Protocol Title: A PHASE 2 STUDY OF PEMBROLIZUMAB IN PATIENTS WITH HISTIOCYTE/DENDRITIC CELL NEOPLASMS AND BIOLOGICALLY SELECTED SUBTYPES OF RELAPSED/REFRACTORY AGGRESSIVE LYMPHOMAS.

DF/HCC Principal Research Doctor / Institution: Eric Jacobsen, MD/DFCI

DF/HCC Site-Responsible Research Doctor(s) / Institution(s): Jeffrey Barnes, MD/MGH

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have an aggressive lymphoma or a histiocyte or dendritic cell neoplasm (tumor) that has not responded to or has come back after other treatments. This research study is studying a drug called pembrolizumab as a possible treatment for this diagnosis.

The name of the study drug involved in this study is:

- Pembrolizumab

For purposes of this research, you will be referred to as a "participant".

It is expected that about 30 people will take part in this research study.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. is a pharmaceutical company who is supporting this research study by providing funding as well as the study drug, pembrolizumab/KEYTRUDA.

It is possible that certain researchers on this study may have earned money from, or own some publicly-traded stock in, the company that makes or is developing the study drug. The amount of money that a researcher may earn and still take part in research is limited by the Harvard Medical School Faculty of Medicine Policy on Conflicts of Interest and Commitment. If you have further questions, please speak with a member of the study team or contact the Dana-Farber Cancer Institute Office of Research Integrity at 617-432-4557 or researchintegrity@dfci.harvard.edu.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits

of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the safety and effectiveness of an investigational drug to learn whether the drug works in treating a specific disease. "Investigational" means that the drug is being studied.

The FDA (the U.S. Food and Drug Administration) has not approved pembrolizumab for your specific disease but it has been approved for other uses.

The study drug is an antibody that targets a molecule called PD-1. PD-1 is used to turn down the immune system. In general, this is used by the body to prevent the immune system from being too active. However, several cancers appear to use this pathway to prevent the immune system from attacking them. The theory behind this study is that by blocking PD-1, we may be able to prevent the cancer from hiding from the immune system and allow the immune system to attack the cancer more effectively. There is evidence that the type of lymphoma you have may use PD-1 to escape the immune system.

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 (i.e. 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.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment including chemotherapy
- Take part in another research study.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **An assessment of your tumor** by one or more of the following standard assessment tools: CT (Computerized Tomography) scan, MRI (Magnetic Resonance Imaging) or PET (Positron Emission Tomography) scans
- **Blood tests** (approximately 2 tablespoons) for laboratory tests which measure your blood chemistry, including kidney and liver function, count your red and white blood cells and platelets, measure your thyroid function, check your blood's ability to clot, and check for HIV, hepatitis B and C infection. Your HIV, hepatitis B and C tests must be negative for you to participate in the study.
- **Urine test**.
- **Blood test,** approximately 3 tablespoons for research purposes only

- **Your previously collected and stored tissue (archival tissue) will be obtained for tests** and sent to the lab for special testing. If your doctor decides to take a new tumor sample as part of your clinical care, or if there is no tumor tissue left from your prior biopsy, you will be asked to have a new biopsy to participate in the study.
- **Bone marrow aspirate & biopsy** will be conducted to see if your bone marrow has tumor cells.
- **Pulmonary Function Test (PFT)** will be performed to measure how well your lungs work and make sure there are no problems taking in and releasing air.
- **Pregnancy test:** if you are a woman of child-bearing potential, a urine or blood pregnancy test will be performed.

If these tests show that you are eligible to participate in the research study, you may begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Study Treatment Overview:

- **Infused Study Drug:** You will be given the study treatment(s) once every 3 weeks into your vein (by intravenous infusion) over about 30 minutes. This will continue for up to 35 cycles.
- **Pre-medications:** You may be pre-medicated with drugs to reduce the chance of having a sensitivity reaction to the study treatment. If you tolerate the study treatment without a reaction, then pre-medications may be changed by your doctor.

If you take part in this research study, you will receive the study drug on Day 1 of each treatment cycle. Treatment cycles are about 3 weeks (21 days). The time between doses may increase if you experience bad side effects. During the study you will be followed by your health care providers to monitor your status and side effects that may occur from the study drug.

On Day 1 of each cycle you will receive the following:

- **Infused Study Drug(s):** pembrolizumab
- **Clinical Exams***:* During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Medical history**
- **Performance status**, which evaluates how you are able to carry on with your usual activities.

