Official Title: A Pilot Study Evaluating the Safety, Tolerability, and Efficacy of Doxorubicin and Pembrolizumab in Patients With Metastatic or Unresectable Soft Tissue Sarcoma
NCT03056001
IRB-Approved Date: 6/13/2022

ATRIUM HEALTH
CONSENT TO PARTICIPATE IN A RESEARCH STUDY
For
SUBJECTS WHO TURN 18 & PARENTAL/GUARDIAN PERMISSION

Sponsor / Study Title:	**Levine Cancer Institute / A Pilot Study Evaluating the Safety, Tolerability and Efficacy of Doxorubicin and Pembrolizumab in Patients with Metastatic or Unresectable Soft Tissue Sarcoma**
Protocol Number:	**LCI-SAR-STS-PEM-001**
Principal Investigator:	**Michael Livingston, MD**
Telephone:	[redacted] **(24 Hours)** [redacted] **(24 Hours)**
Address:	**Levine Cancer Institute** [redacted]

If you are the parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When "you" appears in this form, it may refer to you or your child; "we" means the study doctors and study staff.

INTRODUCTION

Dr. Livingston and his associates (the investigators) are asking you to participate in a research study at Levine Cancer Institute (LCI) and Atrium Health (AH) of doxorubicin and pembrolizumab in subjects with metastatic (cancer that has spread to new areas) or unresectable (cannot be removed by surgery) soft tissue sarcoma. You are being asked to take part in this study because you have advanced sarcoma (cancer of the soft tissue inside the body) that has spread (metastatic) or returned and/or is unable to be surgically removed (unresectable). The purpose of this study is to determine the safety, tolerability (if side effects are acceptable) and efficacy (how well it works) of the drugs doxorubicin and pembrolizumab for the study treatment of your sarcoma.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You have also been told that you have the option not to participate. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation. If you decide to take part in this study, you must sign and date your name at the end of this form. You cannot take part in this research study until you sign and date this form.

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This study is being carried out under the support of Dr. Michael Livingston with Levine Cancer Institute (LCI). Merck is the company providing the drug pembrolizumab that will be used in this study.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to evaluate the safety, tolerability and efficacy of doxorubicin in combination with pembrolizumab in subjects with metastatic or unresectable soft tissue sarcoma. Based on previous studies, pembrolizumab may be an effective study treatment.

Pembrolizumab has been approved by the Food and Drug Administration (FDA) in the United States for the treatment of a type of advanced skin cancer, melanoma, certain types of metastatic lung cancer (PD-L1+), and recurrent or metastatic squamous cell carcinoma of the head and neck. However, it has not been approved for the treatment of soft tissue sarcoma. Doxorubicin is an FDA-approved anticancer drug and is a standard chemotherapy used to treat soft tissue sarcoma.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

You will be one of approximately 30 people involved in this research project at AH. The length of your participation will depend upon your personal treatment and care. The study is expected to be open for approximately 5 years.

HOW THE STUDY WORKS

Before you begin the study (Screening; one visit):
You will need to have the following tests and procedures done to determine if you can be in the study. These exams, tests, and procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history
- Physical examination including vital signs (heart rate, blood pressure, breathing rate, temperature) and height/weight measurements
- Documentation of any medicines you are taking
- You will be asked about the extent of your physical activity and how you are generally feeling
- CT (computed tomography – special x-ray using computers) scan with contrast dye or MRI (magnetic resonance imaging – special x-ray using magnets and a computer) of the tumor site, chest, abdomen and pelvis
- Electrocardiogram (ECG), a paper tracing of the electrical activity of your heart and echocardiogram (ECHO), a test of the action of the heart using ultrasound waves
- Pregnancy test (urine or blood) if you are a female of childbearing potential
- Blood work to check blood counts, blood chemistry (measure of chemicals in the blood), and blood clotting
- Urine test

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The following tests and procedures will be done specifically for this study and are not part of regular cancer care:

- Tumor biopsy – you will be asked to have a tissue sample taken from an area where your disease is located. You will sign a separate consent for this procedure.
  If you are unwilling to have this biopsy or if your study doctor determines that a biopsy would be unsafe, we may collect tissue from a recent biopsy within 12 months of beginning study treatment.
- Blood work to test thyroid hormone levels
- Blood work for correlative (related) studies (looks at certain features in your blood that may be related to your disease).
- You will be asked to have **additional** blood for correlative studies (optional) if you agree. We will further explain the optional blood studies at the end of this consent form.

