), and clopidogrel (Plavix). These medications may interfere with blood clotting and can raise the risk of bleeding during treatment with ramucirumab. Your doctor will monitor you closely and may need to stop your treatment with ramucirumab.

Very common side effects (In 100 people receiving Ramucirumab 10 or more may have):

- Lack of energy (fatigue)
- Bleeding gums
- Coughing up blood
- Blood in the urine
- High blood pressure
- Headache
- Nosebleeds
- Nausea
- Diarrhea
- Vomiting
- Decrease or loss of appetite
- High level of protein in the urine
- Swelling and redness in the mouth, sometimes with pain
- Stomach pain
- Low white blood cell count which increases your risk for infection

Common side effects (In 100 people taking Ramucirumab 1-10 may have)

- Low platelet count which increases your risk for bleeding
- Low or severely low red blood cell count which causes anemia and could require a blood transfusion
- Fever
- Swelling in the arms, legs, hands, or feet
- Infusion-related reactions. Symptoms include shaking, back pain or spasms, feeling cold, red skin, trouble breathing, rash, fever, headache, body aches, stomach pain, nausea, vomiting, blurry vision, chest pain and/or tightness, very fast heartbeat, low blood pressure, and tingling or burning in the hands or feet.
- Weakness or weak muscles
- Feeling cold
- Bad taste in the mouth or dry mouth
- Skin problems such as rash, itching, acne, dry skin, or red skin

- Redness, tenderness, and peeling skin on the palms of the hands and soles of the feet
- Hair loss
- Skin condition resembling acne
- Trouble breathing
- Pain in the joints, muscles (with or without cramping), back, chest, arms, or legs.
- Throat pain
- Feeling dizzy
- Weight loss
- Damage to your liver
- Upset stomach
- Blood clots in the veins, which can obstruct the blood flow and may cause pain, swelling, fast breathing, cough, sweats, and/or fatigue. This includes veins in the lung or deep veins in the legs. Clots which block vessels in the heart and brain cause heart attack or stroke.
- Blood clots in arteries which could cause heart attack or stroke
- Tingling, burning, prickling, or numbness, usually in the hands, arms, legs or feet
- Trouble speaking
- Coughing
- High blood sugar
- Damage to your kidneys
- Dehydration or, too little water in the body
- Low levels of sodium, potassium, magnesium, and phosphorus in the blood
- Trouble sleeping
- Heart damage
- Cardiac arrest or cardiorespiratory arrest
- Blurry vision
- Low blood pressure
- Bruising
- Decreased levels of albumin
- Constipation
- Increased production of tears
- High levels of liver enzymes in the blood
- Face swelling
- Weight gain
- Increase in a type of waste material, called creatinine, in the blood
- Hot flash
- Impaired wound healing

Uncommon side effects (In 100 people taking Ramucirumab less than 1 may have)

- Liver failure
- Heart failure

- Lung failure
- Lung infection
- Sinus infection
- Skin infection
- Decreased oxygen in the blood
- Swelling of the lining of the abdominal cavity and abdominal organ
- Swelling of the digestive track
- Irregular heartbeat
- Collapsed lung
- Infection throughout the body
- Damage to the walls of the stomach, intestines, or rectum (causing intestinal perforation – a hole in the wall of the intestine)
- More acid than normal in the blood
- Multi-organ failure
- Difficulty forming blood clots
- Changes in the brain structure and functions that can cause confusion, headache, nausea, vomiting, feeling wobbly, impaired memory, eyesight changes, and feeling tired
- Severe intestinal bleeding and life-threatening bleeding ulcer
- Abnormal vaginal bleeding
- Bruising or bleeding under the skin
- Bleeding in the throat, ear, eye, brain, lung, nail beds, food pipe, stomach and intestines, inside the skull, from the rectum or anus, or at the site of injection
- Tumor bleeding
- Bleeding after a procedure or surgery
- Blood in the stool
- Leukoencephalopathy, a loss of white matter of the brain, which may results in brain dysfunction, and can cause forgetfulness, confusion, headache, delirium, and total or partial blindness.
- Body does not effectively absorb nutrients from food in the intestine
- Abnormal opening between the food pipe and wind pipe
- Occurrence of confusion, altered level of consciousness, and/or coma related to excess of ammonia in the blood
- Sudden death

Possible Side Effects of Paclitaxel
Common, some may be serious (> 20% of patients)

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Infection, especially when white blood cell count is low
- Bruising, bleeding

- Anemia which may cause tiredness, or may require blood transfusions
- Pain
- Sores in mouth which may cause difficulty swallowing
- Diarrhea, nausea, vomiting
- Muscle weakness
- Numbness, tingling or pain of the arms and legs
- Hair loss

Less Common, some may be serious (Between 4% - 20% of patients)

- Abnormal heartbeat
- Blood clot which may cause swelling, pain, shortness of breath
- Damage to the lungs which may cause shortness of breath

Rare, and serious (≤ 3% of patients)

- Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- A tear or a hole in the bowels which may cause pain or that may require surgery
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Additional Risks

Drug Interactions

The other medications you take may affect the study drug(s) in ways that we do not know. For your safety, you must tell the study doctor or nurse about all the prescription drugs, herbal products, over-the-counter (OTC) drugs, vitamins, and natural remedies that you are taking before you start the study and before taking any of these products while you are on the study. Please be sure to tell us also about any changes you make with your medications during your participation.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Imaging Studies Standard of Care

While you are in this research study, CT scans, PET/CT scans, bone scans, x-rays, mammograms, and/or other radioactive agents may be used to evaluate your disease. The frequency of these exams is determined by what you would receive as your regular standard care. You will be exposed to radiation from the CT scans. The amount of radiation has a low risk of harmful effects.

Blood Draw
Blood samples will be drawn through a vein by a needle stick. Risks include: pain, bleeding, bruising, blood clot, feeling faint or fainting and infection with redness and irritation of the vein at the site where blood is drawn.

Biopsy
Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail. Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

You may be exposed to radiation during the CT-guided biopsies, depending on the location of your disease. The amount of radiation has a low risk of harmful effects.

Electrocardiogram (ECG or EKG)
An electrocardiogram, also called an ECG or EKG, is a simple, painless test that detects and records your heart's electrical activity. An EKG can show how fast your heart is beating, whether the rhythm of your heartbeats is steady or irregular, and the strength and timing of the electrical impulses passing through each part of your heart. A nurse or technician will attach up to 12 electrodes to the skin on your chest, arms, and legs. Your skin may need to be shaved to help the electrodes stick. The electrodes are connected by wires to a machine that records your heart's electrical activity on graph paper or on a computer.

After the test, the electrodes will be removed. An EKG has no serious risks. EKGs don't give off electrical charges such as shocks. You may develop a slight rash where the electrodes were attached to your skin. This rash usually goes away on its own without treatment.

Reproductive
You should not get pregnant, breastfeed, or father a baby while in this study. The study drug(s) could be damaging to an unborn baby and breast milk. You must have a negative pregnancy test prior to enrolling in the study and prior to treatment. You must use birth control methods as directed below, unless you completely avoid having heterosexual intercourse. Complete abstinence is considered an acceptable form of contraception. Any birth control method can fail. The reports of birth control failing are more frequent for female subjects who use only a single form of birth control. Using TWO forms of birth control AT THE SAME TIME greatly reduces the chances of pregnancy. Please talk with your doctor if you have questions.

