Phase Ib/II Study of Pembrolizumab with Lanreotide Depot for Gastroenteropancreatic Neuroendocrine Tumors (PLANET)

Trial: NCT03043664

Consent Form

June 23, 2021

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study

Phase Ib/II Study of Pembrolizumab with Lanreotide Depot for Gastroenteropancreatic Neuroendocrine Tumors (PLANET)

PI: Michael Morse, MD

CONCISE SUMMARY
This is a research study to evaluate the safety and efficacy of pembrolizumab and lanreotide drug combination in subjects with progressive, advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) who have progressed on front line somatostatin analogue (SSA) therapy.

If you are one of the first 6 subjects enrolled in this study, you will receive Pembrolizumab 200 mg intravenous (IV) every 3 weeks and Lanreotide depot 90 mg subcutaneous (SQ) every 3 weeks. These 21-day cycles will be repeated until your cancer gets worse or you are no longer able to tolerate the study drugs. If the first 6 subjects tolerate these doses well (have few or easily manageable side effects), 20 additional subjects will be enrolled at the same dose. If more than one of the first six subjects have bad side effects at this dose, the study will be stopped. You will have tests, exams and procedures that are part of your standard care and for study purposes.
There are risks to this study drug that are described in this document. Some risks include: itching of the skin, loose or watery stools, cough, stomach pain, muscle pain, vomiting, headache and others.

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

You are being asked to take part in this research study because you have a neuroendocrine tumor of the gastrointestinal (GI) tract or pancreas (GEP-NET). 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. Michael Morse will conduct the study and it is funded by Merck & Co and Ipsen Biopharmaceuticals, Inc. The supporters of this study, Merck & Co and Ipsen, will pay Duke University to perform this research, and these funds may reimburse part of Dr. Morse's salary. Dr. Morse has received personal compensation from Ipsen Biopharmaceuticals, Inc and personal compensation for speaking and consulting for Merck & Co. in the past, and may receive personal compensation from these sponsors in the future.

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WHO WILL BE MY DOCTOR ON THIS STUDY?

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

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to evaluate the safety and efficacy of pembrolizumab and lanreotide drug combination in subjects with progressive, advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) who have progressed on front line somatostatin analogue (SSA) therapy. The combination of these drugs is investigational. The word "investigational" means the study drugs are still being tested in research studies and not approved by the U.S. Food and Drug Administration (FDA).

HOW DO THESE DRUGS WORK?

- **Pembrolizumab (KEYTRUDA)** is an I.V. (intravenous, meaning given through a vein) drug that targets a factor called "PD-1" and 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, but is considered investigational in GEP-NET. The word "investigational" means the study drugs are still being tested in research studies and not approved by the U.S. Food and Drug Administration (FDA).

- **Lanreotide (SOMATULINE DEPOT)** is a drug that is injected subcutaneously (meaning given through the fat). This drug is a peptide analogue of the natural hormone somatostatin, which may prevent signals that help cancer cells survive and grow. Lanreotide is FDA approved for unresectable, locally advanced or metastatic GEP-NET. However, lanreotide is considered investigational in combination with pembrolizumab.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 50 people will take part in this study at Duke University Medical Center.

WHAT IS INVOLVED IN PARTICIPATING IN THE STUDY?

Once you understand what is involved with participating in this study and all your questions have been answered, you will be asked to sign and date this consent form to show that you want to take part in this research study.

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For your safety, you will be monitored, or watched carefully, to be sure side effects are prevented or minimized. This will require regular clinic visits, blood and urine tests, and radiology tests (such as CT scans, which are a computerized series of x-rays). These tests to check you and your cancer are part of your routine care. If you have side effects or have other medical problems, you may need more monitoring or procedures (tests).

In addition, you will have some tests that are only for research purposes. These research tests are not part of your regular care and they will not affect your study regimen. All of the research tests performed are being done to help find out which subjects are most likely to benefit or have side effects from the study drug combinations. Thus, all of the blood, urine, and tumor tissue collections mentioned in this form are required in order for you to participate in this study.