- **Scans (or Imaging tests):** We will assess your tumor by PET and/or CT scans at cycles 3, 6 and 9 and then every 12 weeks thereafter
- **Blood tests** (approximately 2 tablespoons) for routine care and for research purposes
- **Optional repeat lymph node biopsy** at cycle 2. Please refer to Section O for additional information regarding optional studies.

Research Study Plan:

	Screening	Treatment Cycles									End of treatment visit (EOT)	Post-treatment	
							To be repeated beyond 9 cycles until EOT unless otherwise noted						
		1	2	3	4	5	6	7	8	9[a]	30 days after last dose	60 days post-treatment	Follow-up (every 12 weeks)
Pembrolizumab		X	X	X	X	X	X	X	X	X			
Blood test	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine test	X												
Medical history	X												
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG	X												
Bone marrow biopsy	X			X[b]			X[b]			X[b]		X[b]	
Pulmonary function tests	X												
Scan (PET/CT or CT)	X			X			X			X		X	

a – after cycle 9 radiology tests will occur every 4 cycles (approximately every 12 weeks) until cycle 33
b- bone marrow biopsy only needs to be repeated to confirm complete response (CR)

Planned Follow-up:

Even if you stop receiving treatment on the study we would like to keep track of your medical condition. We would like to do this by calling or emailing you or

your primary care doctor approximately every 12 weeks to see how you are doing. Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study.

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this research study for up to 36 months.

You may be taken off the research study drug for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- You are a female and become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a study drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Pembrolizumab:

VERY COMMON

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

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

COMMON

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

- Joint pain
- Fever
- Back pain
- Rash
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)

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

UNCOMMON

Out of 100 people who received 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, fel tired, have loose or watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure, at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the bowels/gut, so you may feel stomach pain with loose or watery stools or stools that are black tarry, sticky or have blood and mucus (colitis)
- Inflammation of the skin so you may have widespread peeling of the skin, itching, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection (Severe skin reactions, including Steven-Johnson syndrome/or toxic epidermal necrolysis).
- Neutropenia- condition in which the number of white blood cells called neutrophils is abnormally low, which can increase the risk of infection.
- Thrombocytopenia- low number of platelets, which may cause bleeding and bruising.

RARE

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-Barre Syndrome)
- Inflammation of the muscles, so you may feel weak or have pain in your muscles (myositis)

- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels), so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in behavior, double vision, few to no menstrual cycles (for women), 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 the 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 (fits), changes in personality

and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis). Symptoms will depend on the particular blood vessels that are involved in the inflammatory process, for example; if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue.
- Low levels of parathyroid hormone (a hormone made by 4 tiny glands in your neck) which may result in low blood calcium and cause muscle cramps or spasms; fatigue or weakness; numbness, tingling or burning in your fingertips, toes or lips (hypoparathyroidism)

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).

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

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

Patients treated with pembrolizumab **BEFORE** going on to receive an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), should inform their transplant physicians that they have received pembrolizumab in the past.

In patients with any hematologic malignancy (cancers of the blood like Hodgkin lymphoma, multiple myeloma): There is a potential for an increased risk of severe complications following allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor) in patients who previously received pembrolizumab **BEFORE** an allogeneic stem cell transplant.

Reports of clotting of blood within the liver and severe graft versus host disease (which can include skin, liver and gastrointestinal symptoms), including death, have been received for patients who received pembrolizumab **BEFORE** an allogeneic stem cell transplant after pembrolizumab therapy.

Cancer research often includes biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures done only for the purposes of research.

Risks Associated with Biopsies:
Biopsies are normally performed under the guidance of an imaging technique. Each procedure requires a separate consent prior to the biopsy. The risks may include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.

- Rarely, an infection at the biopsy site.

Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

Risks Associated with Bone Marrow Biopsies:
For this procedure, a numbing drug is injected into the skin over one of your hipbones. A needle is then inserted into the hipbones and a small piece of bone is removed. The risks may include:

- Moderate pain and discomfort
- Bleeding at the biopsy site
- Scarring at the biopsy site
- Rarely, an infection at the biopsy site
- Rarely, nerve injury at the biopsy site

Risks Associated with Bone Marrow Aspiration:
For this procedure, a numbing drug is injected into the skin over the same hipbone. A needle is then inserted into the hipbone and a sample of bone marrow fluid is removed. Risks of this procedure are small, but may include:

- Pain from the needle sticks
- Pain from aspirating the bone marrow with a syringe
- Bleeding
- Infection
- Local nerve damage

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, CT scans or PET/CT scans utilizing radioactivity may be used to evaluate your disease. In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the CT scan. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If

there is any change in your kidney function, we may have to remove you from the study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
The drugs used in this research study may affect a fetus. While participating in this research study, you should not become pregnant or father a baby, and should not nurse a baby. We can provide counseling about preventing pregnancy for either male or female study participants. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

In the event that your partner becomes pregnant, it may be critical to share information regarding your participation in this research study with that person. Your research doctor should also be told if this happens. The study sponsor may want to collect data on your partner's pregnancy.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

We do not know if taking part in this study will help you. This study may help researchers learn information that could help people in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the drug. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for participating in this study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You will not be charged for pembrolizumab. It is possible that pembrolizumab may not continue to be supplied free for some reason. If this would occur, your research doctor will talk with you about your options.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Brigham and Women's Hospital: (617) 732-5524 or (617) 732-7485
- Dana-Farber Cancer Institute: (617) 632-3455
- Massachusetts General Hospital: (617) 726-2191

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance

company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

K. WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to your insurance company. You will be responsible for deductibles and co-payments. There are no plans to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The results of this research study may be published. You will not be identified in publications without your permission.

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.

M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Dana-Farber Cancer Institute

- Eric Jacobsen, MD: (617) 632-6633

Massachusetts General Hospital

- Jeffrey Barnes, MD (617-724-4000 or 617-726-1818)

24-hour contact: Eric Jacobsen, MD at (617) 632-6633 or page at (617) 632-3000 beeper 41475.

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at Dana-Farber Cancer Institute (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

N. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug(s) used in the study and for the purpose of this or other research relating the study drug(s) and their use in cancer;
- To better understand the diseases being studied and to improve the design of future studies; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, representatives, business partners, and its agent(s): Merck, Inc.
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or

other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

O. OPTIONAL RESEARCH STUDIES:

You are being asked to participate in some optional studies. If you decide not to participate in any of the optional studies, you can still participate in the main research study. Please take your time to make your decision and discuss it with others and your primary care physician.

Your participation in these optional research studies is voluntary, and you will not be penalized or lose any benefits if you refuse to participate or decide to stop.

Optional Study #1: Biomarkers

The purpose of this sub-study is to find out more about what causes disease and the differences in the way that people respond to drugs and therapies. We will look at components of your samples and how they relate to the way that drugs and therapies work and relate to human disease and health. Many differences in the way people respond to drugs can be learned by studying differences in genes, which are found in your DNA.

For example, with some drugs we know that there are differences in genes that can change how long the drug stays in the body. Scientists are also learning more about differences in genes that may predict whether a subject will be at risk for disease. The more we learn about these differences, the more it will help to improve our understanding and treatment of patients. These tests are exploratory research. They are different from testing done to diagnose you with a genetic **disease or find out your risk of having a genetic disease.**

We may also use your samples to look for "biomarkers". A biomarker is something found in the blood, other body fluids, or tissues that can be used to measure the progress of disease or the effects of treatment. An example of a biomarker is looking at the fat levels of your blood to predict your risk of heart disease.

All samples will be used by the Sponsor or designees. We may also use your samples to look for biomarkers.

You are being asked to provide:
a) Any leftover DNA samples collected in the main study
b) Any leftover bone marrow biopsy/aspirate samples, tissue samples, and lymph node biopsy samples collected in the main study that would routinely be thrown out after the main study is over

Are there any risks to giving these biological samples?

The main study may already involve blood or other sample collection. The risks in providing blood samples for this research study are the same as when blood for the main study is taken or for purposes of your standard medical care. You may have pain, bruising, lightheadedness, and rarely, infection.

There is also a risk that if people other than the Sponsor or its affiliates get your health data and genetic information, they could misuse it for purposes other than those outlined in this consent. The Sponsor has strict privacy and confidentiality protection procedures in place to prevent this from occurring so the chance of this happening to you is extremely small. To help prevent others from finding out anything about you, your name and other information that directly identifies you **will not be included with your sample or your medical and genetic information.**

How will information that identifies me be protected?