Primary Forms	Secondary Forms
Tubal sterilization (tubes tied)	Male latex condom with or without spermicide
Partner's vasectomy	Diaphragm with spermicide
Intrauterine device (IUD)	Cervical cap with spermicide
Hormonal contraception (oral, transdermal patch, injectables, implantables)	Vaginal sponge (contains spermicide)

If you or your female partner becomes pregnant, you must tell your doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. Additionally, the pregnancy will be followed until conclusion. For female participants who become pregnant while on this study, the study drug will be stopped immediately.

Female participants:
Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use birth control from the time of signing the informed consent form, throughout the entire study drug period, and for 120 days (4 months) after the last dose of study drug. This timeframe applies to breastfeeding and egg donation as well.

Male participants:
You should not have unprotected intercourse with your partner for the timeframe described below. Even if you are surgically sterilized (i.e., have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex condom with a spermicidal agent) from the time of treatment initiation, throughout the entire study drug period, and for 120 days (4 months) after last dose of study drug. This timeframe applies to sperm donation.

Confidentiality risk
As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

Are there reasons you might leave this research study early?

You can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?
The study doctor may take you off the study if:

- There is evidence your cancer has worsened (disease progression) and further study treatment is not in your best interest.
- You are unable to tolerate the study treatment due to side effects
- The study drug(s) are delayed for more than 42 days
- You require reduction of your study drug(s) more than two times
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the sponsor-investigator, Harry H Yoon, MD MHS, the Funder, Merck, IRB, FDA, or other Health Authorities for any reason.

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.

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 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. The study sponsor-investigator, Dr. Yoon or Merck will not pay for medical treatment for injury.

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

There may be a higher chance your tumor will shrink and stay inactive for a longer period of time when pembrolizumab is given before ramucirumab/paclitaxel, as compared to pembrolizumab being given after ramucirumab/paclitaxel. Our experience also suggests the order in which these agents are given can help prolong their benefit. It is not possible to know now if this treatment sequence will do a better, same, or worse job of shrinking your tumor compared to the usual approach. That is why we are doing this clinical trial. We hope this study will help you. This study will also help the study doctors learn things that will help people in the future.

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

You may choose:

- To have the usual approach described above
- To take part in a different study, if one is available
- Not to be treated for your cancer, but you may choose to receive palliative care which is comfort care to relieve symptoms. Comfort care tries to keep you as active and comfortable as possible.

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

The pembrolizumab will be supplied at no charge while you take part in this study. The study will also pay for the cost of the pharmacy getting the study drug ready, but you or your insurance company will be responsible for the intravenous administration costs. The ramucirumab and paclitaxel will be billed to you or your insurance company as they are standard of care for the treatment of your type of cancer. You or your insurance company will be billed for any imaging

(CT, MRI, or PET-CT imaging) as these will only be conducted as needed for your routine clinical care. You or your insurance company will also be billed for the pregnancy testing as part of the screening visit.

You will not be responsible for these other study-specific costs:

- Blood and tissue analysis done during the study for research (correlative samples).
- Electrocardiogram (ECG) conducted during the screening visit

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

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

You will not be paid for participating in this study.

There is a very small chance that some commercial value may result from the use of your sample. This could include new products like a drug or a test to diagnose a disease. If that happens, you will not be offered a share in any profits.

Will your information or samples be used for future research?

Additional information on study specific testing
This section will describe study specific testing that will be performed throughout the study. You will not be billed for these studies. Some of the testing may be required to participate in the study. Other testing may be optional, and you will decide if you want to participate. Researchers hope the results will help other people with cancer in the future.

Optional Banking for Future Cancer Related Research
This research study also involves banking of leftover samples for future research related to this study. A sample available for use by researchers is referred to as a "banking sample." These samples are stored in a "biorepository". Hoosier Cancer Research Network, Inc. (HCRN) manages the biorepository for the samples collected in this study. Only Mayo Clinic investigators and staff maintaining the biorepository will be able to access the samples.

The research that may be done is unknown at this time. The purpose of banking the samples is to make them available to researchers involved with this study. We will also collect information

during your participation in this study that is related to your health and/or disease history. Some examples include results of tests, medical procedures, images (such as X-rays), and medicines you take. Researchers at Mayo Clinic will use this information to better understand how genes affect health and response to treatment. The information collected will not contain your date of birth or medical record number but will be identified only by a code. This will take place for as long as your sample is stored until the conclusion of this study, unless you tell us to stop.

Unless you give your permission below, your information or samples collected for this study will not be used or shared for future research, even if the identifiable information such as your name, Mayo Clinic number or date of birth is removed.

We would like to keep your information and samples for future research. You can still take part in this current study even if you don't want your information or samples used for future research.

If you approve the release of your information and/or samples by checking 'yes' below, Mayo Clinic may send the information and/or samples to other researchers who request them, but Mayo will not send your name, address, phone number, social security number, or any other identifying information with the information and/or samples. Your information and/or samples may be sent with a code, and only the researchers for this study at Mayo Clinic would be able to link the code to you.

Some future studies may examine your DNA, the genetic information you inherited from your parents (genetic testing). If there are findings which may be useful for your health care, the researchers may contact Mayo Clinic, so Mayo Clinic can give you the option of learning the results. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

To support future research, de-identified genetic information may be placed in databases accessible by the internet. Some of the information may be available to anyone using the internet, and some will be released only to approved researchers. Combined study information (including genomic summary results) may be published, but the information will not identify you.

Even though information traditionally used to identify you will not be shared, people may develop ways in the future to allow someone to link your genetic information back to you. For this reason, confidentiality cannot be guaranteed. It is also possible that reidentified information could be used in discriminating ways, and there could be additional unknown risks. We will make every effort to protect your confidentiality.

Approval Date: **May 15, 2026**
Not to be used after: **December 9, 2026**

Please read the following statements and mark your choices:

1. I permit my information and samples to be stored and used in future research of advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma at the HCRN biorepository:

   ☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my information and samples 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 information and samples to researchers at other institutions:

   ☐ Yes ☐ No Please initial here: _____Date: _____

You may withdraw your consent for future use of your information and/or samples at any time, by writing to the Principal Investigator at the address provided in the "Contact Information" section of this consent form.

Your information and/or samples would be removed from any repository where they are stored, if possible. Information and/or samples already distributed for research use will not be retrieved.

WHAT ARE THE POSSIBLE BENEFITS OF SAMPLE BANKING?
You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

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.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Your privacy is very important to us and the researchers will make every effort to protect it. We cannot guarantee absolute confidentiality. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Your identity will be held in confidence in reports in which the study may be published.
Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the sponsor-investigator in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Some individuals and organizations may have access to and may inspect your records. They must keep your information confidential, unless the law requires them to disclose information or you consent to the disclosure. Some of these individuals and organizations are:

- The sponsor-investigator Dr. Yoon and individuals working under the direction of the sponsor-investigator for the study
- Outside individuals or entities that have a need to access this information to perform activities relating to the conduct of this research, such as analysis by outside laboratories
- Other researchers and institutions that are conducting or participating in this study,
- Merck, the founder of the study and its authorized agents. Merck is also providing pembrolizumab for this study.
- The organization managing this study, Hoosier Cancer Research Network, and any companies that they use to oversee, manage, or conduct the research,

- The Office for Human Research Protections in the U.S. Department of Health and Human Services, the United States Food and Drug Administration (FDA) and other federal and state agencies that have the right to use the information as required by law, and
- The members and staff of any Institutional Review Board (IRB) and Data and Safety Monitoring Board that oversee this study

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. This research follows the Genetic Information Nondiscrimination Act (GINA), a federal law which generally makes it illegal for health insurance companies, group health plans, and most employers to request the genetic information we get from this research and discriminate against you based on your genetic information. Despite the GINA protections and the best efforts of the research team, there may still be a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

There can also be a risk in finding out new genetic information about you. This may include information about inherited traits that might affect you or your blood relatives could be found during a study.

