A Single Arm, Phase II Study of Pembrolizumab, Oxaliplatin, and Capecitabine in the First Line Treatment of Patients with Gastro-esophageal Cancer (KeyLARGO)

Trial: NCT03342937

Duke University Main Consent Form (May 18, 2020)

Duke University Consent Addendum (January 9, 2023)

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
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Concise Summary

The purpose of this study is to assess the safety, tolerability, and efficacy of the combination of pembrolizumab, oxaliplatin and capecitabine in patients with previously untreated metastatic esophagogastric adenocarcinoma.

The study will be conducted in two stages: 1) safety validation and 2) dose expansion. During the Study Drug Period, subjects will receive pembrolizumab and oxaliplatin intravenously (into your vein) on Day 1 and capecitabine orally (by mouth) on Days 1-14 of each 21-day cycle until: 1) disease progression; 2) the occurrence of unacceptable treatment-related toxicity; or 3) other reason(s) for subject discontinuation. Your study drug regimen may last for up to 35 cycles (about 2 years).

Throughout the study you will have tests, exams and procedures as part of your standard of care as well as for study purposes. There are risks that may be associated with the use of the study drugs that are described in this document. Some of these risks include skin conditions, mouth sores, loose stool, changes to blood cells that fight infection and clot the blood, cough, nausea, vomiting and other possible side effects that could be serious and potentially life-threatening.

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

You are being asked to take part in this research study because you have adenocarcinoma of the esophagus or stomach. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

Dr. Hope Uronis will conduct this Duke Cancer Institute study and it is funded by Merck & Co. The supporting company for this study, Merck & Co., will pay Duke University to perform this research, and these funds may reimburse part of Dr. Uronis' salary. One of the doctors working on this study, Dr. Michael Morse, receives personal compensation from Merck for consulting work.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, ***Dr. Uronis*** will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

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WHY IS THIS STUDY BEING DONE?
The purpose of this study is to find out what effects, good and/or bad, the combination of Pembrolizumab, Oxaliplatin, and Capecitabine has on you and your gastro-esophageal cancer.

HOW DO THESE DRUGS WORK?

- Pembrolizumab (KEYTRUDA) is a drug that is given through a vein (intravenous, or I.V.) that targets a factor called "PD-1". By blocking the interaction between PD-1 and its targets, PD-L1 and PD-L2, it allows your immune system to attack your cancer more effectively. Pembrolizumab is FDA approved for indications including metastatic melanoma, advanced non-small cell lung cancer, metastatic head and neck cancer, classical Hodgkin Lymphoma, urothelial carcinoma, and MSI-H or mismatch repair deficient solid tumors that have progressed following prior treatment, and in gastric and gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1. However, pembrolizumab used in combination with other study drugs for (previously untreated) gastric and esophageal cancer is considered investigational. The word "investigational" means the study drugs are being tested in research studies and not approved by the U.S. Food and Drug Administration (FDA).

- Oxaliplatin is a platinum-based anti-cancer agent given by infusion into the vein (IV), that inhibits tumor cell growth and replication. It is approved by the FDA for use in colorectal cancer. Its use in gastric and esophageal cancers is investigational.

- Capecitabine is an oral chemotherapy drug that works by damaging cancer cells, which causes them to grow more slowly and die. It is approved by the FDA for use in colorectal and breast cancers. Its use in gastric and esophageal cancers is investigational.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 50 people will take part in this study at Duke, and sites within the Duke Cancer Network.

WHAT IS INVOLVED IN THE STUDY?

<u>This study will involve the collection of the following research samples:</u>
<u>Blood</u>
Blood collected throughout the study will be used to assess your safety as well as your body's response to the study drugs. This includes routine laboratory blood tests (blood counts, liver and kidney function, blood clotting ability, and other safety tests), biomarker (proteins in your blood) assessment, and genetic analysis to examine the effects of the study drug(s) on your cancer and your body's response to the study drug(s).

