CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY
AND
AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Study Title:	**Neoadjuvant lenvatinib plus pembrolizumab in resectable merkel cell carcinoma**
Protocol Number:	**MCC 20773**
Sponsor:	**Moffitt Cancer Center**
Principal Investigator: (Study Doctor)	**Andrew Brohl, MD**
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This form is for use in a research study that may involve participants who may or may not have the capacity to consent to take part in the study. When the participant cannot legally consent to take part, pronouns “you” and “your” should be read as referring to the participant rather than the person (legally authorized representative) who is signing and dating this form for the participant. In cases where the participant’s representative gives consent, the participant should be informed about the study to the extent possible given his/her understanding. During the course of the study, if the participant regains the capacity to consent, informed consent will be obtained from the participant and the participant offered the ability to leave the study if desired.

This consent and authorization form explains why this research study is being done and what your role will be if you choose to take part. You may choose not to take part in this study.

The goal of this clinical research study is to find if combination of Lenvatinib and Pembrolizumab given prior to your tumor resection surgery is safe and effective in treating your condition of Merkel Cell Carcinoma. Merkel Cell Carcinoma is an aggressive skin cancer. Participants with

this condition who have a high risk variety of this cancer and has a surgery planned as part of the treatment, are being recruited in this study.

If you choose to take part in this research study you will be asked to sign and date this informed consent document. If you qualify to receive the treatment, you will receive 2 cycles (6 weeks) of study drug therapy with the combination of Lenvatinib and Pembrolizumab. The surgery will be performed within 2-4 weeks after the completion of Cycle 2. After the surgery, you may continue to receive Pembrolizumab for a total of 17 cycles or unless you have severe side effects, or if you decide to withdraw your consent to participate in this study, or the study is closed. After you are finished taking the study treatment, the study doctor will ask you to visit the office for safety follow-up exams within 4 weeks of discontinuing the study drug. The study team will also continue to check on your health status every 90 days for a period of 3 years and survival follow-up to continue for a total of 5 years starting from the date of surgery.

Participants will undergo screening procedures that involve a routine examination, blood tests and imaging scans. After the screening visit is complete, if you qualify to continue in the study, you will undergo the study treatment visit. The study treatment phase consists of 2 phases which will involve study drug administration and other clinic visits covered later in this document. After study treatment, you will have a few outpatient visits and follow-up phone calls which involve evaluating your health condition by routine clinic examination and procedures, later described in detail.

About 26 participants will participate in this study.

Your participation is voluntary, and you may stop your participation at any time. There will be no penalties or loss of benefits or opportunities if you do not participate or decide to stop once you start. Alternatives to participating in the study are later described in this document.

We do not know if you will receive any benefit from your participation. There is no cost to participate. You will not be compensated for your participation.

The most common and most serious risks related to Pembrolizumab and Lenvatinib are detailed later in this consent form. The most common side effects of lenvatinib when given with pembrolizumab include:

- Abdominal pain
- Acute kidney injury
- Constipation
- Decreased appetite
- Vomiting
- Diarrhea
- Dysphonia (voice changes)
- Fatigue (feeling tired)
- Headache
- Hemorrhagic events (excessive bleeding)
- Hepatotoxicity (liver damage)
- Hypertension (high blood pressure)
- Hypothyroidism
- Musculoskeletal disorders (bone and muscle abnormalities)
- Nausea

- Palmar-plantar erythrodysesthesia (redness, pain or discomfort in palms of hands or soles of feet)
- Proteinuria (protein in your urine)
- Rash
- Stomatitis (sores in the mouth or esophagus)
- Urinary tract infection
- Weight loss

Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be provided to you.

Even if we publish the findings from this study, we will keep your study information private and confidential. Anyone with the authority to look at your records must keep them confidential.

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

WHAT IS THIS STUDY ABOUT?

The purpose of this study is to find out the safety and effectiveness of study drugs Lenvatinib and Pembrolizumab.

You may be eligible to participate in this study if you meet certain requirements. Before you decide to participate, you need to understand the purpose of the study, the possible risks and benefits, and what would be expected of you. This process is called informed consent.

You are being asked to participate in a research study of the investigational drugs, Lenvatinib and Pembrolizuamb because the study doctor has recommended that you have surgery to treat your type of skin cancer (Merkel Cell Carcinoma). This research study will be referred to as the "study" throughout this form.

The main reason for this study is to see if Lenvatinib and Pembrolizumab combination is safe and can activate your immune system against the cancer cells in your tumor(s) if you take it before you have surgery and later continue Pembrolizumab after your surgery.