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 (or "authorization") to Mayo Clinic.

Your health information may be collected from:

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

Your health information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was conducted following the approved study plan, and applicable rules and regulations.

Your health information may be used and shared with:

- Mayo Clinic research staff involved in this study.
- Other Mayo Clinic staff involved in your clinical care.
- Researchers involved in this study at other institutions.
- The sponsor investigator and funder of this study and the people or groups hired by the them to help perform this research.
- The Mayo Clinic Institutional Review Board that oversees the research.
- 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.
- A group that oversees the data (study information) and safety of this research.

How your information may be shared with others:

While taking part in this study, you will be assigned a code that is unique to you, but does not include information that directly identifies you.

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 this study are made public (for example, through scientific meetings, reports or media) information that identifies you will not be used.

In addition, individuals involved in study oversight and <u>not</u> 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 Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying 'no' will not harm your relationship with your own doctors or with Mayo Clinic.

If you cancel your permission for Mayo Clinic 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.

You can cancel your permission for Mayo Clinic 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
Plummer Building PL 3-02
200 First St. SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Participant Advocate at: ResearchParticipantAdvocate@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 for Mayo Clinic to use and share your health information lasts until the conclusion of this study, unless you cancel it.

Any samples stored in this study will be coded and stored for a maximum of 15 years. There is no expiration or end date related to the sponsor investigator or funder use of your health information received from Mayo Clinic as part of this study.

Enrollment and Permission Signatures

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

	/ /	: AM/PM
Printed Name	Date	Time

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.

	/ /	: AM/PM
Printed Name	Date	Time

Signature

MAYO CLINIC

Name and Clinic Number

Approval Date: **May 15, 2026**
Not to be used after: **December 9, 2026**

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: HCRN GI18-333: Phase 2 study of novel SEQUEnced immunotherapy (pembrolizumab) with anti-angiogenesis and chemotherapy in advanced gastric and gastroesophageaL junction (GEJ) adenocarcinoma (SEQUEL) **(Cohort 2)**

IRB#: 19-010617

Principal Investigator: Dr. Harry Yoon and Colleagues

Key Study Information

This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. **Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision.** You should not sign this form if you have any questions that have not been answered.	
It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits or rights you would normally have if you choose not to take part.
Research Purpose	The purpose of this research is to see if giving pembrolizumab helps anticancer therapy (specifically ramucirumab and paclitaxel) work better, compared to giving ramucirumab and paclitaxel without pembrolizumab. An additional question addressed by the study is whether giving pembrolizumab at the same time as ramucirumab and paclitaxel is better than pembrolizumab alone followed by ramucirumab and paclitaxel alone. You have been asked to take part in this research because you have cancer in or near your stomach that is advanced.
What's Involved	Study participation involves Induction Immunotherapy with pembrolizumab. Pembrolizumab will be given on Day 1 of each 21 day Cycle (every 3 weeks) as an intravenous infusion (IV) over 30 minutes. You will continue to receive pembrolizumab as long as your disease is responding.

	If your disease becomes active (progresses) you will move on to Combination Immunotherapy treatment which has two arms- Arm A and Arm B. You will have an equal chance of being in Arm A or Arm B through a process called randomization. You will need to have what is called a "Screening Visit", during which exams, tests, or procedures will be performed to find out if you can participate in this study. Most of these exams, tests, or procedures are part of your regular cancer care and will be billed to you or your insurance company. If you have had some of the tests done recently, they may not need to be repeated. You will have doctor visits, blood tests, urine tests, radiology imaging, electrocardiogram (ECG), and we may use your tissue from the biopsy you would normally receive for your care.
Key Information	Participation may result in the following: • Spend more time in the hospital or doctor's office. • Be asked sensitive or private questions about things you normally do not discuss. • May not be able to take part in future studies. **Very Common side effects seen in patients treated with pembrolizumab include the following:** • Itching of the skin • Fatigue • Cough • Decreased appetite **Common side effects in people taking Ramucirumab** • Infusion-related reactions • Increase risk of bleeding such as nose bleeds **Possible Side Effects of Paclitaxel** • Hair loss • Nausea and vomiting • Numbness and tingling in your hands or feet (neuropathy) • Joint and muscle pain • Low neutrophil count (type of white blood cell) You will not be paid for participating in this study.

Learn More	If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.

Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

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 either a printed or electronic copy of this form to keep. A copy of this form will be put in your medical record.

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.

MAYO CLINIC

Name and Clinic Number

Approval Date: **May 15, 2026**
Not to be used after: **December 9, 2026**

Contact Information

If you have questions about …	You can contact …
▪ Study tests and procedures ▪ Materials you receive ▪ Research-related appointments ▪ Research-related concern or complaint ▪ Research-related injuries or emergencies ▪ Withdrawing from the research study	**Principal Investigator** Dr. Harry Yoon (Rochester) **Phone:** (507) 284-2511 **Institution Name and Address:** Mayo Clinic 200 First St SW Rochester, MN 55905
▪ Rights of a research participant	**Mayo Clinic Institutional Review Board (IRB)** **Toll-Free:** (866) 273-4681
▪ Rights of a research participant ▪ Any research-related concern or complaint ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study	**Research Participant Advocate (RPA)** **(The RPA is independent of the Study Team)** **Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** ResearchParticipantAdvocate@mayo.edu
▪ Billing or insurance related to this research study	**Patient Account Services** **Toll-Free:** (844) 217-9591

Other Information:
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.

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

We are asking you to take part in this research study because you have cancer in or near your stomach that is advanced.

Why is this research study being done?

This study is being done to see what is the most effective way of giving chemotherapy (specifically paclitaxel) when it is given with pembrolizumab and ramucirumab (giving it continuously or giving breaks).

To clarify, there is no "placebo" in this study: all patients receive the study treatment. The only way that the study physicians will know whether one treatment is better than the other is by comparing results from past studies (where patients received ramucirumab/paclitaxel by itself without immunotherapy) to the results of this study.

What is the usual approach to my cancer?
There is no single standard treatment for front-line (first) treatment of this type of cancer. Chemotherapy is used, including with nivolumab or pembrolizumab in some situations, but the disease often returns despite treatment.

Second-line (second) treatment many times includes ramucirumab and paclitaxel chemotherapy or other chemotherapy regimens. Chemotherapy kills cancer cells and also damages normal healthy cells.

Ramucirumab is a monoclonal antibody that targets cancer cells and leaves healthy cells alone. Ramucirumab works by finding and attaching with the vascular endothelial growth factor receptor-2 (VEGFR-2) and blocks the activation of VEGF. When there is too much VEGF, it can help the cancer grow and spread to other places in the body. Ramucirumab can stop VEGF from becoming active and control or slow down tumor growth by decreasing the blood supply to the tumor.

Pembrolizumab is a monoclonal antibody that blocks the programmed cell death protein 1 (PD-1) pathway. PD-1 can help cancer cells hide from the immune system and grow. Pembrolizumab attaches to PD-1 and blocks it so that the immune system can identify cancer cells and work to destroy them.

Paclitaxel is a type of chemotherapy called a taxane. Paclitaxel kills rapidly dividing cells which include both cancer cells and normal cells.

There will be about 33 people taking part in Cohort 2 of this study.

Information you should know

Who is Funding the Study?
The cancer centers conducting this study are part of a network called the Hoosier Cancer Research Network. Harry H. Yoon MD MHS is the sponsor-investigator (the physician in charge) of this research study. He works at the Mayo Clinic. Merck, the company supplying pembrolizumab for this study, has provided a grant to fund this study.

