Protocol Title: Phase II Trial of Ipilimumab and Nivolumab in Leptomeningeal Metastases

DF/HCC Principal Research Doctor / Institution:
Priscilla Brastianos, MD/ Massachusetts General Hospital

DF/HCC Site-Responsible Research Doctor / Institution:
Eudocia Kalem Quant Lee, MD, MPH/ Dana Farber Cancer Institute

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have leptomeningeal metastases. This research study is studying a combination of two drugs as a possible treatment for this diagnosis.

The names of the study interventions involved in this study are:

- Ipilimumab
- Nivolumab

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

It is expected that about 18 people will take part in this research study.

Melanoma Research Alliance, a non-profit organization, is supporting this research study by providing funding for the study. Bristol-Meyers Squibb, a pharmaceutical company, is supporting this research study by providing the study drugs.

Dana-Farber Cancer Institute has a financial interest in the investigational agent used in this trial (Nivolumab) which may be affected by the outcome of this research. The Institute has taken steps to manage any actual or potential conflict of interest created by this financial interest, which are more fully described in the Information Sheet available to all participants. More information about these measures can be obtained by contacting Roberta Driscoll, JD, Director of the Office of Research Integrity at 617-632-4557 or by email at Roberta_Driscoll@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

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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 intervention to learn whether the intervention works in treating a specific disease. "Investigational" means that the intervention is being studied.

The FDA (the U.S. Food and Drug Administration) has approved Nivolumab and Ipilimumab as a treatment option for melanoma, but has not approved them for use when cancer cells spread to the cerebrospinal fluid.

Researchers hope to study the effects of the combination of Nivolumab and Ipilimumab. Many cancers use specific pathways (such as PD-1/PD-L1 and CTLA-4) to evade the body's immune system. Nivolumab and ipilimumab work by blocking the PD-1/PD-L1 and CTLA-4 pathways and thus releasing the brakes on the immune system so it can stop or slow cancer.

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: radiation or chemotherapy.
- Take part in another research study.
- Receive the same drugs alone, but not as part of a 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?

Melanoma, small cell lung cancer, breast cancer, bladder cancer, renal cancer, and other solid tumor participants will be treated with a combination regimen of nivolumab with ipilimumab, followed by nivolumab on its own. Nivolumab and ipilimumab will be given every 3 weeks for 4 doses. Then, depending on your cancer type, nivolumab will be given every 2 weeks or every 4 weeks.

For nonsmall cell lung cancer and head and neck cancer participants, nivolumab will be given every 2 weeks and ipilimumab will be given every 6 weeks throughout study participation.

Nivolumab and ipilimumab are both administered intravenously, and the infusion time is 30 minute for each. On days that nivolumab and ipilimumab are given together, nivolumab will be given first, followed by ipilimumab. The Research Study Plan on the next page describes the frequency of the visits.

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 and demographics,** which includes questions about your health, current medications, and any allergies. Your height will be taken.
- **Review medications you are currently taking**
- **A physical examination,** including a neurological assessment, recording of your weight, and collection of vital signs (blood pressure, body temperature, pulse rate, and breathing rate)
- **Performance status**, which evaluates how you are able to carry on with your usual activities.

- **Blood collection and testing,** approximately 2 tablespoons of blood. Blood collection will be used to look for markers of cancer, including genetic markers or markers of your immune system in the blood
- **Disease testing on blood samples:** blood tests will be performed to test for Hepatitis B, Hepatitis C, and HIV and if you are positive for any of these diseases you cannot participate in the study.
- **Electrocardiogram (EKG),** a test that checks for problems with the electrical activity of your heart. This will be done at screening and then as clinically indicated
- **Serum pregnancy test,** for women of childbearing potential
- **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
- **Cerebrospinal fluid** will be collected to assess disease status. Any extra cerebrospinal fluid that is collected may be used for research. We will look for common mutations that could predict resistance to the therapies. These studies could provide suggestions as to other therapies that might help treat melanoma.

- **Archival tissue collection,** which is the collection of a previously-taken biopsy of your tumor, if there is such tissue available. We will examine this data for genetic biomarkers to help identify possible biomarkers that will identify those that will respond to therapy. We will look for common mutations that could predict resistance to the therapies. These studies could provide suggestions as to other therapies that might help treat melanoma.