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Tumor Tissue
When you were first told you had cancer or at some other time during your illness, you may have had surgery or a biopsy to collect tissue containing a sample of your cancer. Your tissue sample may hold important clues that might help researchers understand more about cancer and why people do or do not respond to the study drugs. By signing this consent form, you give permission to obtain these (archived) samples for testing if they are available. In addition, a pre-study regimen, and on-study regimen biopsy will be taken 1 week before starting the study regimen, and on Day 8 prior to start of oxaliplatin and capecitabine study regimen, respectively. Biopsy is the removal of a small piece of your tissue for examination. It can be done with a needle or small surgery, and it is usually done with local anesthesia (shots to numb the skin). Your study doctor will discuss with you the safest method and location to perform these biopsies. You will only have biopsies that the study team believes to be not a significant risk to you.

Some portion of your archival tissue block and tumor biopsy tissue will be taken for biomarker (proteins and genes that tell you about your disease), and genetic analyses. It may take many years to complete this research, so your samples will be stored indefinitely or until they are all used up. Your tissue samples and related medical information will be used only for research and will not be sold. Your samples will **not** be used for research involving human cloning (growing human tissue from this material). Information from this research will be from all the subjects who participate in this study as a group, not just from your samples. You will not be informed of new analyses on retained samples.

Consent for future use of biomarker samples
If there is any leftover tissue samples from your biopsies or archived tumor, you may opt to allow them to be retained for future research. Any unused samples will be stored and used to better understand the mechanisms of sensitivity and resistance to pembrolizumab in metastatic gastro-esophageal cancer.

Please initial below with whether you voluntarily agree to give your leftover tissue samples for future research

Yes _____ (initials) No _____ (initials)

Screening:
If you agree to be in this study, you will be asked to sign this consent form. You will have the following tests and procedures to make sure that you are eligible to participate and to ensure that the study drug does not pose a special risk to you:

- Physical exam and medical history
- Vital signs (breathing rate, heart rate, temperature, blood pressure, height and weight)
- Demographics
- CT scans or MRI scans for tumor measurement.

- Blood will be taken for the following:
  - Routine blood tests – these tests will evaluate blood cell counts, blood chemistry, liver and kidney function, thyroid function
  - Blood tumor markers – blood test that can indicate whether your tumor is responding to study drug.
  - Blood immune cells (cells that help the body fight infections and cancer) – the levels of some type of immune cells may be important in determining who may respond to different types of therapy. In this study, pembrolizumab may result in changes in these blood immune cells. Some of the blood collected may be used to study the effects of this drug on immune cells in order to better understand who might respond and what changes we can expect for patients on these therapies.
  - Biomarkers – these are factors in the blood that may help indicate how the study drug is affecting your body
  - Pharmacogenomics – this test will help indicate how your genes affect your response to the study drugs by analyzing the genetic changes in your blood and immune cells.
  - If you are a woman able to bear children, you will also have a small blood sample taken for a pregnancy test
- Tumor tissue – archived tumor from your primary diagnosis will be collected (if available) to be used for the following:
  - Biomarker testing and genetic analysis for expression of molecules which may be associated with sensitivity or resistance to the study drugs

Study Drugs

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

If you are in the Safety Validation group, you will be given pembrolizumab and oxaliplatin into a vein in your arm or central line on the first day of every 21 days. Capecitabine will be taken by mouth twice daily from Day1 to Day 14 of each 21-day cycle.

If you are in the Dose Expansion group, you will receive only pembrolizumab on the first day of study regimen. You will start to receive oxaliplatin and capecitabine on the eighth day of study regimen. The capecitabine will be taken by mouth on days 8 to 21, then you will take one week off drug. On day 29 of study regimen, you will start to receive pembrolizumab and oxaliplatin on day one of each 21 days and capecitabine on days 1 to 14 of each 21 days. This will continue for the duration of your participation in the study.

For both groups, pembrolizumab (200 mg) will be given over 30 minutes. Oxaliplatin (130 mg/m^2) will be given over two hours. The two daily doses of capecitabine should be taken approximately 12 hours apart, within 30 minutes after eating and swallowed with approximately one cup of water. You will be

asked to complete a drug diary card each day while taking capecitabine. You will need to bring this drug diary with you each time you see your doctor.