Information Regarding Conflict of Interest:
Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study.

How long will you be in this research study?

For Combination treatment you will be randomized to Arm A or Arm B. Both Arms will receive combination treatment with pembrolizumab, ramucirumab and paclitaxel. Our approach is intended to maximize the synergy (increase the ability for the medications to work together) between prior immunotherapy and ramucirumab/paclitaxel.

You will continue Combination treatment as long as your disease responds (i.e., does not worsen).

After you finish your treatment, your doctor and study team will watch you for side effects. They will check in on you approximately every 2-3 months for 2 years after treatment.

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

You will need to have the following exams, tests, or procedures to find out if you can be part of the study. Most of these exams, tests, or procedures are part of your regular cancer care and will be billed to you or your insurance company. If you have had some of the tests done recently, they may not need to be repeated. Your doctor will talk to you about what testing is required to participate in the study. Some tests or procedures will be performed just for this research study. They will be paid for by the study and are marked below.

"Screening" tests are done before any study treatment and the results will help the study doctor see if you are eligible for this study. The tests and procedures outlined below may not have to be completed in one day but if so, you can take breaks in between testing.

Before you begin, you will need to have the following screening procedures:

- You will have a chance to review the consent form with your study doctor and ask any questions you might have. Before any testing can be done, you will need to sign the informed consent.
- You will have a medical history done where the study doctor will ask you questions about your health including your cancer and if you are having any side effects now. If you've had prior PD-L1 or genetic testing, researchers would like to have those results. If you do not have PD-L1 results available, the testing will be ordered as part of your standard of care. Additional biomarker information may be obtained. You will also be asked about all medications you are taking.
- A physical examination including vital signs (temperature, heart rate, blood pressure, weight, height, and oxygen saturation) will be performed. You will also be asked if you are having trouble with your usual activities such as bathing, getting dressed, going to the store, or working (ECOG performance status).
- ECG/EKG also called an electrocardiogram. It shows the electrical activity of you heart and how it's working.
- You will have the following tests done as a part of your standard disease care:
    - About 1½ teaspoons of blood to check how your bone marrow, liver, and kidneys are functioning. These tests are called a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel including magnesium
    - About 1 teaspoon of blood to check how your thyroid gland is working. These tests are called TSH, freeT3 and T4
    - About ½ teaspoon of blood to check a marker for your type of cancer. This is called CEA
    - About ½ teaspoon of blood to check albumin and lactate dehydrogenase (LDH)

  - FOR WOMEN OF CHILD-BEARING POTENTIAL (WOCBP) About ½ teaspoon of blood or urine will be sent for a pregnancy test
  - Urine test to see if there is too much protein, sugar or blood in your urine and to check your creatinine levels
- Radiology Imaging: you will have a CT scan of your chest, abdomen and pelvis as part of your standard of care disease assessment
- Tissue will be requested specifically for research purposes. More information about correlative samples is provided at the end of this consent.
  - Researchers will request samples of tissue stored from a previous biopsy or surgery (archival). If you do not have archival tissue available, you will be asked to undergo a research biopsy. If you do not have archival tissue available and you are not able to undergo a research biopsy, you are not eligible for this study.

We will use a computer to assign you to one of the study Arms. This process is called "randomization." It means that your doctor will not choose, and you cannot choose which study arm you are in. You will be put into an arm by chance (like flipping a coin). You will have an equal chance of being in Arm A or Arm B (50:50). Both arms will receive three medications: (1) ramucirumab IV over 60 minutes, (2) paclitaxel IV over 60 minutes and (3) pembrolizumab IV over 30 minutes.

If you are randomized to Arm A, the first cycle is 63 days long and you will receive: (1) pembrolizumab on Days 1, 22 and 43, (2) ramucirumab on Days 1, 22 and 43 and (2) paclitaxel on Days 1, 8, 43 and 50. Subsequent cycles are 43 days long and you will receive: (1) pembrolizumab on Days 1 and 22, (2) ramucirumab on Days 1 and 22 and (3) paclitaxel on Days 22 and 29. You will continue this combination as long as your disease is responding to the treatment.

If you are randomized to Arm B, the first cycle is 63 days long and you will receive: (1) pembrolizumab on Days 1, 22 and 43, (2) ramucirumab on Days 1, 22 and 43 and (2) paclitaxel on Days 1, 8, 22, 29, 43 and 50. Subsequent cycles are 43 days long and you will receive: (1) pembrolizumab on Days 1 and 22, (2) ramucirumab on Days 1 and 22 and (3) paclitaxel on Days 1, 8, 22 and 29.You will continue this combination as long as your disease is responding to the treatment.

On either arm, to enable short chemo holidays, Day 1 of study treatment can be delayed by up to 2 weeks if you meet a certain criteria and you and your doctor decide it is in your best interest. In order to do this, you must talk with your doctor at least 6 weeks in advance of that cycle.

After you finish study treatment, the research staff will continue to monitor you for side effects and follow your condition about every 3 months for about 2 years after you stop treatment. This may mean a phone call or email to you or your local physician.

What exams, tests, and procedures are involved in this study?

ARM A: Day 1 of each Combination Immunotherapy Cycle

- A physical examination including vital signs and ECOG performance status.
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following tests done
    - About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel including magnesium
    - C2 then every cycle thereafter: About 1 teaspoon of blood to check TSH, freeT3 and T4
    - About ½ teaspoon of blood to check CEA and albumin
    - Cycle 1 Day 1 only: about ½ teaspoon of blood to check LDH
    - About ½ teaspoon of blood may be collected to check troponin and creatinine kinase
    - C1D1, C2D1, C3D1, then every other cycle: Urine test to see if there is too much protein, sugar or blood in your urine and to check your creatinine levels
- Radiology Imaging: you will have a CT scan of your chest, abdomen and pelvis as part of your disease assessment. These scans will occur before every cycle starting with Cycle 3 for about 9 months; then disease assessment will occur about every 3 months.
- PRIOR TO C1D1: You will be asked to complete a Quality-of-Life Questionnaire
- PRIOR TO C1D1 and C2D2: Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
    - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.
- Tissue will be requested if you are having a standard of care biopsy.
    - Researchers will request a tissue sample if you are having a standard of care biopsy. This is called a correlative sample and it is required if a standard of care biopsy is performed.

ARM A: Cycle 1; Days 8, 22, 43 and 50 of Combination Immunotherapy Cycle

- D22 and D43: A physical examination including vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- Vital signs and ECOG performance status
- You will have the following blood tests done
    - About 1 teaspoon of blood to check a complete blood cell count (CBC) with differential

  - D22 and D43: About 1 teaspoon to check a Chemistry Panel including magnesium
  - D22 and D43: About ½ teaspoon of blood to check CEA and albumin
  - D43: About ½ teaspoon of blood may be collected to check troponin and creatinine kinase
- PRIOR TO C1D8, C1D22, C1D43: Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
  - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

ARM A: Cycle 2 and subsequent; Days 22 and 29 of each Combination Immunotherapy

- CYCLE 2 and CYCLE 3; D22: A physical examination
- CYCLE 2-4 DAY 22: You will be asked to complete a Quality-of-Life Questionnaire
- Vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following blood tests done
  - About 1 teaspoon of blood to check a complete blood cell count (CBC) with differential and platelets
  - D22: About 1 teaspoon to check a Chemistry Panel including magnesium
  - D22: About ½ teaspoon of blood to check CEA and albumin

Safety Visit after Combination Immunotherapy (Day 30 after last dose of study treatment)

If you stop study treatment during Combination Immunotherapy and are not going to receive additional therapy, you will have a safety visit about 30 days after your last dose of study treatment. Listed below is what will be included in this visit.