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

Research Study Plan for Participants of Melanoma, Small Cell Lung Cancer, Breast Cancer, Bladder Cancer, Renal Cancer, and Other Solid Tumors:

		Cycle 1 & Cycle 2					
	S	W1 W7	W2 W8	W3 W9	W4 W10	W5 W11	W6 W12
Medical History	X						
Concurrent meds	X	X	X	X	X	X	X
Physical exam and vitals	X	X	X	X	X	X	X
Weight	X	X			X		
Performance status	X	X			X		
Blood Testing	X	X			X		
Research Blood	X	X			X		
EKG	X						
Serum Pregnancy Test	X						
Radiologic evaluation	X						X
Cerebrospinal fluid	X	X			X		
Archival tissue collection	X						
Ipilimumab		X			X		
Nivolumab*		X			X		

S= Screening W=Week

*Nivolumab alone after Cycle 2. For melanoma, renal cancer, and other solid tumor participants, nivolumab is given every 4 weeks; for small cell lung cancer, breast cancer, and bladder cancer participants, nivolumab is given every 2 weeks.

	Cycle 3 & Cycle 4 & Beyond								Off Study	Follow Up
	W13 W21	W14 W22	W15 W23	W16 W24	W17 W25	W18 W26	W19 W27	W20 W28		
Medical History										
Concurrent meds	X	X	X	X	X	X	X	X		
Physical exam and vitals	X		X		X		X		X	X
Weight	X		X		X		X		X	X
Performance status	X		X		X		X		X	X
Blood Testing	X		X		X		X		X	X
Research Blood	X				X				X	X
EKG										
Serum Pregnancy Test	X									X
Radiologic evaluation								X	X	
Cerebrospinal fluid	X				X					
Archival tissue collection									X	X
Ipilimumab										
Nivolumab*	X		X		X		X			

S= Screening W=Week
*Nivolumab alone after Cycle 2. For melanoma, renal cancer, and other solid tumor participants, nivolumab is given every 4 weeks; for small cell lung cancer, breast cancer, and bladder cancer participants, nivolumab is given every 2 weeks.

Cerebrospinal fluid will be collected every 3 weeks during the first 12 weeks and then every 4 weeks after that. Cerebrospinal fluid will be used to assess the response of cancer to therapy. Extra cerebrospinal fluid will be sent for additional research studies.

Research Study Plan for Participants of Nonsmall Cell Lung Cancer and Head and Neck Cancer:

		Cycle 1 & Cycle 2 & Beyond						Off Study	Follow Up
	S	W1 W7	W2 W8	W3 W9	W4 W10	W5 W11	W6 W12		
Medical History	X								
Concurrent meds	X	X	X	X	X	X	X		
Physical exam and vitals	X	X	X	X	X	X	X	X	X
Weight	X	X			X			X	X
Performance status	X	X			X			X	X
Blood Testing	X	X		X		X		X	X
Research Blood	X	X				X			X
EKG	X								
Serum Pregnancy Test	X								X
Radiologic evaluation	X						X	X	X
Cerebrospinal fluid	X	X				X			
Archival tissue collection	X							X	X
Ipilimumab		X							
Nivolumab		X		X		X			

Planned Follow-up:
End of treatment assessments ("Off Study") will be performed within 7 days after last day of study drug administration or within 7 days after the decision to end treatment.

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

You will be in this research study for as long as you are responding to and tolerating study therapy.

The research doctor may decide to take you off the research study 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
- 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.

Leptomeningeal carcinomatosis can be diagnosed with cancer in the spinal fluid or by MRI. In some very rare circumstances, the MRI can have aberrant positive results when the cytology from the spinal fluid is negative and can lead to a different diagnosis. Although *there is a very small risk that you may be treated without leptomeningeal disease due to this imaging aberrancy, your physicians will carefully review scans and ensure that the MRI scans are consistent with leptomeningeal carcinomatosis to try to minimize this risk of an aberrant result.*

Risks Associated with Nivolumab

Most common side effects (5%-30% chance of happening) are:

- Drowsiness, fatigue
- Skin reactions: including rash, itching, hives, redness, and dry skin
- Diarrhea, which is frequent, loose watery stools, which can cause dehydration and may require hospitalization and treatment with intravenous fluids. Severe and prolonged diarrhea can be life-threatening.
- Nausea
- Abdominal pain
- Decreased appetite
- Low number of red blood cells (anemia) that can cause tiredness and shortness of breath. This may require a blood transfusion.
- Fever
- Joint pain or stiffness

Less common side effects (between 2-4% chance of happening**)** are:

- Bowel inflammation, which may cause abdominal pain, diarrhea, and fever
- Abnormally high levels of enzymes produced by the liver, meaning that your liver is not functioning properly and can cause fatigue and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, this can be serious or life threatening.
- Loss of color (pigment) from areas of skin
- Dry mouth
- Vomiting
- Weight loss

- Thyroid gland abnormalities may cause fatigue, weight gain, fluid retention, weight loss, rapid heartbeat, sweating, nervousness, sensitivity to cold, and mental apathy. Can be serious or life threatening. May require medical intervention to resolve symptoms.
- Blood chemistry abnormalities, including low blood phosphate, low levels of magnesium in the blood which can cause weakness and muscle cramping and low potassium levels, which can cause an abnormal heart rate or an irregular heartbeat, and may be serious and life threatening.
- Excess amount of uric acid in the blood (gout), which can cause pain in the joints as well as decrease kidney function. May cause kidney failure, which may be reversible.
- Lung inflammation: Inflammation of the lungs, which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.
- Cough
- Dizziness
- Headache
- Decreased number of a type of white blood cells. This is associated with an increased risk of infection.
- Chills
- Muscle soreness, weakness, stiffness, spasms or paralysis. May require medical intervention to resolve symptoms.
- Pain in arms or legs
- Tingling, burning, or numbness in hands and feet
- Shortness of breath
- Abnormal taste
- Sudden reddening of the face and/or neck (flushing)
- High or low blood pressure, which can cause trouble breathing and other impairments
- Allergic reaction, which may cause a rash, hives, and/or difficulty breathing
- Increased sensitivity of skin to sunlight
- Constipation
- Difficulty swallowing
- Heartburn, which causes chest discomfort
- Decreased number of blood cells that help to clot blood (platelets). This is associated with an increased risk of bleeding.

Rare (less than 2% chance of this happening):

- Low blood oxygen level, which may cause shortness of breath, confusion, or drowsiness
- Acute lung injury or failure, which can cause severe issues with breathing
- Collection of fluid around the lungs, which can cause shortness of breath and may require treatment
- Inflammation of the appendix (appendicitis), which causes abdominal pain, nausea, and/or vomiting
- Increase in inflammatory blood proteins (e.g., lipase) which may indicate inflammation of the pancreas, which could result in abdominal pain and discomfort and could require hospitalization and intravenous treatment.
- Adrenal gland abnormalities due to a decreased production of steroids by the body, which may cause weakness, confusion, fatigue, listlessness, low blood pressure, dizziness, weight loss, and loss of appetite. May also cause abdominal cramps, nausea, vomiting and diarrhea and changes in electrolytes (body salts). Symptoms may be worse at times of stress, such as high fevers, infection, surgery or a serious accident.
- Inflammation of the pituitary gland which may cause headaches, changes in eyesight, few to no menstrual cycles (for women), increased thirst, and increased frequency of passing urine
- Changes in vision (including decreased or blurry vision), inflammation of nerve in the back of the eye (optic nerve), or bleeding into the eye, which can also cause eye pain
- Liver inflammation or abnormally high levels of enzymes produced by the liver which could become severe and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening.
- Kidney failure which is when both of your kidneys fail and your body holds fluid which can be serious or life threatening. Your blood pressure rises and harmful wastes build up in your body. You may experience fatigue, nausea, and loss of appetite. When this happens, you need treatment to replace the work of your failed kidneys such as dialysis.
- Abnormal blood cell production which results in a significant decrease in red blood cells (which carry oxygen to tissues), white blood cell (which fight infections), and platelets (which help in blood clotting)
- Inflammation of the mouth and lining of the digestive tract, which can lead to difficulties with eating and digesting
- Swelling of hands, face, arms or legs
- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening.

- Back pain
- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis): A disorder in which the body's immune system attacks part of the peripheral nervous system. Symptoms of this disorder include varying degrees of weakness or tingling sensations in the legs. In many instances, the weakness and abnormal sensations spread to the arms and upper body. These symptoms can increase in intensity until certain muscles cannot be used at all and, when severe, the participant is almost totally paralyzed. In these cases, the disorder is life threatening, potentially interfering with breathing and, at times, with blood pressure or heart rate.
- Heart beats that are fast and hard (heart palpitations)
- Inflammation of the heart or its lining or collection of fluid around the heart which may manifest as chest pain that varies with each breath. Pain often increases when lying down and decreases upon sitting up. Fever, cough, and palpitations are common as well.
- Collection of fluid around the heart where the heart is unable to pump correctly due to the external pressure.
- Excess blood sugar if severe may require hospitalization and urgent treatment (diabetes)
- Dehydration: If severe it may require medication, IV fluids and possibly hospitalization.
- Infections: including sepsis, lung infections, and skin infections
- Decreased movement of the intestines (Ileus), which can cause abdominal cramps, bloating and constipation
- Disorientation
- Inflammation or loss of the lining of the brain (which may cause a headache) and spinal cord which may be serious or life threatening and may require medical intervention
- Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes, and internal organ involvement (including liver, kidney, and lung); known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Myasthenia gravis: a nerve disease that may cause joint pain, weakness of eye, face, breathing, and swallowing muscle which can become severe and life threatening.
- Abnormal brain function due to brain inflammation (encephalitis), potentially life-threatening or fatal.
- Toxic epidermal necrolysis: a severe skin and stomach lining reaction that may include rash and sloughing or breakdown of tissue. This may manifest as various blisters, hives, and other lesions in various locations

on the body including palms and soles, face & other extremities. This is serious and may be life threatening.

- Rhabdomyolysis is a breakdown of muscle fibers. It occurs when muscle cells die and release cell contents into the blood stream. It can cause muscle pain and a number of health problems, including damage to the kidneys. If severe, this could be life threatening.
- Rarely, subjects developed radiation necrosis (the death of tissue caused by radiation therapy), which can cause neurologic symptoms. These cases were reported in subjects with a history of prior brain radiation for metastatic melanoma. It is unknown whether this was due to radiation alone or combination of radiation and ipilimumab. Cerebral (brain) radiation necrosis is a known late onset radiation-induced side effect and is one of the most frequent forms of late radiation toxicity following brain irradiation

Risks Associated with Ipilimumab:

Most common side effects (5%-30% chance of happening):

- Diarrhea, which is frequent, loose watery stools, which can cause dehydration and may require hospitalization and treatment with intravenous fluids. Severe and prolonged diarrhea can be life-threatening.
- Inflammation of the colon (colitis), which can cause issues with the digestive tract
- Abnormally high levels of enzymes produced by the liver, meaning that your liver is not functioning properly and can cause fatigue, and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, this can be serious or life threatening
- Fatigue
- Skin Itchiness
- Skin Rash
- Nausea
- Fever
- Decreased Appetite
- Vomiting
- Abdominal Pain
- Headache
- Constipation
- Adrenal Gland Abnormalities, occurs when there is decreased production of steroids by the body. This may cause weakness, confusion, fatigue, listlessness, low blood pressure, dizziness, weight loss, and loss of

appetite. May also cause abdominal cramps, nausea, vomiting and diarrhea and changes in electrolytes (body salts). Symptoms may be worse at times of stress, such as high fevers, infection, surgery or a serious accident.
- Inflammation of the pituitary gland which may cause headaches, change in eyesight, few to no menstrual cycle (for women), increased thirst, and increased frequency of passing urine

Less common side effects (between 2-5% chance of happening):
- Chills
- Weakness
- Muscle Pain
- Redness of Skin

Rare (less than 2% chance of this happening but potentially serious):
- Allergic reactions, which can include rash, hives, fever, and/or difficulty breathing.
- Inflammation of the liver which could become severe and cause nausea and vomiting, fever and rapid heart rate.
- Low number of red blood cells (anemia) that can cause tiredness and shortness of breath. This may require a blood transfusion.
- Loss of color (pigment) from areas of skin
- Peripheral neuropathy (weakness, numbness, and pain from nerve damage, usually in the hands and feet)
- Inflammation of the kidneys, which may cause you to pass less urine, have cloudy urine, have blood in your urine, have swelling and lower back pain.
- Myasthenia gravis: a nerve disease that may cause joint pain, weakness of eye, face, breathing, and swallowing muscle which can become severe and life threatening.
- A serious condition that occurs in response to an infection that causes widespread inflammation, resulting in poor blood supply to vital organs (sepsis). Symptoms may include a fast heart rate, fever, confusion and rapid breathing. Sepsis can rapidly lead to a life threatening clinical deterioration), lung infections, and skin infections
- Bowel perforation (a hole in the intestines) that could result in a serious, life-threatening infection that may require surgery. This may occur at higher rates if bowel metastases are present.
- Ulcers of the large intestines. This may cause abdominal pain, cramps, and loose discharges of pus, blood, and mucous from the bowel.

- Blistering and peeling of the top layer of skin resembling that of a severe burn has occurred (epidermal necrolysis). This condition can be life threatening.
- Eye problems, including inflammation of various parts of the eye and changes in the color of the eye. These conditions may interfere with vision, and cause double vision, blurry vision, eye pain, and/or blindness if untreated.
- Thyroid gland abnormalities may cause fatigue, weight gain, fluid retention, weight loss, rapid heartbeat, sweating, nervousness, sensitivity to cold, and mental apathy.
- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis): A disorder in which the body's immune system attacks part of the peripheral nervous system. Symptoms of this disorder include varying degrees of weakness or tingling sensations in the legs. In many instances, the weakness and abnormal sensations spread to the arms and upper body. These symptoms can increase in intensity until certain muscles cannot be used at all and, when severe, the participant is almost totally paralyzed. In these cases, the disorder is life threatening, potentially interfering with breathing and, at times, with blood pressure or heart rate.
- Multi organ system problems with liver, kidney, heart, muscles, blood vessels, and lung (many of the issues listed above occurring at once)
- Infection of the connective tissue surrounding the brain and spinal cord that occurs when the white blood cell count is low (meningitis). This can cause headache, nausea and vomiting, stiff neck, and sensitivity of your eyes to light.
- Death of healthy tissue caused by radiation therapy (radiation necrosis)
- Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes, and internal organ involvement (including liver, kidney, and lung); known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- A sudden rapid death of cancer cells in response to treatment, which causes the cancer cells to spill their inner contents which then accumulate faster than they can be eliminated. The debris from the cancer cells can change the balance of the chemistry of the body, which can be dangerous. This may cause severe nausea and vomiting, shortness of breath, and irregular heartbeat.

Reproductive Risks:

The drugs used in this research study may affect a fetus. Women of child bearing potential should avoid pregnancy for the duration of treatment and for up to 23 weeks after the last dose. Male subjects should avoid impregnating a partner for

up to 31 weeks after the last dose. 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?

Taking part in this study may or may not help you because researchers do not know how this combination of drugs will compare to the usual approach. This study may help researchers learn things that may 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 study drugs. In some cases, the abrupt stopping of a drug can have risks in itself. 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 to participate 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 either of the study drugs. 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 is:

- 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 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. The treating hospital may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for any of the sponsors of this study to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

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:

Massachusetts General Hospital

- Priscilla Brastianos, MD: (617) 724-8770

Dana Farber Cancer Institute

- Eudocia Kalem Quant Lee, MD, MPH: (617) 632-2166

24-hour contact: Please call MGH at (617) 724-4000 and ask that the study doctor be paged.

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at DFCI (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)
- 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 for the purpose of this or other research relating the study drug and its use in cancer
- 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 of the study, its subcontractors, and its agent(s): DF/HCC
- The funder (s) of the study, its subcontractors, and its agent(s): Bristol Myers Squibb and Melanoma Research Alliance
- 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. 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
or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

DFCI Protocol Number: 16-136	Approved Date (DFCI IRB Approval): 03/07/2019
Date Posted for Use: 04/03/2019	

Adult Participants

To be completed by person obtaining consent:

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, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ 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 illiterate

The consent form was read to the participant who was given the opportunity to ask questions.

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

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