The study doctor will use the information from the study to better understand the following:

- Whether Lenvatinib is safe when given before the surgery
- How Lenvatinib works in the body, including the tumor site and the lymph nodes
- Side effects that may be experienced by people taking Lenvatinib
- Whether taking the drug before surgery may make it possible to activate your immune system against the tumor, including the tumor site, the lymph nodes and the blood
- Whether taking the drug before surgery may make the cancer less likely to come back after surgery

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

Pembrolizumab in this study is investigational. An investigational use is one that is not approved by the United States Food and Drug Administration (FDA).

Lenvatinib has been approved by the U.S. Food and Drug Administration (FDA) for treatment of certain types of cancer but is not approved by the FDA for treatment of your type of cancer. The use of Lenvatinib in this study is investigational. An investigational use is one that is not approved by the United States Food and Drug Administration (FDA).

WHAT WILL HAPPEN DURING THIS STUDY?

Before you begin the main part of the study...

If you choose to participate in this study you will have several screening tests to see if you can take part. Most of these are procedures you will have as part of your regular cancer treatment even if you did not participate in this study. You will also have some procedures that are only being done because you are in the study. If you have had some of these procedures recently, they may not need to be repeated. This will be up to your study doctor.

You must complete your Screening procedures within 10-28 days prior to receiving the study drugs. Your screening visit may take up to 3-4 hours depending on which procedures you have done.

Screening Visit

- Medical history - You will be asked about your health, any current and past illnesses, as well as prior surgeries and cancer therapies related to the treatment of your melanoma
- Physical exam, including measurements of vital signs (blood pressure, heart rate, respiratory rate, and temperature), height, and weight
- Performance status (measuring your disease status)
- Questions about how your disease is affecting your daily life
- Review of your current medications
- Blood (up to 2 tablespoons) will be drawn:
    - For routine laboratory tests (Chemistry and Hematology). Some of your blood may be tested for HIV, Hepatitis B or Hepatitis C. The study doctor may be required by law to report the result of these tests to the local health authority.
    - For thyroid function tests
- Pregnancy test - if you are a woman of childbearing potential – must be completed within 72 hours prior to starting the study drugs
- Urinalysis
- EKG

- Tumor assessment by computed tomography (CT) scan of chest, abdomen, pelvis, and extremities (if your disease is present here) or Positron Emission Tomography (PET)-CT.
    - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you will be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material will be given intravenously. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. After you have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the radiology department and takes about half an hour.
    - A PET-CT scan helps doctors see changes due to cancer in organs and tissues inside your body (see risk section for additional information).

During the main part of the study:

If the screening exams, tests and procedures show that you can be in the main part of the study, and you choose to take part, you will have the following procedures. Your clinic visits will take about 1-2 hours. If your visit includes tumor assessments (such as imaging, biopsies, etc.), your clinic visit may take up to 3-4 hours.

This study has 2 parts. Part 1 of the study will take place before your surgery. Part 2 will take place after your surgery. In Part 1 of the study, all participants will receive Lenvatinib and Pembrolizumab

In this research study, each “cycle” of study treatment usually lasts 21 days (3 weeks).

- In Part 1, the participant will receive one dose of Pembrolizumab every 3 weeks and Lenvatinib daily during Cycles 1 and 2.
- Surgery at least 2 weeks after end of Cycle 2
- In Part 2, (post-surgery) the participant will receive Pembrolizumab for a total of 17 cycles

Cycle 1 and 2

- Physical exam and weight
- Pembrolizumab and Lenvatinib Administration
- Vital signs
- Questions about how your disease is affecting your daily life
- Urinalysis
- Blood (less than 1 tablespoon) will be drawn for routine laboratory tests
- Adverse Event (AE) toxicity assessment (side effects),
- Review of your current medications

HOW WILL I BE GIVEN THE STUDY DRUG?

Study Drug	Dose/Potency	Dose Frequency	Routes of administration	Study Treatment period
Pembrolizumab	200 mg	Once every 3 weeks	IV Infusion (into the vein)	Day 1 of each 3 weeks cycle
Lenvatinib	20 mg	Daily	Orally (by mouth)	Day 1-21 of each 3 weeks cycle for cycle 1 and 2 before the surgery

Surgery

You were asked to join this study because you plan to have surgery to remove your type of skin cancer. The surgery will happen at the end of Cycle 2 of the study. This is planned to happen within 2-4 weeks of Cycle 2. However, your surgery may happen sooner if the study doctor decides that an earlier surgery is in your best interest.

Before you start Pembrolizumab, the study doctor will also document the plan for your surgery and post-surgery study treatment before you start Pembrolizumab. Your study doctor may plan for radiation therapy as per standard of care of the treating institution. Once your surgery is finished, the study doctor will document the actual surgery that was done and the recommended study treatment plan following your surgery.

Cycle 3

- Physical exam and weight
- Pembrolizumab Administration
- Pregnancy Test
- Vital signs
- Questions about how your disease is affecting your daily life
- Blood (less than 1 tablespoon) will be drawn for routine laboratory tests
- Adverse Event (AE) toxicity assessment (side effects),
- Review of your current medications
- Tumor assessment by CT scan of chest, abdomen, pelvis, and extremities (if your disease is present here) or PET-CT.