- A physical examination including vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following tests done
  - About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel including magnesium
  - About ½ teaspoon of blood to check TSH, freeT3 and T4 and about ½ teaspoon of blood to check CEA and albumin
  - About ½ teaspoon of blood may be collected to check troponin and creatinine kinase

- Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
    - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

After your Day 30 safety visit, the research staff will continue to monitor you for side effects and follow your condition about every 3 months for about 2 years after you stop treatment. This may mean a phone call or email to you or your local physician.

ARM B: Day 1 of each Combination Immunotherapy Cycle

- A physical examination including vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following tests done
    - About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel including magnesium
    - About 1 teaspoon of blood to check TSH, freeT3 and T4
    - About ½ teaspoon of blood to check CEA and albumin
    - C1D1: About ½ teaspoon of blood to check LDH
    - About ½ teaspoon of blood may be collected to check troponin and creatinine kinase.
    - C1D1, C2D1, C3D1 THEN EVERY OTHER CYCLE: Urine test to see if there is too much protein, sugar, or blood in your urine and to check your creatinine levels
- Radiology Imaging: you will have a CT scan of your chest, abdomen and pelvis as part of your disease assessment. These scans will occur before every cycle starting with Cycle 3 for about 9 months; then disease assessment will occur about every 3 months.
- PRIOR TO C1D1: You will be asked to complete a Quality-of-Life Questionnaire
- PRIOR TO C1D1 and C2D1: Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
    - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.
- Tissue will be requested if you are having a standard of care biopsy.
    - Researchers will request a tissue sample if you are having a standard of care biopsy. This is called a correlative sample and it is required if a standard of care biopsy is performed.

ARM B: Cycle 1; Days 8, 22, 29, 43 and 50 of Combination Immunotherapy Cycle

- D22 and D43: A physical examination including vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- Vital signs and ECOG performance status
- You will have the following blood tests done
    - About 1 teaspoon of blood to check a complete blood cell count (CBC) with differential
    - D22 and D43: About 1 teaspoon to check a Chemistry Panel including magnesium
    - D22 and D43: About ½ teaspoon of blood to check CEA and albumin
    - D43: About ½ teaspoon of blood may be collected to check troponin and creatinine kinase.
- PRIOR TO D8, D22, D29 and D43: Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
    - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

ARM B: Cycle 2 and subsequent; Days 8, 22 and 29 of each Combination Immunotherapy

- CYCLE 2 and CYCLE 3; D22: A physical examination
- CYCLE 2-4 DAY 22: You will be asked to complete a Quality-of-Life Questionnaire
- Vital signs and ECOG performance status
- You will be asked if you are having any side effects and what medications you are taking
- You will have the following blood tests done
    - About 1 teaspoon of blood to check a complete blood cell count (CBC) with differential and platelets
    - D22: About 1 teaspoon to check a Chemistry Panel including magnesium
    - D22: About ½ teaspoon of blood to check CEA and albumin
- PRIOR TO C2 AND C3; D22: Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
    - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

Safety Visit after Combination Immunotherapy (Day 30 after last dose of study treatment)
If you stop study treatment during Combination Immunotherapy and are not going to receive additional therapy, you will have a safety visit about 30 days after your last dose of study

treatment. Listed below is what will be included in this visit.

- A physical examination including vital signs and ECOG performance status
- You will have the following tests done
    - About 1½ teaspoons of blood to check a complete blood cell count (CBC) with differential and platelets and a Chemistry Panel including magnesium
    - About 1½ teaspoon of blood to check TSH, freeT3 and T4 and about ½ teaspoon of blood to check CEA and albumin
- Blood will be collected specifically for research purposes and paid for by the study. More information about correlative and banking samples is provided at the end of this consent.
    - Researchers will collect about 10 teaspoons of blood for study specific testing. This is called a correlative sample and it is required. More information about correlative samples is provided at the end of this consent.

After your Day 30 safety visit, the research staff will continue to monitor you for side effects and follow your condition about every 3 months for about 2 years after you stop treatment. This may mean a phone call or email to you or your local physician.

Required Samples

The samples below are required to participate in this study because the research done on them is an important part of the study.

Required Correlative Blood Draw

Whenever possible blood will be collected at a time when blood is being obtained for other tests your doctor has ordered. Risks of blood collection are described above.

If you've had prior PD-L1 or other genetic testing, researchers would like a copy of those results for entry into the database for this study. If available, these results are required.

You will have about 2 teaspoons of blood drawn for germline DNA testing at the following time points: (1) prior to treatment Cycle 1 Day 1 (C1D1).

Germline variations or "mutations" are present at birth and are in all your cells. These variations are passed on to future generations. Someone who inherits a germline variation will have that variation in all the cells of his or her body (since it was present at conception). Germline variations may not cause any problems, may cause disease, or may produce beneficial genetic diversity.

You will also have about 10 teaspoons of blood drawn for peripheral blood mononuclear cells (PBMCs) and plasma prior to treatment (1) C1D1, (2) C1D8, (3) C1D22, (4) C1D43, (5) C2D1, (6) C2D22, (7) C3D22, and (8) at progression/safety visit.

These samples will be used to look at PD-L1 which is a protein in your blood that affects the way your immune system responds to cancer. There will also be analysis of immune cells to see how they change during throughout study treatment.

You may not get health benefits from any of these studies, but they are an important part of the research. The results will not be added to your medical records and you or your study doctor will not know the results. The results of this testing would only be used for research as described above and not to guide your medical care.

Required Correlative Tissue Collection/Biopsy
A sample of tissue from a previous biopsy or surgery (archival) will be requested after you are registered to the trial. If you do not have archival tissue available and are having a biopsy that is considered standard of care, part of this tissue will be requested and is required if a standard of care biopsy is being performed. If archival tissue is not available and you do not have a standard of care biopsy scheduled, you will be asked to have an additional research biopsy that will not be considered part of your routine clinical care.

In addition, during treatment on the study if you have a standard of care biopsy, a part of the tissue is required for correlative analysis. The risks of a biopsy have been described above.

This sample will be used to look at microsatellite instability (MSI) and tumor mutational burden (TMB), as well as other immune markers. A high MSI means that the DNA repair mechanisms in the tumor cells are faulty, and as a result, they can acquire a significant number of mutations that can make them easily recognizable by the immune system, potentially making these tumors good candidates for immunotherapy. TMB measures the number of mutations within a tumor. These tests together could help determine people that will respond to immunotherapy treatment.

PD-L1 and other immune markers which may or may not have been previously tested in some form, will also be analyzed with the hope that this information can someday help other people going through this type of cancer treatment.

You may not get health benefits from any of these studies, but they are an important part of the research. The results may not be added to your medical records and you or your study doctor will not know the results. The results of this testing would only be used for research as described above and not to guide your medical care.

Special Considerations
Because we need to understand how the study treatment affects the cancer and your body, we are requesting one additional item as a condition of participation in this study. **Please note: Responding "No" to will prevent you from taking part in this study**.

Please check the appropriate boxes and initial and date below:

We ask that you be willing to enrollment in a parallel biopsy protocol entitled: "Exploration of tumor biology in patients with metastatic esophageal and gastric cancer (biorepository protocol for prospective tissue collection)". A separate consent form will be provided for the parallel protocol that will detail the requirements for participation.