During the study (Intervention; number of visits/cycles):
If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will begin study treatment as described below:

- You will receive doxorubicin (60-75 mg/m^2 up to a total dose over time of 450 mg/m^2) and pembrolizumab by IV (through a vein – intravenous) on Day 1 of each 21-day cycle. Your first dose of doxorubicin will be 60 mg/m^2. If you tolerate that dose well, your next dose(s) may be increased to 75 mg/m^2. This will be your study doctor's decision. If you are 18 years of age or older, you will receive 200 mg of pembrolizumab with each dose. If you are 12 to 17 years of age, the dose of pembrolizumab will be calculated from your weight (2 mg/kg, with a maximum dose of 200 mg).

You will be given study treatment on 21-day cycles until the time your disease progresses, you are unable to tolerate the side effects of the study treatment, you decide you no longer wish to receive study treatment, or if your study doctor decides it is no longer in your best interest to receive study treatment. Your study doctor may discontinue the doxorubicin once you have received a specified number of doses but the pembrolizumab may continue as long as you are tolerating it and your disease is not worsening, but no longer than 24 months or after you have received 35 cycles, whichever comes first. If you are having unfavorable side effects, the study treatment may be stopped for a while, or the dose may be reduced. Your study doctor will also discuss with you whether it is in your best interest to continue study treatment.

During the study, you will need the following exams, tests, and procedures. They are part of regular cancer care:

- Physical examination including vital signs and weight measurements.
- You will be asked about the extent of your physical activity and how you are generally feeling.

- CT scan (contrast dye preferred but not required) or MRI of the tumor site, chest, abdomen and pelvis every 6 weeks while you are receiving study treatment.
- Blood work for blood counts and blood chemistry.
- ECHO after every third dose of doxorubicin.

The following tests and procedures will be done specifically for this study and are not part of your regular cancer care:

- Blood work for correlative (related) studies prior to every other cycle during your initial study treatment and also during the Second Course Phase (possible re-study treatment with pembrolizumab that some subjects may be eligible to participate in - please see the next page for more information) if you receive this.
- You will be asked to have **additional** blood for correlative (related) studies (optional) prior to every other cycle during your initial study treatment and also during the Second Course Phase if you receive this. We will further explain the optional blood studies at the end of this consent form.
- You will be asked to have a tumor biopsy (optional) anytime during your initial study treatment. We will further explain the optional tumor biopsy at the end of this consent form.

After you complete the intervention (Post-intervention; one visit):
After you complete study treatment, you will have a post-study treatment safety follow-up visit. You will need the following exams, tests, and procedures. They are part of regular cancer care:

- Physical examination including vital signs and weight measurements.
- You will be asked about the extent of your physical activity and how you are generally feeling.
- CT scan or MRI of the tumor site, chest, abdomen and pelvis.
- Heart monitoring:
    - ECHO and ECG approximately 30 days after your last dose of doxorubicin. This may be required before the post-study treatment safety follow-up visit if you stop doxorubicin before you stop pembrolizumab

The following tests and procedures will be done specifically for this study and are not part of your regular cancer care:

- Blood work for correlative (related) studies either at your end of study treatment visit or if your disease worsens.
- You will be asked to have additional blood for correlative studies (optional) either at your end of study treatment visit or if your disease worsens

Additional Post-Study Treatment Follow-Up:
After you stop study treatment and have a post-study treatment safety follow-up visit, you will have additional post-study treatment follow-up visits to monitor your disease status until your disease

worsens or you start new cancer treatment. Your disease status will be monitored per your study doctor's preference approximately every 9 weeks (+/- 7 days) for up to one year and then approximately every 12 weeks (+/- 7 days) unless your study doctor feels you need to have more frequent scans. You will also have periodic tests to monitor your heart as indicated below.

Heart Monitoring:

- ECHO approximately once every 5 years from your last dose of doxorubicin
- If you experience any problems with your heart after treatment with doxorubicin, you will be referred to a doctor who specializes in evaluating and treating problems with the heart (cardiologist). Any procedures required to monitor your heart function will be determined by the cardiologist.

***Note*:** Under certain circumstances, you may be eligible to re-start study treatment with pembrolizumab for up to one additional year after you have moved to the follow-up portion of the study. This is called the Second Course Phase and will follow the same study treatment plan as previously given in the study. You will be evaluated to make sure it is safe to re-start study treatment with pembrolizumab before you re-start study treatment.

Survival Follow-Up:
At the time of disease progression or start of a new anti-cancer therapy, you will move into the survival follow-up phase. You will be contacted by telephone every 6 months to check your health status until death, withdrawal of consent, or end of the study, whichever comes first. The procedures under "Heart Monitoring" in the section above will still be required during Survival Follow-up.

RISKS

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long-lasting, or may never go away. A severe side effect rarely may be life-threatening. You should tell your study doctor immediately if you experience any side effects.

This study has several risks. First, it is possible that you will get the new study treatment but do less well than you have been doing. Second, because the study treatment is new, we may not yet know all the side effects and something unexpected could happen. The following known side effects of pembrolizumab and doxorubicin are listed below.

Pembrolizumab

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. 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. These side effects may be serious (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, some may be serious (for example, causing hospitalization, life-threatening or where noted, may cause death); seen in 20% or more of subjects treated with pembrolizumab include the following:

- Diarrhea (loose or watery stools)
- Itching of the skin
- Cough
- Nausea
- Fatigue

Common side effects, some may be serious; seen in 5% to less than 20% of subjects treated with 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, and/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, some may be serious; seen in 1% to less than 5% of subjects treated with pembrolizumab include the following:

- Too much thyroid hormone so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, and/or have loose or watery stools (hyperthyroidism)
- Inflammation of the lungs so you may feel short of breath and cough (pneumonitis)
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools and black, tarry, sticky stools with blood or mucus (colitis)
- Inflammation of the skin so you may have widespread 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,

including Stevens-Johnson syndrome/or toxic epidermal necrolysis, which may be serious or potentially life-threatening)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever and/or 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.

Rare side effects, some may be serious; seen in less than 1% of subjects treated with pembrolizumab include the following:
- 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, pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) 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)
- 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 muscles so you may feel weak or have pain in the muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe upper abdominal pain 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, sensitive to light, have eye pain, see floaters or have headaches (uveitis)
- 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 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 (inability to move) (Guillain-Barré syndrome)
- 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)

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- 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 (encephalitis) 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
- Inflammation of the spinal cord (myelitis) 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
- Inflammation of the blood vessels (vasculitis)

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 the right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis)
- Hypoparathyroidism, a condition in which the body produces abnormally low levels of parathyroid hormone (PTH) which results in low blood levels of calcium and high blood levels of phosphorus. Some symptoms include tingling or burning in the fingertips, toes and lips, muscle aches or cramps in the legs, feet, stomach or face, twitching or spasms of muscles, particularly around the mouth, but also in the hands, arms and throat, and fatigue (tiredness)or weakness.

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 study doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant that you have had.