For your safety, you will be monitored to be sure any side effects are prevented or minimized. This will require regular clinic visits, blood tests, and radiology tests. These tests to check you and your cancer are part of your routine care. You will continue to receive study drug until your cancer gets worse or if you experience excessive side effects or choose to withdraw from the study.

Assessments During Drug Regimen:

Cycle 1 of Safety Validation Group

- Up to 7 days prior to starting study drug:
  - Routine blood tests, including blood cell count and blood chemistry
- Day 1
  - Physical exam
  - Vital signs
  - Pembrolizumab administration over 30 minutes
  - Oxaliplatin administration over two hours
  - Begin taking capecitabine twice daily for days 1 to 14
- Day 8 and Day 15
  - Physical exam
  - Vital signs
  - Routine blood tests
- Day 22
  - Return to your doctor's office for your next physical exam and to begin the next cycle.

Cycle 1 of Dose Expansion Group

- Up to 7 days prior to starting study drug:
  - Routine blood tests, including blood cell count and blood chemistry
  - Urine sample
  - Pre-study regimen tumor biopsy (if amenable to safe biopsy) to be used for the following:
    - Biomarker testing and genetic analysis for expression of molecules which may be associated with sensitivity or resistance to the study drugs
- Day 1
  - Physical exam
  - Vital signs
  - Pembrolizumab administration over 30 minutes
- Day 8
  - Physical Exam
  - Vital signs
  - Routine blood tests

  - Blood immune cells
  - Blood biomarkers
  - On-study regimen tumor biopsy (if amenable to safe biopsy) to be used for the following (can be completed on Day 7):
    - Biomarker testing and genetic analysis for expression of molecules which may be associated with sensitivity or resistance to the study drugs
  - Oxaliplatin administration over two hours
  - Begin taking capecitabine twice daily for days 8 to 21
- Day 15 and Day 22
  - Physical Exam
  - Vital signs
  - Routine blood tests
- Day 29
  - Blood immune cells
  - Blood biomarkers
  - Return to your doctor's office for your next physical exam and to begin the next cycle.

All Remaining Cycles

- Up to 7 days prior to starting study regimen:
  - Routine blood tests, including blood cell count and blood chemistry
- Day 1
  - Physical exam
  - Vital signs
  - Pembrolizumab administration over 30 minutes
  - Oxaliplatin administration over two hours
  - Begin taking capecitabine twice daily for days 1 to 14
- Day 22
  - Return to your doctor's office for your next physical exam and to begin the next cycle.

All Study Groups (Safety Validation and Dose Expansion)

- Every 9 weeks (+/- 1 week)
  - Blood test to check thyroid function
  - Pregnancy test for women who are able to bear children
  - CT scan or MRI scan
  - Blood tumor marker test
  - Blood immune cells
  - Blood biomarkers
- 30 days (+/-7 days) after you stop the study drug regimen
  - Physical exam
  - Vital signs
  - Routine blood tests

  - Blood test to check thyroid function
  - Pregnancy test for women who are able to bear children
  - Blood immune cells
  - Blood biomarkers
- If you stop study drug regimen, but your disease did not get worse and you did not start new treatment
  - CT Scan or MRI scan every 12 weeks or until your disease gets worse
  - Blood tumor markers every 12 weeks or until your disease gets worse

HOW LONG WILL I BE IN THIS STUDY?
You will be asked to take pembrolizumab, oxaliplatin, and capecitabine as long as your disease does not get worse and you are able to tolerate the side effects of the study drug regimen. The maximum duration to receive pembrolizumab will be up 35 cycles (about 2 years). We would then like to keep track of your medical condition for up to 2 years after the last subject starts the study drug regimen (~January 2022) or until the study is closed (whichever comes first). We may review your medical record or contact you by phone every 12 weeks during this time. Keeping in touch with you and checking on your condition helps us look at the long-term effects of the study.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you. The study doctor may stop you from taking part in this study at any time if she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose. All anti-cancer treatments, including immune based therapies, may have side effects. Most side effects from the drugs used in this study are expected to be mild and reversible. However, side effects may rarely be severe, long lasting, and very rarely may even be lethal. Side effects may require additional treatments, procedures, hospitalization, or surgery. Because the body's immune system is so multi-faceted, immune related side effects may affect essentially any part of the body. While the lists of side effects below are meant to be comprehensive, there can also be side effects not specifically listed or side effects that have not been seen before. We cannot predict in advance whether these or other medical problems may occur as the combination of oxaliplatin and capecitabine with pembrolizumab has not been tested thoroughly. For these reasons, you will be watched closely and you should also let your medical team know right away if you have any new problems.

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Side Effects Associated with PEMBROLIZUMAB:

Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but is not approved to treat your type of cancer. Pembrolizumab works by helping your immune system to fight your cancer.

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

Very Likely ***(seen in 20% or more of patients)***

- Itching of the skin (Pruritus)
- Loose or watery stools
- Cough

Likely ***(seen in 5% to 20% of patients)***

- Joint pain
- Fever
- Back pain
- Rash
- 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 (also called hypothyroidism)
- 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 (hyponatremia)

Less Likely ***(seen in 1% to less than 5% of patients)***

- Inflammation of the lungs so you may feel short of breath and cough. Sometimes this might lead to death (also called pneumonitis)
- Too much thyroid hormone so you may feel anxious, angry, unable to sleep, weak, tremble, sweat, tired, have loose and watery stools (also called hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus (also called colitis)

- Inflammation of the skin so you may have peeling of the skin, itching, and/or skin redness. The skin inflammation (such as peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection(Severe skin reactions, including Stevens-Johnson syndrome/or toxic epidermal necrolysis). These severe conditions can sometimes lead to death.

Rare but Serious ***(less than 1% of patients)***

- 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 (also called Guillain-Barré syndrome)
- Inflammation of the muscles so you may feel weak or have pain in your muscles (also called 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 (also called pancreatitis)
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches (also called 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 (also called 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 (also called 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 (also called Addison's Disease)
- 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 (also called nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death (also called myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy (also called thyroiditis)

- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (also called myasthenic syndrome)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (also called sarcoidosis)
- Inflammation of the brain such as 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 (also called 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 (also called myelitis)

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

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant you have had.

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 even coma.
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)

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Side Effects Associated with OXALIPLATIN:

Very Likely ***(seen in 20% or more of patients)***

- Nerve damage that causes abnormal tingling sensation (Peripheral sensory neuropathy)
- Decrease in a type of white blood cell called neutrophils (Neutropenia)
- Decreased number of blood cells (platelets) that help to clot the blood, which could put you at increased risk of bleeding (Thrombocytopenia)
- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (Anemia)
- Nausea
- Abnormal liver function tests, which may indicate that your liver is not functioning properly (Increase in transaminases and alkaline phosphatase)
- Diarrhea
- Vomiting (Emesis)
- Fatigue
- Inflammation of the mouth, tongue, lips or throat (Stomatitis)
- Fever
- Constipation
- Alteration in taste (Dysgeusia)

Less Likely ***(seen in less than 20% of patients)***

- Cough
- Trouble breathing (Dyspnea)
- Nosebleed (Epistaxis)
- Headache
- Rash
- Weight loss

Rare but Serious ***(seen in less than 3% of patients)***

- Serious allergic reactions, including anaphylaxis, that may be fatal.
- Rare event characterized by headache, confusion, seizures, high blood pressure and changes in vision (Reversible Posterior Leukoencephalopathy Syndrome)
- Damage to lung tissue (Pulmonary fibrosis)
- Abnormal heart rhythm that causes fast, chaotic heartbeats (QT prolongation)
- Damage to muscle tissue that causes damage to the kidneys (Rhabdomyolysis)

Side Effects Associated with CAPECITABINE:

Very Likely ***(seen in 20% or more of patients)***

- Loose stools (Diarrhea)
- Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (Mucositis)
- Feeling sick to your stomach (Nausea)
- Redness or sores of the palms of the hands or soles of the feet (Palmar-plantar erythrodysesthesia- "hand-foot syndrome")
- Dry skin (Xerosis)
- Itching sensation (Pruitis)

Likely risks ***(seen in less than 20% of patients)***

- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (Anemia)
- Decreased white blood cells, which are the infection fighting cells, which could put you at risk for infection (Leukopenia)
- Decreased number of blood cells (platelets) that help to clot the blood, which could put you at increased risk of bleeding (Thrombocytopenia)
- Throwing up (Vomiting)
- Stomach or abdominal pain
- Loss of appetite, not feeling hungry (Anorexia)
- Difficulty passing stools (Constipation)
- Heart burn (Dyspepsia)
- Feeling tired (Fatigue)
- Generalized weakness and loss of strength (Asthenia)
- Hair loss (Alopecia)
- Rash
- Red, sore eyes
- Fever (Pyrexia)
- Sensation of lightheadedness, dizziness, or spinning sensation (Vertigo)
- Headache
- Pain, including joint (arthralgia), muscle (myalgia), or bone.
- Infection

Rare but Serious ***(seen in less than 3% of patients)***

- Blood clots and/or bleeding
- Excessive or abnormal loss of body fluids (Dehydration)
- Abnormal liver function tests,which may indicate that your liver is not functioning properly
- Lack of oxygen to the heart muscle which can cause damage to the heart (Heart attack)
- Abnormal heartbeat (Arrhythmia)

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For Those of Reproductive Potential:

Female
Being a part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. If you are a woman of childbearing potential, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you can continue in this study. If sexually active, you must agree to use appropriate contraceptive measures for the duration of the study and for 120 days afterwards. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

Male
Your participation in this research may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for 120 days afterward. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should promptly notify her doctor.

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

Risk of CT Scan:
Computed Tomography (CT) is a way to make x-ray images of the inside of the body. The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures that show structures inside your body more clearly than regular x-ray pictures. During the procedure, a technologist will take you into the CT scan room where you will lie down on the subject table (usually on your back) inside of the CT machine. You should get comfortable because it is very important that you not move during certain parts of the test.

CT examinations differ depending on the part of your body being studied. For example, if your abdomen is being studied, a series of pictures will be taken from your lower chest to your lower pelvis. During the study, you will be asked to hold your breath so that the pictures will not be blurred. The machine will

make some noise, and the table will move during the scan. Also, you may receive signals from the technologist or from the machine about your breathing. Before or during the study, you may be given an injection of contrast liquid in your vein to allow the radiologist to obtain clearer images of your organs. If you have any discomfort during the test or after the injection, be sure to tell the technologist.

Risk of MRI Scan:
Magnetic resonance imaging (MRI) uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask you about metal within your body (this includes certain dyes found in tattoos). If there is any question about potentially hazardous metal within your body, you will be excluded from participation in this research study. We will also keep the examining room locked so that no one carrying metal objects can enter while you are in the scanner.

The study involves entering a large room in which a magnet is present. You will be placed on a narrow bed and then slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. You will be asked to lie still for about one hour on this bed. You will hear a loud machine-like noise. You may be asked to have a harmless monitoring device applied during the study. During the study, you can have voice contact and physical contact with someone in attendance if you desire.

Risks of Radiation:
You will have a number of CT scans or MRI scans that are part of the regular care for your condition, and you would have them whether or not you participate in this research. These studies will not add to the risk due to participating in the research. However, if you have concerns about the overall radiation exposure or MRI safety issue, you should discuss them with your physician.

Sometimes subjects have allergic reactions to the dyes used in imaging scans. This is rare. It can involve itching or rash. In severe cases, you may have difficulty breathing and dangerous lowering of your blood pressure. If you know that you have an allergy to the dye, or to iodine or shellfish, please let your study doctor and radiologist know.

Risks of Core Needle Biopsy:
You may experience pain from this procedure that could also include bruising, soreness or scarring at the biopsy site. Rarely, a subject may experience infection and/or internal bleeding,depending on the location of the biopsy. The biopsy procedure is usually performed while the patient is under local anesthesia (for example lidocaine), meaning that the skin site where the needle will be inserted is numbed. Side effects from the local anesthesia are rare but may include convulsions or seizures, breathing problems, chest pain, rapid heart rate, irregular heartbeat, dizziness, bluish lips and fingernails, drowsiness, headache, itching, nausea and/or vomiting, raised red swellings on the skin, lips, tongue, or in the throat, restlessness, unusual tiredness or weakness, back pain, difficulty in opening the mouth,

inability to hold bowel movement and/or urine, loss of sexual function, temporary paralysis (loss of function) of legs, persistent or prolonged numbness or tingling ("pins and needles" sensations) of lips and mouth, and shivering.

Imaging equipment may be used to guide the needle to the desired site. This may involve ultrasound or CT. If CT is used, a subject will be exposed to a small dose of radiation. In addition, a patient may be injected with a contrast dye (for example iodine). This may cause some side effects including hives, itching, lightheadedness, nausea and a metallic taste in the mouth. Rarely, the iodine may result in a severe allergic reaction, including shock, very low blood pressure and cardiac arrest.

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

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

The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:
-Health insurance companies and group plans may not request genetic information from this research;
-Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
-Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

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

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, the investigational study drug regimen may help control your cancer. This may or may not make you feel better or live longer. We hope that in the future the information learned from this study will benefit other people with your condition.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?
Your other choices may include the following:

- Getting treatment or care for your cancer without being in a study
- Depending on the therapies that you have already received, there may be other potentially beneficial approved treatments available for your cancer. These treatments may shrink tumors, delay progression of cancer, provide symptom relief, or prolong your life and could include chemotherapy (for example, platinum-based chemotherapy) or drugs that target a specific abnormality in some cancers. You should discuss these options with your doctor.
- Taking part in another study
- Getting no treatment
- Getting comfort care (also called palliative care) only. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly.

Talk to your doctor about your choices, including the risks and benefits of each choice, before you decide if you will take part in this study.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?

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

As part of the study, results of your study-related laboratory tests, x-rays, and procedures may be reported to Merck & Co. and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives of the Office of Human Research Protection, representatives of the Department of Health and Human Services, representatives of the National Institutes of Health, representatives of Merck & Co (affiliates, collaborators, licensees, auditors, monitors), the Duke Cancer Institute, Duke Office of Audit, Risk, and Compliance, and the Duke University Health System Institutional Review Board. If any of these groups review your research record, they may also need to review your entire medical record.

The supporting company (Merck & Co.) and those working for Merck, which may include affiliates, may use health data sent to them:

- To see if the study drug works and is safe;
- To compare the study drug to other drugs;
- For other activities (such as development and regulatory) related to the study drug

For these uses, the supporting company may share this health data with others involved in these activities, as long as they agree to only use the health data as described here. Once the research team shares health data about you with others, it may no longer be covered by the federal privacy regulations.

As part of this study, you will be asked to have certain tests and/or procedures performed. Some of these tests and/or procedures would have been done as part of your regular care. The study doctor will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record and will be reported to the research data office at Duke and representatives and affiliates of Merck & Co. Results of tests and studies done solely for this research study and not as part of your regular care will not be included in your medical record.

The study results will be retained in your research records for 6 years after the study ends. At that time either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

This information may be further disclosed by the funding company of this study. If disclosed, the information is no longer covered by federal privacy regulations.
If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

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

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

WHAT ARE THE COSTS?
You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out-of-pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays than with a Medicare Advantage plan. Please discuss the costs of the

study with Dr. Uronis. At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

Merck & Co., has agreed to pay for services and procedures that are done solely for research purposes. Please talk with the PI/study team about the specific services and procedures that the sponsor will pay for, and the ones for which you or your insurance will be responsible.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

Merck & Co. will provide the pembrolizumab free of charge to you. The cost of the pembrolizumab infusion, as well as the oxaliplatin and capecitabine, will be billed to you or your insurance. There will be no charges for research related visits, tests, or procedures. The physical examinations, radiographic evaluations (CT scans or MRI), and diagnostic procedures are considered part of the standard care for patients with your disease. The costs associated with each test will be charged to you or your insurance provider in the same manner as if you were not part of this research study. Therefore, you or your insurance provider will need to assume responsibility for these costs. You will be billed for all costs or co-payments that are not paid by your insurance provider. Your study doctor may request that you return for a checkup before you stop your study drug/biologic if he/she thinks that stopping it suddenly may harm you and may ask you to complete the tests that would ordinarily occur when a person completes the study.

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

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

For questions about the study or research-related injury, contact Dr. Uronis at (919) 668-1861 during regular business hours. After hours and on weekends and holidays, please call the Duke paging operator at (919) 684-8111, and ask the operator to page Dr. Uronis.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
Participation in this study is voluntary. You are free to withdraw your consent and to discontinue participation in the study at any time.

If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to Merck.

If you decide to participate, you will be told of any important new information learned during the course of this research study that might affect your condition or your health, welfare, or willingness to stay in this study. If you agree to continue participation, you will be asked to sign an updated consent form.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Uronis in writing and let her know that you are withdrawing from the study. Her mailing address is:

c/o Duke University Medical Center
Protocol Office
DUMC Box 2823
Durham, NC 27710

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at anytime without your consent. If this occurs, you will be notified and your study doctor will discuss other options with you.

We will tell you about new clinically relevant information that may affect your health, welfare, or willingness to stay in this study.

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

The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples other than what is described in this consent form.
A description of this clinical trial will be available on https://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.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
A Single Arm, Phase II Study of Pembrolizumab, Oxaliplatin, and Capecitabine in the First Line Treatment of Patients with Gastro-esophageal Cancer (KeyLARGO)

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Uronis at (919) 668-1861 during regular business hours. After hours and on weekends and holidays, please call the Duke paging operator at (919) 684-8111, and ask the operator to page Dr. Uronis.

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

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
A Single Arm, Phase II Study of Pembrolizumab, Oxaliplatin, and Capecitabine in the First Line Treatment of Patients with Gastro-esophageal Cancer (KeyLARGO)

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

_____
Printed Name of Subject

_____ _____ _____
Signature of Subject Date Time

"I have explained the research to the subject and answered all of his/her questions."

_____
Printed Name of Person Obtaining Consent

_____ _____ _____
Signature of Person Obtaining Consent Date Time

Duke University Health System

Consent To Participate In A Research Study
A Single Arm, Phase II Study of Pembrolizumab, Oxaliplatin, and Capecitabine in the First Line Treatment of Patients with Gastro-esophageal Cancer (KeyLARGO)

PI: Hope Uronis
Consent Form Addendum – Research Blood Collection

You are being asked to sign this consent addendum because you are participating in a research study at Duke entitled "*A Single Arm, Phase II Study of Pembrolizumab, Oxaliplatin, and Capecitabine in the First LineTreatment of Patients with Gastro-esophageal Cancer (KeyLARGO)".*

Please read this consent addendum carefully and take your time making your decision. As your study doctor or study staff discusses this addendum with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to sign this consent addendum.

Signing this addendum is optional. You do not have to sign this addendum to remain in the study.

PURPOSE OF THIS ADDENDUM

The purpose of this addendum is to allow for the collection of additional research blood from subjects who completed the full course of study treatment and whose disease has remained in a complete response (no evidence of disease on your scans).

Except for the activities described in this addendum, the terms of your original consent form remain in full effect.

PROCEDURES

Every three months doing your regular clinic visits we will collect the below blood samples:

- Blood immune cells (approximately 5 teaspoons)
- Blood biomarkers (approximately 4 teaspoons)

These samples will be collected until the study closes in February 2023, you withdrawal your consent to sample collection, or until your disease progresses, whichever comes first.

QUESTIONS REGARDING THIS ADDENDUM

If you have any questions, concerns or complaints concerning this consent addendum, please contact Dr. Hope Uronis, at (919) 668-1861 during regular business hours and at the Duke paging operator at (919) 684-8111 after hours and on weekends and holidays.

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

Duke University Health System

Consent To Participate In A Research Study
A Single Arm, Phase II Study of Pembrolizumab, Oxaliplatin, and Capecitabine in the First Line Treatment of Patients with Gastro-esophageal Cancer (KeyLARGO)

PI: Hope Uronis
Consent Form Addendum – Research Blood Collection

STATEMENT OF CONSENT

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

_____
Printed Name of Subject

_____ _____ _____
Signature of Subject Date Time

"I have explained the research to the subject and answered all of his/her questions."

_____
Printed Name of Person Obtaining Consent

_____ _____ _____
Signature of Person Obtaining Consent Date Time