I understand and agree with this request:

☐ Yes ☐ No Please initial here: _____Date: _____

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

If you choose to take part in this study, there is a risk that the approach being studied may not be as good as the usual approach to treating your cancer. There is also a risk that you could have side effects from the study medication(s). These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Ramucirumab- increased risk of bleeding such as nose bleeds. Reaction to the infusion.
- Paclitaxel- hair loss, nausea and vomiting, numbness and tingling in your hands or feet (neuropathy) and joint and muscle pain, and low neutrophil count (type of white blood cell).
- Pembrolizumab- fatigue, cough, rash with itching and decreased appetite

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

Participation may also result in the following:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

Genetic Testing Risks
This study will use genetic tests that may identify changes in the genes in your blood. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer.

Some of the samples will be used for research tests that will include genetic studies and testing. The intent is not to give participants (or his/her medical providers) the results of any testing done for research purposes; however, incidental germline (heritable) mutations may be identified of which a participant may or may not already be aware. In the case that an incidental genetic finding is identified, the sponsor-investigator of this project will be notified. The possible decisions for handling incidental findings may include notification of the participant (and provider); recommendation for genetic counseling, which may or may not include genetic testing (e.g., if the finding was not done in a CLIA certified laboratory); or, neither. In general, a member of the participant's treating team will be given the information to help with notification. In all cases, the current policy of the treating institution and local/participating site IRB, as applicable, will be followed and any additional approvals that may be required prior to participant notification will be secured in advance.

Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

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

All health insurance companies and group health plans must follow this law.

Be aware that this new Federal law doesn't protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.
The study treatment may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health. Tell the study doctor if you notice or feel anything different. The study doctor may be able to treat some side effects or adjust the study drug(s) to try to reduce side effects.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

The sections below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Side Effects of Pembrolizumab

Pembrolizumab works by helping your immune system to fight your cancer. However, Pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects that may become serious or life-threatening, and in some cases, may lead to death and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Very Common side effects seen in ≥20% of patients treated with pembrolizumab include the following:

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

Common side effects seen in ≥5% to < 20% of patients treated with pembrolizumab include the following:

- Anemia- decrease in red blood cells which carry oxygen throughout your body. This may cause fatigue (extreme tiredness), dizziness or shortness of breath
- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach
- Decreased appetite

- Headache
- Dizziness

Uncommon side effects seen in ≥1% to < 5% of patients treated with pembrolizumab include the following:

- Inflammation of the lungs (pneumonitis) so you may feel short of breath and cough. Sometimes this might lead to death
- Thyroid hormone imbalance so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism).
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut (colitis), which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. These severe conditions can sometimes lead to death. Severe skin reactions, including Stevens-Johnson syndrome or toxic epidural necrolysis.
- Lung infection (pneumonia)
- Low white count and low neutrophil count (certain type of white blood cell) which can increase your risk for infection
- Low platelet count (thrombocytopenia) which can increase your risk of bleeding

Rare side effects seen in < 1% of patients treated with pembrolizumab include the following:

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis (Guillain Barre)
- Inflammation of the muscles so you may feel weak or have pain in your muscles (myositis).
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, vomiting that gets worse when you eat (pancreatitis); exocrine pancreatic insufficiency (inability to digest food properly).
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches (uveitis).

- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis).
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting (hypophysitis).
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency).
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall (myocarditis) that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy (thyroiditis).
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis).
- Inflammation of 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)
- Autoimmune thrombocytopenic purpura- low platelet count caused by the immune system destroying platelets and leading to bleeding tendencies
- Inflammation of the stomach (gastritis). You may have pain in your belly, feel full, or sick to your stomach. You may also experience nausea, vomiting or loss of appetite.
- Low number of red blood cells (cells that carry oxygen) due to destruction of red blood cells (hemolytic anemia). You may feel weak, tired, lightheaded, short of breath, or have a fast heartbeat. You may also experience difficulty with exercise, pale or yellow skin, dark urine, or fever.
- Not enough pancreatic enzymes (proteins that break down food) that leads to poor digestion of food (exocrine pancreatic insufficiency). You may have bloating, gas, discomfort in your belly, diarrhea, abnormal stool that is oily, or weight loss.
- Inflammation of the protective sac surrounding your heart (pericarditis) which can cause sharp chest pain and shortness of breath (especially when lying flat), fever, and a fast or irregular heartbeat. In severe cases, your heart may have difficulty pumping blood throughout your body.

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

- 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 coma (Haemophagocytic lymphohistiocytosis- HLH)
- Vogt-Koyanagi-Harada syndrome (VKH) chronic inflammation of melanocytes, which are specialized cells that produce a pigment called melanin. Melanin gives skin, hair, and eyes their color. Symptoms may include headache, neck stiffness, dizziness, inner ear problems, inflammation of multiple parts of the eye, detached retina, loss of skin color (pigment), and hair loss.
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

- Inflammation or swelling of the nerve fibers of the eye which send visual information from your eye to your brain. This health condition often has a sudden onset of vision loss, loss of color vision, pain when moving your eyes, and/or loss of peripheral vision. It may affect one or both eyes at the same time (optic neuritis).
- Myocarditis-myositis-myasthenia gravis overlap syndrome which is when the body's immune system attacks its own heart muscle (myocarditis), skeletal muscles (myositis), and the nerves that control muscles (myasthenia gravis) all at once. This may cause you to experience chest pain, swelling of the legs, fast or irregular heartbeat, dizziness, fainting, weakness, pain in your muscles, tiredness, drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, and difficulty breathing.
- If you have had a tissue transplant (for example, a corneal transplant in your eye), you may experience rejection of the transplanted tissue. Your doctor should tell you what signs and symptoms you should report depending on the type of tissue transplant that you had.

Please note that the side effects of pembrolizumab such as gastritis, hemolytic anemia and exocrine pancreatic insufficiency may be delayed, late onset or long-term.

Possible Side Effects of Ramucirumab
Tell your doctor about all drugs and supplements you take while participating in this study. Tell your doctor if you take vitamin E, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen (Advil, Motrin), and naproxen (Aleve, Naprosyn), warfarin (Coumadin), ticlopidine (Ticlid), and clopidogrel (Plavix). These medications may interfere with blood clotting and can raise the risk of bleeding during treatment with ramucirumab. Your doctor will monitor you closely and may need to stop your treatment with ramucirumab.

Very common side effects (In 100 people receiving Ramucirumab 10 or more may have):
- Lack of energy (fatigue)
- Bleeding gums
- Coughing up blood
- Blood in the urine
- High blood pressure
- Headache
- Nosebleeds
- Nausea
- Diarrhea
- Vomiting
- Decrease or loss of appetite
- High level of protein in the urine

- Swelling and redness in the mouth, sometimes with pain
- Stomach pain
- Low white blood cell count which increases your risk for infection

Common side effects (In 100 people taking Ramucirumab 1-10 may have)

- Low platelet count which increases your risk for bleeding
- Low or severely low red blood cell count which causes anemia and could require a blood transfusion
- Fever
- Swelling in the arms, legs, hands, or feet
- Infusion-related reactions. Symptoms include shaking, back pain or spasms, feeling cold, red skin, trouble breathing, rash, fever, headache, body aches, stomach pain, nausea, vomiting, blurry vision, chest pain and/or tightness, very fast heartbeat, low blood pressure, and tingling or burning in the hands or feet.
- Weakness or weak muscles
- Feeling cold
- Bad taste in the mouth or dry mouth
- Skin problems such as rash, itching, acne, dry skin, or red skin
- Redness, tenderness, and peeling skin on the palms of the hands and soles of the feet
- Hair loss
- Skin condition resembling acne
- Trouble breathing
- Pain in the joints, muscles (with or without cramping), back, chest, arms, or legs.
- Swelling and redness in the mouth, sometimes with pain
- Throat pain
- Feeling dizzy
- Weight loss
- Damage to your liver
- Upset stomach
- Blood clots in the veins, which can obstruct the blood flow and may cause pain, swelling, fast breathing, cough, sweats, and/or fatigue. This includes veins in the lung or deep veins in the legs. Clots which block vessels in the heart and brain cause heart attack or stroke.
- Blood clots in arteries which could cause heart attack or stroke
- Tingling, burning, prickling, or numbness, usually in the hands, arms, legs or feet
- Trouble speaking
- Coughing
- High blood sugar
- Damage to your kidneys
- Dehydration or, too little water in the body