Screening:

- Recording of your demographic information, including your age, sex, and race/ethnicity
- You will be asked some questions about your past health and medical history, your current cancer illness including your functional status, treatments you have received, how you are feeling and the medications, vitamins and herbal supplements you are taking right now.
- A physical exam (including height and weight) will be done, and your vital signs (blood pressure, pulse, respiratory rate, and temperature) will be taken.
- Review the medications you have taken and your current medications.
- Have radiographic assessments of your cancer by Computed Tomography (CT) Scan (a computerized series of x-rays) or Magnetic Resonance Imaging (MRI, body pictures created by using magnetic energy rather than x-ray energy).
- Collect blood to measure Chromogranin A levels (a marker of your tumor)
- Collect blood and urine for safety tests
- Collect blood for pregnancy testing
- Collect blood for exploratory research tests (markers of your tumor and immune system)
- Collect tumor tissue for biomarker testing. If archived tissue is not available, a fresh tumor biopsy will be required to participate in the study.

After completing the screening tests, your study team will check the results to determine whether you are eligible to participate in this study.

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Study drugs:

Pembrolizumab and lanreotide will be given in periods that will last for 3 weeks. This period of time is called a "cycle". For this study each "cycle" will last about 21 days. The doses that you will receive are based on when you enter the study. Your study doctor will tell you exactly what doses you will be receiving.

If you are one of the first 6 subjects enrolled in this study, you will be given:

- Pembrolizumab 200 mg intravenous (IV) every 3 weeks and
- Lanreotide depot 90 mg subcutaneous (SQ) every 3 weeks

These 21-day cycles will be repeated until your cancer gets worse or you are no longer able to tolerate the study drugs.

If the first 6 subjects tolerate these doses well (have few or easily manageable side effects), 20 additional subjects will be enrolled at the same dose. If more than one of the first six subjects have bad side effects at this dose, the study will be stopped. Your study doctor will discuss this with you further.

Assessments During Drug Regimen:

The following visits to the study center will occur during the study. Most of these tests and procedures are part of your regular medical care, but they may be done more often for this study. Study drug cycles will be repeated until the study is stopped or until your cancer gets worse.

Day 1 of every cycle (every 21 days):

- You will be asked some questions about your current cancer illness including your functional status, how you are feeling and the medications, vitamins and herbal supplements you are taking right now.
- Review any side effects you are having.
- A physical exam (including weight) will be done, and your vital signs (blood pressure, pulse, respiratory rate, and temperature) will be taken.
- Collect blood and urine for safety tests
- Collect blood for research tests (markers of your tumor and immune system)

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Every 12 weeks (every 4 cycles):

- A CT scan or an MRI will be done to measure the amount and size of the tumors in your body
- Collect blood to measure Chromogranin A levels (a marker of your tumor)
- Collect blood for pregnancy testing
- Collect blood for exploratory research tests (markers of your tumor and immune system)

Evaluations After You Stop Receiving Study Drug:
The following evaluations will take place approximately 30 days after you get your final dose of study drug:

- You will be asked some questions about your current cancer illness including your functional status, how you are feeling and the medications, vitamins and herbal supplements you are taking right now.
- Review any side effects you are having.
- A physical exam (including weight) will be done, and your vital signs (blood pressure, pulse, respiratory rate, and temperature) will be taken.
- Collect blood and urine for safety tests
- Collect blood for research tests (markers of your tumor and immune system)

Continuing Study Drug Regimen After Disease Progression:

With most anti-cancer drugs, an increase in the size or number of tumors that is detected with CT or MRI scans or a physical examination is a signal that your disease has progressed and that you should consider switching to another therapy.