Doxorubicin
Possible side effects of doxorubicin include:

Common (more than 20%)
- Hair loss
- Vomiting
- Red colored urine, saliva, or sweat

Less Common (4% to 20%)
- Heart failure or heart attack which may cause shortness of breath, swelling of ankles, cough or tiredness which may occur years after the dose
- Swelling of the body which may cause shortness of breath
- Swelling and redness at the site of the study drug injection or area of previous radiation
- Belly pain
- Sores in the mouth, throat or stomach
- Nausea, diarrhea
- Hepatitis (liver infection) which may cause yellow eyes and skin
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Cancer of the bone marrow (leukemia) caused by chemotherapy
- Damage to organs which may cause infection, bleeding, may require transfusions (receiving blood from another person)
- Darkening of the nail beds or skin or hands and feet
- Loss of nails

Rare but Serious (3% or less)
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Severe blood infection

Reproductive Risk:
You should not become pregnant or father a baby while on this study and for 4 months after the last dose of pembrolizumab and 6 months after the last dose of doxorubicin because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study and for 4 months after the last dose of pembrolizumab and 6 months after the last dose of doxorubicin. If you are of childbearing potential, you must agree to use an acceptable method of birth control during the study and for 4 months after the last dose of pembrolizumab and 6 months after the last dose of doxorubicin. Your study doctor will discuss with you which birth control methods are considered acceptable.

Should you become pregnant or suspect you are pregnant while on this study, you should inform your study doctor immediately.

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If you become pregnant, you will be removed from the study and may also be asked questions about your pregnancy and the baby. Male subjects should also inform the study doctor immediately if their sexual partners become pregnant while the subject is receiving study treatment.

Allergic Reaction
As with all medications, side effects may include allergic reaction. Allergic reactions may range from mild to severe reactions, such as itching or rash, to major life-threatening reactions which can result in death.

Blood Drawing
Risks associated with blood drawing may include pain, bruising, and infection. Rarely, a person faints.

CT Scan/MRI
A CT scan exposes you to a small dose of radiation. Although all radiation you receive builds up over a lifetime, this amount of radiation should not create a significant risk to your health. Contrast dye is usually injected when you a get a CT scan. The contrast dye may cause pain or burning when it is injected and may worsen kidney function in people who already have kidney disease or who are dehydrated (have not had enough liquids for that day). The contrast dye may also cause an allergic reaction, which could be severe and life threatening.

There are risks from an MRI if you are pregnant or have one of the following: an artificial heart valve, pacemaker, metal plate, pin, or other metallic objects in your body (including gun shot or shrapnel). You may also become anxious from lying in a tight space without moving. The MRI scan does not cause any pain and does not expose you to x-ray radiation.

ECG
The risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing patches.

Tumor Biopsy
The risks of a biopsy can include bleeding, pain, and infection. To reduce these risks, the site of the biopsy will be numbed, and sterile techniques will be used. You will sign a separate consent for this procedure.

Specimen Confidentiality
There is a small risk that your protected health information may be released during the processing of your specimens for research. Everything possible will be done to ensure your privacy and confidentiality is maintained. Your specimens will be labeled with a code that does not identify you. Only your study doctor, clinic staff, and a small number of study staff will know your identity.

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WILL I BENEFIT FROM PARTICIPATING IN THIS STUDY?

This study may or may not improve your condition. The information gained from your participation may benefit others with your condition.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

You do not need to take part in this research study. Your study doctor is willing to discuss the benefits and side effects of other forms of treatment other than this study that are available. These include:

- Other usual chemotherapy for your type of cancer.
- Other investigational research studies with chemotherapy, hormones, radiation therapy, or new anti-cancer agents that may be available for your disease.
- Choosing no further 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 doctor.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Some of the tests or treatments used in this study may be part of your standard care used to maintain your health even if you did not take part in this study. You and/or your health plan/insurance will need to pay for some or all of the costs related to your standard treatment. The study drug pembrolizumab, tests, and procedures done for the sole purpose of the study [including the tissue biopsy and blood correlative (related) studies done for research purposes] will be provided at no cost to you. If you require a biopsy as part of your standard care during any of the time-points when a research biopsy is required, the cost of the biopsy will be billed to you or your insurance. After tissue has been collected from a biopsy, a portion of the tissue will be used for the purposes of the study. If you do not require a biopsy as part of your standard care during the time-point when a research biopsy is required, you will have a biopsy for research purposes only and the cost of the biopsy will not be billed to you or your insurance.

Doxorubicin is a standard chemotherapy drug that is commercially available and will not be covered by the study.

You will not receive payment for taking part in this study. For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage You can print a copy of the "Clinical Trials and Insurance Coverage" information from this web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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You may wish to discuss coverage with your insurance company before agreeing to participate in this research study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

If you become ill or are hurt while you are in the study, get the medical care that you need right away.

In the event that you are harmed as a result of your participation in this study, inform your study doctor immediately so you can access medical treatment. You and/or your health plan will be charged for this treatment in the usual manner. The study will not pay for standard medical treatment.

You still have the right to make a claim through the legal system even if you sign and date this form, accept medical care, or accept payment for medical expenses.

WHAT IF I WANT TO QUIT THE STUDY LATER ON?

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide not to be in the study, that will not in any way harm your relations with your doctors or with Atrium Health. You are free to stop being in the study if you change your mind after entering it. This would not harm your relations with your doctors or Atrium Health.

Information contributed to the study will remain in the study even if you choose to withdraw. If you choose to withdraw from the study, please notify the study doctor in writing at:

Michael Livingston, MD
[redacted]

The study doctor may choose to involuntarily withdraw you from the study for any reason.

We will tell you about new medical findings that may affect your willingness to continue in the study.

If you stop taking part in this study, any specimens which may have already been collected and processed will remain de-identified and part of the study. Any specimens which may have been collected but have not yet been processed may be destroyed upon your written request. No specimens will be returned to you.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

The records of this study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify a patient. Your record for this study may, however, be reviewed and/or photocopied by Atrium Health, Merck, Inc. (funding company),

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or by representatives of the Food and Drug Administration or other government agencies. To that extent, confidentiality is not absolute.

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location.

Your de-identified specimens for research (with only your unique ID number) will be stored in a biospecimen repository (a "bank" of specimens) at Atrium Health.

Your specimens may be used to determine the sequence of some or all of your genes (DNA – traits passed in families). However, this study is not intended to identify diseases causing mutations that can affect the health of close family members (such as your parents, siblings, or children). All specimens for research collected for the purposes of this study will be considered donated materials and will be stored indefinitely.

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.

AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

If you wish to take part in this clinical study, you will be asked to sign this consent form. It allows the study Sponsor-Investigator (Dr. Livingston) to collect and process any relevant personal health information collected from you during the study. These are activities routinely carried out during all clinical studies.

You have been told that personal information about you (including sensitive personal health information, such as your medical history and your racial/ethnic origin if relevant to the study) will be reviewed, collected on a computer database, stored in electronic or manual files, audited, and/or otherwise processed by:

- the clinical study sponsor-investigator, investigators and research staff,
- regulatory or other governmental authorities of the United States and other countries,
- other persons authorized by the study sponsor,
- Merck, Inc. employees,
- Atrium Health employees,
- other persons or agencies as required by law or allowed by federal regulations.

You have been told that your personal data are being collected and processed to:

- check your suitability to take part in the study,
- monitor your treatment with the study drug,
- compare and pool study treatment results with those of other subjects in clinical studies,

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- support the development of the study drug,
- support the licensing application for regulatory approval of the study drug in the world
- support the marketing, distribution, sale and use of the study drug anywhere in the world.

You have been told that your personal information may be processed within the U.S. or elsewhere in the world or transferred to or from the U.S. for review, processing and/or storage by an associated company or a carefully selected third-party organization.

By signing this document, you explicitly consent to the transfer of your personal information, including sensitive personal information, collected during this clinical study, for review, processing and/or storage. Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the Privacy Rule. However, the groups are committed to keeping your personal health confidential.

You may refuse this authorization to transfer your personal information. If you choose not to agree to this authorization, you might be ineligible to participate in the study. If you decide not to sign this authorization, that will not harm your relations with your doctors or with Atrium Health.

You have the right to inspect your medical record at any time. Your research record may be unavailable until the conclusion of the study. At that point, it will be available. Please speak with the study doctor if you desire to access your record.

You have been told whenever your personal information is processed, it will be kept confidential and secure, to the best of our ability. It will be used only for the purpose for which it was collected.

This Authorization does not have an expiration date. You have been told that according to the guidelines for good clinical practice, the study investigator and sponsor will keep your personal information for at least 6 years. If you do not withdraw this Authorization in writing, it will remain in effect indefinitely. If you wish to revoke authorization to use your personal information, you will notify the study doctor in writing at the address and telephone number listed on the first page of this form. Some of the data obtained from your record prior to your revocation may still be used if considered necessary for the study.

FINANCIAL DISCLOSURE

None of the study doctors asking you to participate in this study have received or will receive money or other benefits for personal use from the company (Merck, Inc.) that developed the drug pembrolizumab used in this study. However, Merck, Inc. will give money or other benefits to a research fund, foundation, educational institution, or other organization with which the study doctor or study staff is associated.

Affix Participant Barcode Label Here

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 subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  [redacted]
- or call **toll free**: [redacted]
- or by **email**: [redacted]

Please reference the following number when contacting the study subject adviser: Pro00020377.

OPTIONAL AND FUTURE STUDIES – BIO SPECIMEN COLLECTION

The study doctor and his associates (the investigators) are asking you to allow your blood and tissue to be collected, tested, and/or banked (stored) for the purposes of research. All information for the main study's informed consent form still applies to this part of the informed consent. Your study doctor would like to collect blood samples from you for research. Some of these blood samples are optional and part of this study, while some may be used for future, currently unplanned research. Regardless of your decision to participate in this optional blood collection, you may still participate in the main study, if you choose to. However, you must participate in the main study in order to be eligible for participation in optional blood collections.

If you agree to participate in the optional and future research - blood collection, we will ask to collect blood prior to the start of study treatment on this study, before every other cycle of study treatment, at the time of disease progression or at your end of treatment study visit. If you re-start pembrolizumab on the Second Course Phase, the blood collection timepoints will be the same as during initial study treatment with pembrolizumab.

If you agree to participate in the optional and future research tumor biopsy, we will ask you to have a tumor biopsy anytime during study treatment. This will only be done during your initial study treatment with pembrolizumab (not during the Second Course Phase study treatment if you receive it).

Affix Participant Barcode Label Here

If you agree to donate samples, they will be stored at the Atrium Health Biospecimen Repository, a place where human samples are securely stored and where any of your remaining samples will be stored.

If you decide, at a later date to withdraw your consent for any reason, you have the option not to allow Levine Cancer Institute to use your blood samples or tissue collected for testing by contacting the study doctor at the telephone number or address listed on the first page of this form. Blood and tissue samples will be destroyed only if they have not already been tested.

Participation in this collection is optional and refusing to participate will not affect your eligibility for the main study or the study treatment given.

1. Do you give permission to have optional blood samples collected as described above to be stored for research?

Yes_____ No_____ Initials_____

2. Do you give permission to have an optional tumor biopsy collected anytime during initial study treatment to be stored for research?

Yes_____ No_____ Initials_____

Affix Participant Barcode Label Here

STATEMENT OF CONSENT

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. I am not giving up any of my legal rights by signing and dating this form.

_____ ____/____/____ _____
Signature of Research Subject (if subject is age 18 or older) Date Time

_____
Printed Name of Research Subject

_____ ____/____/____ _____
Signature of Parent/Legal Guardian (if subject is under age 18) Date Time

_____
Printed Name of Parent/Legal Guardian (if subject is under age 18)

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject or the subject's parent/legal guardian the nature and purpose of the above study. There has been an opportunity for the subject or the subject's parent/legal guardian to ask questions about this research study. I have been available to answer any questions that the subject or the subject's parent/legal guardian has about this study.

_____ ____/____/____ _____
Signature of Person Explaining Consent Date Time

_____
Printed Name of Person Explaining Consent

Affix Participant Barcode Label Here