- Low levels of sodium, potassium, magnesium, and phosphorus in the blood
- Trouble sleeping
- Heart damage
- Cardiac arrest or cardiorespiratory arrest
- Blurry vision
- Low blood pressure
- Bruising
- Decreased levels of albumin
- Constipation
- Increased production of tears
- High levels of liver enzymes in the blood
- Face swelling
- Weight gain
- Increase in a type of waste material, called creatinine, in the blood
- Hot flash
- Impaired wound healing

Uncommon side effects (In 100 people taking Ramucirumab less than 1 may have)

- Liver failure
- Heart failure
- Lung failure
- Lung infection
- Sinus infection
- Skin infection
- Decreased oxygen in the blood
- Swelling of the lining of the abdominal cavity and abdominal organ
- Swelling of the digestive track
- Irregular heartbeat
- Collapsed lung
- Infection throughout the body
- Damage to the walls of the stomach, intestines, or rectum (causing intestinal perforation – a hole in the wall of the intestine)
- More acid than normal in the blood
- Multi-organ failure
- Difficulty forming blood clots
- Changes in the brain structure and functions that can cause confusion, headache, nausea, vomiting, feeling wobbly, impaired memory, eyesight changes, and feeling tired
- Severe intestinal bleeding and life-threatening bleeding ulcer
- Abnormal vaginal bleeding

- Bruising or bleeding under the skin
- Bleeding in the throat, ear, eye, brain, lung, nail beds, food pipe, stomach and intestines, inside the skull, from the rectum or anus, or at the site of injection
- Tumor bleeding
- Bleeding after a procedure or surgery
- Blood in the stool
- Leukoencephalopathy, a loss of white matter of the brain, which may results in brain dysfunction, and can cause forgetfulness, confusion, headache, delirium, and total or partial blindness.
- Body does not effectively absorb nutrients from food in the intestine
- Abnormal opening between the food pipe and wind pipe
- Occurrence of confusion, altered level of consciousness, and/or coma related to excess of ammonia in the blood
- Sudden death

Possible Side Effects of Paclitaxel

Common, some may be serious (> 20% of patients)

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Anemia which may cause tiredness, or may require blood transfusions
- Pain
- Sores in mouth which may cause difficulty swallowing
- Diarrhea, nausea, vomiting
- Muscle weakness
- Numbness, tingling or pain of the arms and legs
- Hair loss

Less Common, some may be serious (Between 4% - 20% of patients)

- Abnormal heartbeat
- Blood clot which may cause swelling, pain, shortness of breath
- Damage to the lungs which may cause shortness of breath

Rare, and serious (≤ 3% of patients)

- Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness

- A tear or a hole in the bowels which may cause pain or that may require surgery
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Additional Risks

Drug Interactions
The other medications you take may affect the study drug(s) in ways that we do not know. For your safety, you must tell the study doctor or nurse about all the prescription drugs, herbal products, over-the-counter (OTC) drugs, vitamins, and natural remedies that you are taking before you start the study and before taking any of these products while you are on the study. Please be sure to tell us also about any changes you make with your medications during your participation.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Imaging Studies Standard of Care
While you are in this research study, CT scans, PET/CT scans, bone scans, x-rays, mammograms, and/or other radioactive agents may be used to evaluate your disease. The frequency of these exams is determined by what you would receive as your regular standard care. You will be exposed to radiation from the CT scans. The amount of radiation has a low risk of harmful effects.

Blood Draw
Blood samples will be drawn through a vein by a needle stick. Risks include: pain, bleeding, bruising, blood clot, feeling faint or fainting and infection with redness and irritation of the vein at the site where blood is drawn.

Biopsy
Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail. Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

You may be exposed to radiation during the CT-guided biopsies, depending on the location of your disease. The amount of radiation has a low risk of harmful effects.

Electrocardiogram (ECG or EKG)
An electrocardiogram, also called an ECG or EKG, is a simple, painless test that detects and records your heart's electrical activity. An EKG can show how fast your heart is beating, whether the rhythm of your heartbeats is steady or irregular, and the strength and timing of the electrical impulses passing through each part of your heart. A nurse or technician will attach up to 12 electrodes to the skin on your chest, arms, and legs. Your skin may need to be shaved to help the electrodes stick. The electrodes are connected by wires to a machine that records your heart's electrical activity on graph paper or on a computer. After the test, the electrodes will be removed. An EKG has no serious risks. EKGs don't give off electrical charges such as shocks. You may develop a slight rash where the electrodes were attached to your skin. This rash usually goes away on its own without treatment.

Reproductive
You should not get pregnant, breastfeed, or father a baby while in this study. The study drug(s) could be damaging to an unborn baby and breast milk. You must have a negative pregnancy test prior to enrolling in the study and prior to treatment. You must use birth control methods as directed below, unless you completely avoid having heterosexual intercourse. Complete abstinence is considered an acceptable form of contraception. Any birth control method can fail. The reports of birth control failing are more frequent for female subjects who use only a single form of birth control. Using TWO forms of birth control AT THE SAME TIME greatly reduces the chances of pregnancy. Please talk with your doctor if you have questions.

Primary Forms	**Secondary Forms**
Tubal sterilization (tubes tied)	Male latex condom with or without spermicide
Partner's vasectomy	Diaphragm with spermicide
Intrauterine device (IUD)	Cervical cap with spermicide
Hormonal contraception (oral, transdermal patch, injectables, implantables)	Vaginal sponge (contains spermicide)

If you or your female partner becomes pregnant, you must tell your doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. Additionally, the pregnancy will be followed until conclusion. For female participants who become pregnant while on this study, the study drug will be stopped immediately.

Female participants:
Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use birth control from the time of signing the informed consent form, throughout the

entire study drug period, and for 120 days (4 months) after the last dose of study drug. This timeframe applies to breastfeeding and egg donation as well.

Male participants:
You should not have unprotected intercourse with your partner for the timeframe described below. Even if you are surgically sterilized (i.e., have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex condom with a spermicidal agent) from the time of treatment initiation, throughout the entire study drug period, and for 120 days (4 months) after last dose of study drug. This timeframe applies to sperm donation.

Confidentiality risk
As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

Are there reasons you might leave this research study early?

You can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?
The study doctor may take you off the study if:

- There is evidence your cancer has worsened (disease progression) and further study treatment is not in your best interest.
- You are unable to tolerate the study treatment due to side effects
- The study drug(s) are delayed for more than 42 days
- You require reduction of your study drug(s) more than two times
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the sponsor-investigator, Harry H Yoon, MD MHS, the Funder, Merck, IRB, FDA, or other Health Authorities for any reason.

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.

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 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. The study sponsor-investigator, Dr. Yoon or Merck will not pay for medical treatment for injury.

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

There may be a higher chance your tumor will shrink and stay inactive for a longer period of time when pembrolizumab is given before ramucirumab/paclitaxel, as compared to pembrolizumab being given after ramucirumab/paclitaxel. Our experience also suggests the order in which these agents are given can help prolong their benefit. It is not possible to know now if this treatment sequence will do a better, same, or worse job of shrinking your tumor compared to the usual approach. That is why we are doing this clinical trial. We hope this study will help you. This study will also help the study doctors learn things that will help people in the future.