However, with immunotherapeutic drugs, including pembrolizumab, an early increase in the size or number of tumors may not always be a sign of disease progression. Pembrolizumab is thought to work by stimulating your immune system to attack your tumors. When cells from your immune system attack your tumors, one result can be an apparent increase in the size or number of those tumors. In some subjects, an early increase can be followed by a later reduction in tumor size. Because of this possibility, you are permitted to continue receiving the study drugs even if a scan performed early in the course of your study regimen shows an increase in your tumors. However, you will only continue the study drug regimen if you and your doctor think you could benefit.

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HOW LONG WILL I BE IN THIS STUDY?

You may receive the study drug regimen for up to two years (or 35 cycles) as long as your cancer does not get worse. Once you stop taking the study drug regimen, you may be followed for up to 48 weeks after the last patient completes study drug regimen.

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.

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 may have side effects. Most side effects from the drugs used in this study are expected to 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. 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. 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.

Risks 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, 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 more than 20% of subjects who received pembrolizumab include the following:

- Itching of the skin (pruritus)
- Loose or watery stools

- Cough

Common side effects seen in 5% to 20% of subjects who received pembrolizumab include the following:

- 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, or have infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatremia)

Uncommon side effects seen in 1% to 5% of subjects who received pembrolizumab include the following:

- Inflammation of the lungs, so you may feel short of breath and cough; rarely this may lead to death (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, or have loose or watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the bowels/gut, which may cause you to feel severe pain in your belly with loose or watery stools, and stools that are black, tarry, sticky with blood or mucus (colitis)
- Inflammation of the skin, so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (for example, 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, a skin condition called pemphigoid and toxic epidermal necrolysis)

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Rare but potentially Serious side effects seen in less than 1% of subjects who received 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-Barré syndrome)
- Inflammation of the muscles, so you may feel weak or have pain in your muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels), so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly, or have yellow eyes and skin and dark urine (hepatitis)
- Inflammation of the pituitary gland, (a gland in the head) which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness, or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, and 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 kidneys, so you may pass less urine or have cloudy or bloody urine, swelling, and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath, and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death. (myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. (thyroiditis)

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- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome or myasthenia gravis, including exacerbation)
- 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, constipation, and could include paralysis (myelitis)
- Inflammation of the blood vessels (vasculitis)

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. (hemophagocytic lymphohistiocytosis)
- Changes in eyesight, eye pain or loss of vision may occur. There may also be neurological signs such as severe headache, dizziness, nausea, and drowsiness. Loss of hearing, loss of hair

(alopecia) and skin color may occur along, with whitening (loss of pigmentation) of the hair and eyelashes (poliosis). (Vogt-Koyanagi-Harada syndrome)

- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

Risks associated with lanreotide:

The data below reflect exposure to lanreotide in 101 subjects with GEP-NETs.

Very common side effects seen in greater than 10% of subjects include the following:

- Stomach pain
- Muscle pain
- Vomiting
- Headache
- Injection site reaction
- Low blood sugar (hypoglycemia)
- High blood sugar (hyperglycemia)
- Gallstones (cholelithiasis)

Common side effects seen in between 1 in 100 to 10 in 100 (1-10%) of subjects:

- Dizziness
- Depression
- Shortness of breath (dyspnea)

Risks from Study Procedures:

Some of the study procedures may have possible side effects, risks and discomforts. You may experience none, some, or all of those listed below.

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.

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Risks of Magnetic Resonance Imaging:
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 Magnetic Resonance Imaging with Contrast Dye:
For some magnetic resonance imaging (MRI) scans, you may get a MRI contrast material (a dye). This is given in your vein using a small needle or plastic tube. You may feel local warmth or pain in the area where the dye is injected. The most common contrast material used for MRIs is gadolinium. Side effects from the dye may include nausea, vomiting, or headache. Persons with decreased kidney function or chronic liver disease experiencing decreased kidney function may develop a severe disease called nephrogenic systemic fibrosis from gadolinium. Nephrogenic systemic fibrosis triggers thickening of the skin, organs and other tissues. The exact cause is unclear, and there is no effective treatment. The MRI contrast material will be given in amounts that have been approved by the FDA. You will not get the MRI contrast material if you have abnormal kidney function. Serious allergic reactions that may be life-threatening are very rare.