Cycle 4

- Physical exam and weight
- Pembrolizumab Administration
- Vital signs
- Questions about how your disease is affecting your daily life

- Blood (less than 1 tablespoon) will be drawn for routine laboratory tests
- Adverse Event (AE) toxicity assessment (side effects),
- Review of your current medications

Cycle 5-17 (Odd cycles)

- Physical exam and weight
- Pembrolizumab Administration
- Vital signs
- Pregnancy test
- Questions about how your disease is affecting your daily life
- Blood (less than 1 tablespoon) will be drawn for routine laboratory tests
- Adverse Event (AE) toxicity assessment (side effects),
- Review of your current medications

Cycle 6-16 (Even cycles)

- Physical exam and weight
- Pembrolizumab Administration
- Vital signs
- Questions about how your disease is affecting your daily life
- Blood (less than 1 tablespoon) will be drawn for routine laboratory tests
- Adverse Event (AE) toxicity assessment (side effects),
- Review of your current medications

When you are finished receiving study treatment ...

You will be asked to return to the clinic within 4 weeks after your last dose of study drug for the following additional tests and procedures.

- Physical exam and weight
- Vital signs
- Pregnancy test
- Questions about how your disease is affecting your daily life
- Blood (less than 1 tablespoon) will be drawn for
    - Routine laboratory tests
    - Thyroid function tests
- AE assessment
- Review of your concomitant medications

Long Term Follow-up Includes:

Long-term follow-up includes standard of care procedures. Suggested frequency of follow up is every 3 months during the first year, every 4 months during the 2nd year, every 6 months during year 3.

The study team will telephone you or your caregivers to check on your health status and ask you about the status of your disease and any new cancer therapies you may have received.

WHAT ELSE DO I HAVE TO DO WHILE PARTICIPATING IN THIS PART OF THE STUDY?

If you participate, you will be asked to do the following things at different times.

Answer Questions About Your Health

The study doctor may ask you about your age, race, ethnicity, medical and surgical history, menopausal history (females only), physical activity, sexual activity, contraception, and previous and current medications (both prescribed and non-prescribed, such as vitamins).

Blood Draws

At several times during the study, you will have blood taken.

Electrocardiogram

An electrocardiogram (ECG) records electrical activity of your heart. For ECG recordings, a few sticky patches, called electrodes, will be placed on your chest.

Height and Weight

Your height will be measured on your first clinic visit. Your weight will be measured at several times during the study.

Physical Examination

A physical exam is a test conducted to check your overall health.

Pregnancy Test

If you are a woman who is able to have children, you will have to take pregnancy tests during the study. To comply with regulatory authorities, a pregnancy test will happen every 3 to 4 weeks. The first test will be done using a blood sample. All other pregnancy tests will be done using either a blood or a urine sample.

Vital Signs

The study staff will take your vital signs, which may include measuring your blood pressure, pulse rate, breathing rate and temperature in a lying, seated, or standing position. Taking your blood pressure measurement requires wrapping and then inflating a blood pressure cuff usually around one of the arms. On days that you receive pembrolizumab, your vital signs will be recorded both before and after your study treatment.

Medical Imaging

Computed Tomography (CT): This is a procedure that uses X-rays and a computer to create a detailed picture of the area of the body that the study doctor wants to see. If required by the study, a dye may be injected into your vein during the CT procedure. CT scans may be used to guide your medical care or to monitor your disease.

Positron Emission Tomography (PET)-CT: this is a nuclear medicine technique which combines both a PET scanner and a CT scanner to acquire sequential images from both devices in the same session, which are combined into a single superposed image. A PET-CT scan helps doctors see changes due to cancer in organs and tissues inside your body.

HOW WILL MY BLOOD SAMPLES BE USED?

In addition to the procedures outlined above, we are asking you to allow us to obtain and store samples of your blood samples for use in future research. Your study doctor will draw some blood to do some tests to see how your immune system is responding to the study treatment and for biomarker research. These samples may be used for research on your disease or condition and others to assist in the development of new treatments. We will use data collected during the study and biological samples obtained for research purposes to know the causes of cancer, its complications and other conditions for which individuals with cancer are at increased risk and to improve future treatment.

In addition to your sample being used for this study and future research, we would like to share it with other researchers, outside of the study. We will code your sample so that the researcher who uses it for other purposes does not know your identity. We will not release the code that links your sample to your personal identifying information for any reason.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

Your sample will not be stored with your name or other identifying information and health information linked to it. We will not share your name or other information that identifies you unless it is required by law. During the conduct of the study, should you choose to withdraw your consent to use the sample at a later date, please contact the study team at the telephone number on the first page of the consent form. The study team will remove your sample from the research and immediately destroy it so that it can no longer be used. Please understand, withdrawal of consent with regard to biosample storage may not be possible after the study is completed. Please understand that part of your sample may have been used prior to the withdrawal of your consent.

Please indicate your preference below:

❒**YES** _____ (initials) I agree to the use of my blood samples as described above.

❒**NO** _____ (initials) I do not agree to the use of my blood samples as described above.

WHO IS PAYING FOR THIS STUDY?

A company called Moffitt Cancer, the sponsor of the study, is paying for this study.

CONFLICT OF INTEREST

Dr. Nikhil Khushalani, an investigator on this study, has received and may receive consultant and/or speaker fees from Merck & Co., the company providing drug for this study. This study has been carefully reviewed to help assure that the professional judgment of the Moffitt Cancer Center doctors and staff will not be compromised. The study will be monitored for your safety and for the proper analysis of data. Any questions you might have about this will be answered by the Moffitt Cancer Center Compliance Office at (813) 745-1869.

Kenneth Tsai, MD, PhD, a person involved with this study, has received and may receive consultant and/or speaker fees from Merck & Co., the company providing drug for this study. This study has been carefully reviewed to help assure that the professional judgment of the Moffitt Cancer Center doctors and staff will not be compromised. The study will be monitored for your safety and for the proper analysis of data. Any questions you might have about this will be answered by the Moffitt Cancer Center Compliance Office at (813) 745-1869.

Ahmad Tarhini, MD, PhD, a person involved with this study, has received and may receive consultant and/or speaker fees from Merck & Co., the company providing drug for this study. This study has been carefully reviewed to help assure that the professional judgment of the Moffitt Cancer Center doctors and staff will not be compromised. The study will be monitored for your safety and for the proper analysis of data. Any questions you might have about this will be answered by the Moffitt Cancer Center Compliance Office at (813) 745-1869.

WILL IT COST ANYTHING TO BE IN THIS STUDY?

You and/or your insurance company will be financially responsible for hospital inpatient, outpatient and follow-up visits that would normally or routinely occur in the management of your disease. Inpatient and outpatient visits could include charges for treatments, medications, physician visits, laboratory tests and procedures. You and /or your insurance company will be responsible for paying for the charges which are considered routine, since you would have received these services even if you were not participating in this study. You will be responsible for any costs not covered by your insurance company, including deductibles, co-payments and all out-of-pocket expenses. Before you agree to be in this study, you should contact your health insurer to see if your plan will cover the costs required as part of your participation.

You and/or your insurance company will not be responsible for paying for study related items and services that are specifically required for this research study and are not considered part of the routine management of your disease if these procedures are performed at Moffitt Cancer Center.

During your participation in this study, the sponsor will be responsible for providing the study drugs, pembrolizumab and lenvatinib, at no additional charge to you. You and/or your insurance company will be responsible for the charges related to the administration of the study drugs.

If you would like more information on the costs of being on this study or have other insurance related questions then please let your clinical trial coordinator know or contact our Business Office at 813-745-8422.

WILL BEING IN THIS STUDY HELP ME?

You may benefit as a result of your participation in this study. There is, however, no guarantee that you will benefit from your participation in this study. Information learned from the study may help other people in the future.

ARE THERE RISKS TO ME IF I AM IN THIS STUDY?

Right now, we do not know for sure if the study drug will help. If it does not help, your condition/disease may get worse.

You may have problems because of the study drug used in this study. These problems are called side effects. Some side effects are just bothersome. Others could harm you. There may be some side effects that we do not know about yet. The research might involve risks to you that are currently unforeseeable. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, or may never go away.

RISKS AND POSSIBLE SIDE EFFECTS OF LENVATINIB

A lot of the side effects seen with Lenvatinib are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. Some side effects do not need treatment while others generally get better with treatment. Some participants may need to delay doses of Lenvatinib to allow the side effects to get better. Side effects like these have also been seen in clinical studies with other drugs that are very similar to Lenvatinib

The side effects of Lenvatinib are as follows:

Serious Side Effects:

COMMON (may affect between 1 in 100 up to 1 in 10 people)

- Stroke, mini-stroke or bleeding in the brain – may result in numbness or weakness on one side of the body
- Blood clot in the legs or lungs (pulmonary embolism) – may cause swelling of the calf associated with warmth or tenderness, sudden onset of shortness of breath, rapid breathing, tightening of chest or chest pain, cough or coughing up blood, rapid heart rate and a blue tinge to the lips
- Heart problems, heart palpitations or heart attack – may cause chest pain or pressure, pain in the arms, back, neck or jaw, shortness of breath, rapid or irregular heart rate, coughing, bluish color to lips or fingers, feeling very tired