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

You may choose:

- To have the usual approach described above
- To take part in a different study, if one is available
- Not to be treated for your cancer, but you may choose to receive palliative care which is comfort care to relieve symptoms. Comfort care tries to keep you as active and comfortable as possible.

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

The pembrolizumab will be supplied at no charge while you take part in this study. The study will also pay for the cost of the pharmacy getting the study drug ready, but you or your insurance company will be responsible for the intravenous administration costs. The ramucirumab and paclitaxel will be billed to you or your insurance company as they are standard of care for the treatment of your type of cancer.

You or your insurance company will be billed for any imaging (CT, MRI, or PET-CT imaging) as these will only be conducted as needed for your routine clinical care. You or your insurance company will also be billed for the pregnancy testing as part of the screening visit.

You will not be responsible for these other study-specific costs:

- Blood and tissue analysis done during the study for research (correlative samples).
- Electrocardiogram (ECG) conducted during the screening visit

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

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

You will not be paid for participating in this study.

There is a very small chance that some commercial value may result from the use of your sample. This could include new products like a drug or a test to diagnose a disease. If that happens, you will not be offered a share in any profits.

Will your information or samples be used for future research?

Additional information on study specific testing
This section will describe study specific testing that will be performed throughout the study. You will not be billed for these studies. Some of the testing may be required to participate in the study. Other testing may be optional, and you will decide if you want to participate. Researchers hope the results will help other people with cancer in the future.

Optional Banking for Future Cancer Related Research
This research study also involves banking of leftover samples for future research related to this study. A sample available for use by researchers is referred to as a "banking sample." These samples are stored in a "biorepository". Hoosier Cancer Research Network, Inc. (HCRN) manages the biorepository for the samples collected in this study. Only Mayo Clinic investigators and staff maintaining the biorepository will be able to access the samples.

The research that may be done is unknown at this time. The purpose of banking the samples is to make them available to researchers involved with this study.
We will also collect information during your participation in this study that is related to your health and/or disease history. Some examples include results of tests, medical procedures, images (such as X-rays), and medicines you take. Researchers at Mayo Clinic will use this information to better understand how genes affect health and response to treatment. The information collected will not contain your date of birth or medical record number but will be identified only by a code. This will take place for as long as your sample is stored until the conclusion of this study, unless you tell us to stop.

Unless you give your permission below, your information or samples collected for this study will not be used or shared for future research, even if the identifiable information such as your name, Mayo Clinic number or date of birth is removed.

We would like to keep your information and samples for future research. You can still take part in this current study even if you don't want your information or samples used for future research.

If you approve the release of your information and/or samples by checking 'yes' below, Mayo Clinic may send the information and/or samples to other researchers who request them, but

Mayo will not send your name, address, phone number, social security number, or any other identifying information with the information and/or samples. Your information and/or samples may be sent with a code, and only the researchers for this study at Mayo Clinic would be able to link the code to you.

Some future studies may examine your DNA, the genetic information you inherited from your parents (genetic testing). If there are findings which may be useful for your health care, the researchers may contact Mayo Clinic, so Mayo Clinic can give you the option of learning the results. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

To support future research, de-identified genetic information may be placed in databases accessible by the internet. Some of the information may be available to anyone using the internet, and some will be released only to approved researchers. Combined study information (including genomic summary results) may be published, but the information will not identify you.

Even though information traditionally used to identify you will not be shared, people may develop ways in the future to allow someone to link your genetic information back to you. For this reason, confidentiality cannot be guaranteed. It is also possible that reidentified information could be used in discriminating ways, and there could be additional unknown risks. We will make every effort to protect your confidentiality.

Please read the following statements and mark your choices:

1. I permit my information and samples to be stored and used in future research of advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma at the HCRN biorepository:

   ☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my information and samples 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 information and samples to researchers at other institutions:

   ☐ Yes ☐ No Please initial here: _____Date: _____

You may withdraw your consent for future use of your information and/or samples at any time, by writing to the Principal Investigator at the address provided in the "Contact Information" section of this consent form.

Your information and/or samples would be removed from any repository where they are stored, if possible. Information and/or samples already distributed for research use will not be retrieved.

WHAT ARE THE POSSIBLE BENEFITS OF SAMPLE BANKING?
You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

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.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Your privacy is very important to us and the researchers will make every effort to protect it. We cannot guarantee absolute confidentiality. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you.

Your identity will be held in confidence in reports in which the study may be published.

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

Some individuals and organizations may have access to and may inspect your records. They must keep your information confidential, unless the law requires them to disclose information or you consent to the disclosure. Some of these individuals and organizations are:

- The sponsor-investigator Dr. Yoon and individuals working under the direction of the sponsor-investigator for the study
- Outside individuals or entities that have a need to access this information to perform activities relating to the conduct of this research, such as analysis by outside laboratories
- Other researchers and institutions that are conducting or participating in this study,
- Merck, the funder of the study and its authorized agents. Merck is also providing pembrolizumab for this study.
- The organization managing this study, Hoosier Cancer Research Network, and any companies that they use to oversee, manage, or conduct the research,
- The Office for Human Research Protections in the U.S. Department of Health and Human Services, the United States Food and Drug Administration (FDA) and other federal and state agencies that have the right to use the information as required by law, and
- The members and staff of any Institutional Review Board (IRB) and Data and Safety Monitoring Board that oversee this study

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.

- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. This research follows the Genetic Information Nondiscrimination Act (GINA), a federal law which generally makes it illegal for health insurance companies, group health plans, and most employers to request the genetic information we get from this research and discriminate against you based on your genetic information. Despite the GINA protections and the best efforts of the research team, there may still be a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small.

However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

There can also be a risk in finding out new genetic information about you. This may include information about inherited traits that might affect you or your blood relatives could be found during a study.

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 (or "authorization") to Mayo Clinic.

Your health information may be collected from:

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

Your health information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was conducted following the approved study plan, and applicable rules and regulations.

Your health information may be used and shared with:

- Mayo Clinic research staff involved in this study.

- Other Mayo Clinic staff involved in your clinical care.
- Researchers involved in this study at other institutions.
- The sponsor investigator and funder of this study and the people or groups hired by them to help perform this research.
- The Mayo Clinic Institutional Review Board that oversees the research.
- 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.
- A group that oversees the data (study information) and safety of this research.

How your information may be shared with others:

While taking part in this study, you will be assigned a code that is unique to you, but does not include information that directly identifies you.
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 this study are made public (for example, through scientific meetings, reports or media) information that identifies you will not be used.

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 Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying 'no' will not harm your relationship with your own doctors or with Mayo Clinic.

If you cancel your permission for Mayo Clinic 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.

You can cancel your permission for Mayo Clinic 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
Plummer Building PL 3-02
200 First St. SW
Rochester, MN 55905

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

MAYO CLINIC

Name and Clinic Number

Approval Date: **May 15, 2026**
Not to be used after: **December 9, 2026**

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 for Mayo Clinic to use and share your health information lasts until the conclusion of this study, unless you cancel it.

Any samples stored in this study will be coded and stored for a maximum of 15 years.

There is no expiration or end date related to the sponsor investigator or funder use of your health information received from Mayo Clinic as part of this study.

MAYO CLINIC

Name and Clinic Number

Approval Date: **May 15, 2026**
Not to be used after: **December 9, 2026**

Enrollment and Permission Signatures

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

	/ /	: AM/PM
Printed Name	Date	Time

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.

	/ /	: AM/PM
Printed Name	Date	Time

Signature