Risks of Computed Tomography Scan with Contrast Dye:
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 patient 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.

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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 a 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.

Risks of Radiation:
You will have a number of CT scans and 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 issues, you should discuss them with your physician.

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 and depending on the location of the biopsy. The biopsy procedure is usually performed while the patient is under local anesthesia (for example lidocaine), meaning 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.

Risks of Liver Biopsy
For patients undergoing liver biopsy, there may be increased risk in certain circumstances. When doctors perform your liver biopsy, they do so by passing a needle into the liver usually through your side.

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Doctors are usually able to get a large enough piece of liver to examine under the microscope by taking a single biopsy of the liver. However, in some patients, only a small piece is retrieved (not enough to look at under the microscope) and in this case, a second specimen from the liver is taken. After the first attempt, if there is not enough for research purposes, a second piece will be taken.. Thus, by participating in this study, in a small fraction of patients undergoing liver biopsy (less than 5% of all subjects), there will be a chance that a second piece of liver will be taken for research purposes. The additional risk of an additional liver sampling is approximately 1 in 1,000 for increased bleeding, and 1 in 2,000 for other complications such as puncture of a lung or colon. These complications are managed by observation and, in some circumstances, surgery.

If you undergo a liver biopsy you may require sedation. Sedation may include medications such as fentanyl or midazolam. These medications can lower blood pressure, slow down breathing, and decrease your heart rate. If concerning changes in your vital signs occur, a reversing medication can be given.

Risks of Allergic Reaction

Occasionally, people have allergic reactions to medications which may require medical treatment. A severe allergic reaction could be life-threatening. Examples of an allergic reaction include: a rash; shortness of breath; wheezing; difficulty breathing; sudden drop in blood pressure; swelling around the mouth, throat, or eye; fast pulse; and sweating. You should get immediate medical help and contact the study doctor if you have any of these or any other side effects during the study.

Drug and Food Interactions:

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

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

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 two 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.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may be a direct medical benefit to you. This drug may help shrink your cancer or keep it from growing. However, we cannot guarantee any personal benefit. Even, if you do not personally benefit, the knowledge learned from your participation may help doctors and researchers learn more about the use of these study drugs to help other people with cancer.

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
- 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.

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

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people

including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests, x-rays, and procedures may be reported to Merck and Ipsen and their 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 and affiliates of Merck and Ipsen, the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

As part of this study, you will be asked to have certain tests, x-rays, and procedures performed. Some of these tests, x-rays and 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 representatives and affiliates of Merck and Ipsen. 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 record for at least six years after the study is completed. At that time either the research information not already in your medical record will 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 sponsor of this study. If diclosed by the sponsor, 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.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study

Phase Ib/II Study of Pembrolizumab with Lanreotide Depot for Gastroenteropancreatic Neuroendocrine Tumors (PLANET)

PI: Michael Morse, MD

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.

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

The study sponsor, Merck and Ipsen, have agreed to pay for services and procedures that are done solely for research purposes. Please talk with the 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 fins a resolution.

Merck and Ipsen will provide the study drug free of charge to you. At the end of the study, or if you decide to withdraw from the study before it ends, you may be asked to return all unused study drug. Your study doctor may request that you return for a checkup before you stop your study drug if he or 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

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Duke University, Duke University Health System, Inc., your Duke physicians, or the study's supporters Merck & Co and Ipsen Biopharmaceuticals, Inc., 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. Morse 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. Morse.

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 the study sponsor.

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. Morse in writing and let him know that you are withdrawing from the study. His mailing address is:

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

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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. Morse 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. Morse.

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.

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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