- Fistula formation or bowel perforation: abnormal connections between different organs in the body or between an organ and another part of the body such as the skin or windpipe, or formation of a hole in the wall of the gut, which can cause severe abdominal pain
- Bleeding inside the body particularly from the gut – may cause black, tarry, or bloody stools
- Dehydration and kidney failure – may result from diarrhea and vomiting (being sick), which are very common side effects
- Heart failure – a decreased pumping ability of the heart which may cause severe shortness of breath
- Liver damage or failure – may cause yellowing of the skin or eyes (jaundice), tiredness or sickness, loss of appetite, abdominal pain or high temperature
- Hepatic encephalopathy – may result in confusion, drowsiness, poor concentration or loss of consciousness

UNCOMMON (may affect between 1 in 1000 up to 1 in 100 people)

- Posterior reversible encephalopathy syndrome (PRES) is a potentially fatal neurological disorder that may have the following symptoms: headache, confusion, convulsions and vision disturbance. An MRI scan may be required to diagnose this condition.
- Pneumothorax – a leak of air from the lung into the chest so the lung cannot inflate. This may cause sudden chest pain or sudden shortness of breath. There may be a higher chance of this occurring if cancer has spread to the lungs or if treatment is for solid tumor cancers, such as osteosarcoma or soft tissue sarcoma, or in people under the age of 25.
- Aortic dissection – tearing in the wall of the aorta (a large artery), which may cause severe pain in the back, chest or abdomen and internal bleeding.

Other Side Effects of Lenvatinib – Some May Be Serious:

VERY COMMON (affects more than 1 in 10 people and up to 8 in 10 people)

- High or low blood pressure
- Loss of appetite or weight loss
- Nausea (feeling sick) and vomiting (being sick), constipation, diarrhea, abdominal pain, indigestion
- Feeling very tired or weak
- Dry, sore, or inflamed mouth or throat
- High levels of protein in the urine
- Hoarse voice
- Headache
- Hand-foot syndrome (redness, soreness and swelling of the skin on the hands and feet)
- Joint pains
- Cough
- Low level of platelets in the blood, which may lead to bruising
- Musculoskeletal, muscle, limb or back pain
- Swelling of the legs
- Underactive thyroid and change in blood test result for thyroid stimulating hormone (high) – may result in fatigue, weakness, dry skin, hair loss, intolerance to cold

- Rash
- Feeling dizzy
- Bleeding (most commonly nose bleeds, but may include bleeding from other sites, such as blood in the urine, bruising, bleeding from the gums, coughing up blood)
- Odd taste sensation
- Trouble sleeping
- Hair loss
- Urinary infections (increased frequency in urination and pain in passing urine)
- Changes in blood test results for potassium levels (low) and calcium levels (low) – may increase the chance of having an abnormal heart rhythm

COMMON (may affect 1 in 100 up to 1 in 10 people)

- Loss of body fluids (dehydration)
- Dry skin, thickening and itching of the skin
- Feeling bloated or having gas in the bowel
- Malaise (feeling unwell)
- Inflammation of the gallbladder
- Changes in blood test results for liver function
- Changes in blood test results for magnesium (low) – may increase the chance of having an abnormal heart rhythm
- Changes in blood test results for kidney function
- Changes in white blood cells (low) which may increase risk of infections
- Changes in blood test results (high) for lipase and amylase (enzymes involved in digestion)
- Changes in blood test results for cholesterol (high)

UNCOMMON (may affect 1 in 1000 up to 1 in 100 people)

- Painful infection or irritation near the anus
- Splenic infarction which may cause severe pain in the upper left part of the belly (abdomen) and may be associated with fever, chills, nausea and vomiting
- Inflammation of the pancreas, which may cause severe pain in the abdomen or back
- Impaired healing – wounds may take longer to heal
- Osteonecrosis (bone damage) of the jaw – may cause pain in the mouth, teeth, and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw

Generally most of the Lenvatinib related side effects are mild or moderate and temporary in nature; however, severe cases have been described. Your study doctor may treat any of the above conditions with medications or other treatment (including hospitalization), and request additional tests to be performed as medically indicated. In certain situations, dose interruption, reduction (lowering) or permanent discontinuation of the study treatment may be required.

Pembrolizumab:

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. These side effects may be serious (for example, causing hospitalization or be life-threatening), may result in 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

Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

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

COMMON SIDE EFFECTS

Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone, so you may feel tired, gain weight, feel cold, 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

Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs, so you may feel short of breath and cough (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, 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 have pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your bowel with loose or watery stools, and black, tarry, sticky stools or stools 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 (severe

skin reactions, which can be life-threatening, including Stevens-Johnson syndrome/or toxic epidermal necrolysis)

RARE SIDE EFFECTS

Out of 100 people who receive pembrolizumab, less than 1 person may have 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 upper abdomen 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, a pain in the right side of your abdomen, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a pea-sized gland attached to the base of the brain), 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 kidney, so you may pass less urine or have cloudy or bloody urine, swelling, and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall 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 (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).
- 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/myasthenia gravis including exacerbation)

- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures, changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis). Symptoms will depend on the particular blood vessels that are involved in the inflammatory process. For example, if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue.
- Low levels of parathyroid hormone (a hormone made by 4 tiny glands in your neck), which may result in low blood calcium and cause muscle cramps or spasms; fatigue or weakness; numbness, tingling, or burning in your fingertips, toes, or lips (hypoparathyroidism)

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, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).
- Inflammation or swelling of the nerve fibers of the eye, which send visual information from your eye to your brain. This health condition often has a sudden onset of vision loss, loss of color vision, pain when moving your eyes, and/or loss of peripheral vision. It may affect one or both eyes at the same time (optic neuritis).

COULD I HAVE AN 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:

- Rash

- Shortness of breath
- Wheezing
- Difficulty breathing
- Sudden drop in blood pressure
- Swelling around the mouth, throat, or eye
- Fast pulse
- Sweating

You should get immediate emergency medical help and contact the study doctor if you have any of these or any other side effects during the study.

IS THERE ANY RISK TO YOUR UNBORN CHILDREN IF YOU TAKE PART IN THIS STUDY?
FOR WOMEN:

If you are pregnant, you cannot participate in this study, because there may be risks to you and your unborn baby that are currently unforeseeable; risks that we do not know about yet. Breastfeeding (nursing) mothers will not be included in this study, since it is not known whether the drugs in this study will be passed on to the baby in mother's milk. If you are currently breastfeeding and wish to continue breastfeeding, your study doctor may recommend another treatment.

If you are a female of childbearing potential (able to become pregnant), you will be given a pregnancy test before beginning any study drug.

Tell the study doctor right away if:

- You are pregnant.
- You become pregnant.
- You are planning to become pregnant.
- You are breastfeeding.

FOR MEN AND WOMEN:

Whether you are a man or a woman, there may be risks to your unborn children that we don't know about ahead of time; they are unforeseeable.

WOMEN:

If you take part in this study, you must use an effective birth control method as discussed with your study doctor and continue to use it until at least *4* months after your last dose of study drug.

Examples of birth control methods include:

- Oral birth control pills
- Birth control patch
- Implanted (injectable contraceptive hormones or mechanical products such as intrauterine device)
- Barrier methods (such as: diaphragm, condoms, or spermicides)

- Tubal ligation or vasectomy
- Abstinence (no sexual intercourse)

MEN:

If you take part in this study, you must use an effective birth control method as discussed with your study doctor and continue to use it until at least *6* days after your last dose of study drug.

FOR MEN AND WOMEN:

You should discuss the method of birth control which is best for you to use both during study treatment and for a period of time after study treatment.

Whether you are a woman or a man, you should tell your study doctor immediately if you become pregnant or if your partner becomes pregnant. Women who become pregnant during the study will have to leave the study. The study doctor or study staff may ask for information about the pregnancy and the birth of the baby. The study doctor or study staff may share this information with the sponsor and Advarra IRB (a group of people who review research studies to protect the rights and welfare of research participants).

If you are male and your partner becomes pregnant, she will be asked to sign a separate consent form to allow the study staff to collect information about the pregnancy, its outcome, and the health of the child after birth.

RISKS RELATED TO STUDY PROCEDURE

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.

Intravenous injection
You may have bruises, pain or discomfort at the injection sites. In addition, injection reactions, such as high blood pressure, headache and skin rash, pruritus (itching) or urticaria (hives), can occur during or within 24 hours of finishing the injection.

Electrocardiogram (ECG) risks: The ECG involves placing electrodes on the skin. You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own. Please let your study doctor know if you are aware of any allergies.

CT scan risks: 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.

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.

The contrast material (dye) that is injected into your body may cause you to get a metallic taste in your mouth and to feel warm. Rarely, it causes nausea and vomiting. The dye can also cause damage to the kidneys, which may lead to kidney failure. This is a concern if you have poor kidney function. Rarely, the dye can cause a life threatening reaction.

PET-CT risks: The PET/CT scan exposes your body to radiation. The radiation levels come from a tracer which is a radioactive chemical injected into a vein in your arm. The tracer lets the doctor see how your cells are functioning and the radiation levels are very low. You may have an allergic reaction to the chemical used in the scan. For some patients, having to lie still on the scanning table for the length of the procedure may cause some discomfort or pain. After the scan your arm may be a little bit sore or have some redness where the IV was placed in your arm. The radioactive solution does not remain in your system for a long period of time. However, you should wait 2 hours before holding an infant or getting close to a pregnant woman to avoid exposing them to radiation. You should drink fluids after the scan to help remove the solution from your system.

No radiation risk beyond routine clinical care: This study involves radiation exposure as part of routine clinical care. You will not receive additional radiation as a result of participating in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.

Unknown Risks: The experimental study treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

Confidentiality Risk: There is a risk of loss of confidentiality of your information. You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study.

COULD I HAVE ANY OTHER PROBLEMS WITH MY HEALTH IF I DO THIS RESEARCH STUDY?

It is possible that you could have problems and side effects that nobody knows about yet, which include your cancer getting worse or even death. It is possible that taking the study drugs with your regular medications or supplements may change how the study drugs, your regular

medications, or your regular supplements work. It is very important that you tell the study doctor about all medications or supplements you are taking during the study.

RISKS ASSOCIATED WITH STANDARD OF CARE OR ALTERNATIVE TREATMENT

You do not have to be in this study to receive treatment for your condition. Other treatments available for your condition include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study of an investigational drug
- Getting no treatment.

If you decide that you don't want any more active treatment, one of your options is called "comfort care", also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible. If you think you might prefer comfort care, please discuss this with your family, friends and your study doctor.

A more complete listing of side effects for other therapies may be available for you to review if you wish. Please talk with your study doctor about the benefits and risks of any alternative methods of treatment that are available.

NEW INFORMATION

If the study doctor learns any new information that might change your mind about continuing in the study, the study doctor or study staff will tell you about it. The study doctor will also tell you if new treatments become available for your Merkel Cell Carcinoma.

WHAT IF I GET HURT OR SICK WHILE I AM IN THIS STUDY?

If you need emergency care:

- Call 911 or go to your nearest emergency room right away. Moffitt Cancer Center does not have an emergency room or the facilities to provide emergency care.

If you do NOT need emergency care:

- Call or go to your regular doctor. It is important that you tell your regular doctor that you are participating in a research study. If possible, take a copy of this consent form with you when you go.

If you experience a side effect or a change in the way that you feel, call the study doctor at the telephone number listed on the first page of this form.

By signing and dating this informed consent and research authorization form, you have not given up any legal rights to seek compensation for injuries from the sponsor**.**

MOFFITT CANCER CENTER INJURY STATEMENT

If you believe you have been injured as a result of your participation in this study or if you have questions about your rights as a person who is taking part in a research study, you may call the Moffitt Cancer Center Risk Manager at 813-745-7882. Moffitt Cancer Center and its investigators have made no provision for monetary compensation in the event of physical illness or injury resulting from this study. Likewise, Moffitt Cancer Center and its investigators have made no provision for payment of lost wages, disability, or discomfort in the event of physical illness or injury resulting from this study. Florida law (Statute 768.28) limits the liability of Moffitt Cancer Center. This statute provides that damages are available only to the extent that negligent conduct of a Moffitt Cancer Center employee caused your injuries, and are limited by law.

WILL I GET PAID?

You will not get paid for being in this study. You will not be reimbursed for expenses for travel and/or lodging while taking part in this study.

WHILE YOU ARE IN THE STUDY, YOU MUST:

- Follow the instructions you are given.
- Come to the study center for all visits with the study doctor.
- Give correct and accurate information about your medical history and current medical condition.
- Tell the study doctor about any health problems you have during the study.
- Tell the study doctor about any new medicine or drug you take during the study.
- Not take any other drugs or remedies unless the study doctor has approved them beforehand. This includes prescription drugs and over the counter medicine (including vitamins and herbal remedies) that you buy without a prescription.
- Not participate in other medical research studies.
- Not get pregnant or cause your partner to become pregnant.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

DO I HAVE TO REMAIN ON THIS STUDY ONCE I JOIN?

If you want to stop being in the study, tell the study doctor or study staff and return all unused study drug and study materials.

If you stop being in the study early, the study doctor or study staff may ask you some questions about being in the study. To help you leave the study safely, the study doctor may ask you to participate in more tests or return for a final study visit.

ARE THERE REASONS THE STUDY DOCTOR OR SPONSOR MIGHT TAKE ME OUT OF THE STUDY LATER?

Even if you want to stay in the study, there may be reasons the study doctor or study staff will need to take you out of it. Your study doctor has the right to take you out of the study at any time with or without your agreement. Your participation may be ended without your consent for different reasons, including the following:

- If the study doctor believes, for any reason, that it is in your best interest.
- If at any time while you are taking the study drug the study doctor discovers that your disease has worsened.
- If you develop side effects that the study doctor considers unacceptable.
- If you refuse to take the study drug or return for follow-up as recommended by your study doctor, or do not follow the study doctor's instructions.
- If you refuse to have tests that are needed to determine whether the study drug is safe and effective.
- If you require treatment with drugs that are not allowed on this study.
- If other causes prevent you from continuing in this study.
- If the Sponsor decides to end the study.

HOW WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We understand that information about you and your health is personal, and we are committed to protecting the privacy of that information. Because of this commitment and because of federal law, we must obtain your written authorization before we use or disclose your information for this study.

By signing and dating this form, you are permitting researchers at Moffitt Cancer Center to use personal health information for research purposes within its organized health care arrangements. You are also allowing the Moffitt Cancer Center to disclose your personal health information to outside organizations or individuals that participate in this study. We may publish what we find out from this study. If we do, we will not let anyone know your name. We will not publish anything that would directly let people know who you are.

Identifiers might be removed from your identifiable private information or identifiable biospecimens collected during this study and could then be used for future research studies or distributed to another investigator for future research studies without additional informed consent.

WHO WILL DISCLOSE, RECEIVE, AND/OR USE YOUR INFORMATION?

Your records are confidential and they will be kept in a secure environment and protected to the full extent of the law.

To do this research, the following people and/or organization(s) will be allowed to disclose, use, and receive your information, but they may only use and disclose the information to the other parties on this list, to you or your personal representative, or as permitted by law:

- Every research site for this study, including the Moffitt Cancer Center, and each site's study team, research staff and medical staff.
- Any person who provides services or oversight responsibilities in connection with this study.
- Every member of the Moffitt Cancer Center workforce who provides services in connection with this study.
- The person who is responsible for the study nationwide or worldwide (study chairperson).
- Any laboratories, individuals, and organizations that use your health information in connection with this study.
- Any sponsor of the study, including the following sponsors: Moffitt Cancer Center and Merck, Inc.
- Any federal, state, or local governmental agency that regulates the study (such as the U.S. Food and Drug Administration (FDA) and Florida Department of Health (FDH). The U.S. Department of Health & Human Services (DHHS), Office for Human Research Protections (OHRP).
- Other government agencies in this or other countries.
- The designated Protocol Review and Monitoring Committees, Institutional Review Boards such as Advarra IRB, Privacy Boards, Data and Safety Monitoring Board and their related staff that have oversight responsibilities for this study.
- The National Cancer Institute in evaluating the ongoing research of the Moffitt Cancer Center as a Comprehensive Cancer Center.

The organizations and people listed above may employ or pay various consultants and companies to help them understand, analyze and conduct this study. All of these people may not be known now, but if you would like to have more specific information about this at any time during the study, you may ask the study doctor and your questions will be answered.

Moffitt Cancer Center cannot guarantee the privacy of your information, or block further use or distribution, after the information has left the Moffitt Cancer Center. Others listed above may further disclose your information, and it may no longer be covered by federal privacy regulations. If all information that does or can identify you is removed from your records, the remaining information will no longer be subject to this authorization and may be used or shared for other purposes. You might have the right to see and copy your health records related to this research. You might not be able to see or copy some of your records until after all participants finish the study. If it is necessary for your care, your records will be provided to you or your regular doctor

WHAT INFORMATION WILL BE USED OR DISCLOSED?

By signing and dating below, you authorize the use and disclosure of your entire study record and any medical or other records held by Moffitt Cancer Center, including, but not limited to, HIV/AIDS, mental health, substance abuse or genetic information. The purpose for the uses and disclosures you are authorizing is to conduct the study explained to you during the informed

consent and research authorization process and to ensure that the information relating to that study is available to all parties who may need it for research purposes.

Your authorization to use your health information will never expire unless and until you expressly revoke it in writing to the study doctor listed on the first page of this form.

Any data collected before your letter will continue to be used as necessary to preserve the integrity of the study, however no additional information will be collected after you withdraw your authorization.

You do not need to sign this form, but if you do not, you cannot participate in this study.

You will receive a signed and dated copy of this form.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Participant Adviser
  Advarra IRB
  6100 Merriweather Drive, Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Participant Adviser: Pro00049454.

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's (NCI) Information Service at:
1-800-4-CANCER (1-800-422-6237).

Visit the NCI's Websites at:

- CancerTrials: comprehensive clinical trial information at: http://cancertrials.nci.nih.gov
- CancerNet: accurate cancer information including PDQ at: http://cancernet.nci.nih.gov

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.

STATEMENT OF CONSENT AND AUTHORIZATION

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records.

_____
Printed Name of Participant

_____ _____ _____
Signature of Participant Date Time

_____
Printed Name of Legally Authorized Representative

_____ _____ _____
Signature of Legally Authorized Representative Date Time

_____
Authority of Legally Authorized Representative to act on behalf of Subject

STATEMENT OF PERSON OBTAINING INFORMED CONSENT / RESEARCH AUTHORIZATION

I attest that the participant or the participant's legally authorized representative named above had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to be in this study.

_____
Printed Name of Person Explaining Consent

_____ _____ _____
Signature of Person Explaining Consent Date Time