Information about you will be collected and shared as described in the main study consent form. Information will then be used in the sub-study consistent with the main study consent, this sub-study consent and any related consent that you have signed giving permission to use your personal health information. Information in this sub-study will be used together with any other information. All identifying information collected in this sub-study will be kept strictly confidential, except as may be required by law or regulatory authority request. If **any publication results from this research, you will not be identified by name.**

To protect your privacy, we will only use a subject number, instead of your name or other identifiers, on your samples. Your name and other information that directly identifies you will not be disclosed outside of the research clinic and will not be known by the Sponsor. A unique code will be applied to your samples at the site. The study investigator will keep the key linking your personal information to this code at the study site. We have set up study records to keep your participation and all your test results confidential. No test results from this sub-study will be kept in your medical record.

Although all identifying information will be removed from your sample before it is analyzed and stored, it is possible that members of a Health Authority or other persons required by law may have to see your study information. For example, a significant safety finding in the main study may require connecting your study **information with these sub-study samples.**

Will I be provided with the results of these analyses?

No. You will not be provided the results of this sub-study. The sub-study is exploratory research and is not designed to provide any information that is useful to you or your doctor. Exploratory research tests are performed under conditions which are different from the types of laboratory testing that your doctor may do.

Therefore, it would not be appropriate to provide you or your doctor these results. The Sponsor also will not provide the analyses to your family, your insurance company or your employer. Research information from this sub-study will not become part of your medical records.

If there are critical safety findings discovered from the sub-study while you are still actively enrolled in the main study the Sponsor will contact all study doctors and offer to pay for clinical diagnostic testing. If important research findings are discovered after you have stopped taking part in the main study, the Sponsor will publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects.

What will happen to my samples?

Your samples will be shipped to a central laboratory and then sent to the Sponsor's designated storage facility. Your samples will be stored under strict supervision in a limited access facility which operates to assure the security and integrity of the samples.

Your samples will be securely stored, for up to 20 years. At this time, your specimen will be physically destroyed. The Sponsor reserves the right to destroy your samples for any reason, during the storage period. We will only analyze the blood or tissue cells you provide to us. Your blood cells will not be made to grow in the laboratory.
Your samples may be stored for longer than these specified periods if the Sponsor is required to answer questions from a regulatory or governmental agency. In this special circumstance, samples will be stored until these questions have been adequately addressed. During the 20 year period that your samples are stored, no additional permission will be obtained from you and you will not be notified when testing is performed on your sample.

At any time, you may request that the Sponsor destroy your sample by contacting your study site. As long as it is possible to identify your samples (i.e., your samples have not been anonymized or the study site has not destroyed the key), then the Sponsor will destroy the sample. However, data obtained from your samples prior to receiving your request for destruction will not be deleted. If you request destruction of your samples, you will not lose any benefits, medical treatment or legal rights to which you are otherwise entitled.

Withdrawing from the main study does not mean that your samples used for this sub-study will automatically be destroyed. If you want your sub-study samples to

be destroyed after you withdraw from the main study, you will have to make a request for them to be destroyed
Your participation in these optional research studies is voluntary, and you will not **be penalized or lose any benefits if you refuse to participate or decide to stop.**

Please indicate whether or not you want to take part in the optional research study.

- ❑ Not applicable
- ❑ Yes Initials_____ Date_____
- ❑ No Initials_____ Date_____

Optional Study #2**: Continuing Treatment beyond Disease Progression**
Only sign this optional consent at the time or if at disease progression

Accumulating evidence indicates a small number of participants treated with immunotherapies may derive clinical benefit despite initial growth of their tumor(s).

You will be permitted to continue study drug treatment with pembrolizumab beyond your initial tumor growth as long as:

- You continue to meet relevant study eligibility criteria
- Your study doctor assesses that you're receiving clinical benefit from study drug treatment
- You do not have rapid tumor growth or clinical deterioration
- You are tolerating study drug treatment
- Your ability to perform everyday tasks is not decreasing, e.g., the symptoms you are having from your disease are stable
- Your study doctor assesses that continuing study drug treatment will not delay an immediate intervention to prevent serious side effects due to tumor growth (e.g. brain metastases)
- You consent to continue study drug treatment

If you continue study drug treatment, all foreseeable risks or discomforts and other alternative treatment options as described in the main informed consent form are applicable. You will continue with assessments as noted in the treatment period of the main informed consent.

Please indicate your choice to continue treatment beyond disease progression as described above:

☐ Not applicable

☐ Yes _____Initials _____Date

☐ No _____ Initials _____Date

P. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

_____ _____

Signature of Participant Date
or Legally Authorized Representative

_____

Relationship of Legally Authorized Representative to Participant

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate