Protocol Title: A phase II trial of abbreviated MAPK targeted therapy plus pembrolizumab in patients with unresectable or metastatic melanoma

DF/HCC Principal Research Doctor / Institution:

Ryan Sullivan, MD Massachusetts General Hospital

DF/HCC Site-Responsible Research Doctor(s) / Institution(s):

David McDermott, MD / Beth-Israel Deaconess Medical Center
Elizabeth Buchbinder, MD/ Dana-Farber Cancer Institute

Phase II Consent Form

A. INTRODUCTION

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

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

- Pembrolizumab (Keytruda)
- Trametinib (Mekinist)
- Dabrafenib (Tafinlar)

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

It is expected that about 50 people will take part in this research study.

Merck is supporting this research study by providing funds for data management, biopsies, and the study drug pembrolizumab.

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 approved pembrolizumab, dabrafenib, and trametinib for your specific disease but the combination of all three has not been approved.

This study is being conducted to document whether trametinib with or without dabrafenib taken for brief period of time prior to and with pembrolizumab works better than we expect pembrolizumab to work in participants with uresectable and/or metastatic melanoma. All three of these drugs are FDA-approved for unresectable and/or metastatic melanoma; however, they are not FDA-approved for use all together.

Pembrolizumab is a type of antibody that inhibits the cancer cell growth. An antibody is a cell that attaches to other cells to fight off infection. Trametinib is a cell inhibitor that binds to the cancer cells to inhibit the cancer cells' signals to decrease cell growth. Dabrafenib is also a cell inhibitor and works by stopping the cancer cell from duplicating.

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
- Take part in another research study.
- Receive the same drugs on their own, but not as part of a research study.
- 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.
- **Dermatology Exam,** to check for any abnormal spots on the skin that require treatment (removal) or close watching on the study
- **Eye Exam,** to check for any problems in your eyes that might put you at greater risk of eye damage during the course of the study.
- **Physical Exam**
- **Electrocardiogram (ECG),** which measures your heart's electrical activity
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood Tests,** a total of 4 teaspoons of blood will be drawn for routine tests and to see how the combination of the study drugs is affecting your tumor
- **Tumor Assessment** by one or more of the following standard assessment tools: X-ray, CT (Computerized Tomography) scan, MRI (Magnetic Resonance Imaging) or PET (Positron Emission Tomography) scans
- **Echocardiogram (ECHO)/ Multiple Gated Acquisition Scan (MUGA),** which are used to takes pictures of your heart using an ultrasound to see how strong your heartbeat/hear muscles are.

- **Tumor Biopsies,** since understanding how the study drugs change what is happening in your tumor is a critical part of why we are doing this study.

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:

- **Oral Study Drugs:** You will be taking the study drug dabrafenib twice daily and trametinib once daily during each cycle. One cycle consists of 6 weeks.
- **Infused Study Drug:** You will be given pembrolizumab once every 3 weeks into your vein (by intravenous infusion) over about 30 minutes. This will continue for up to 2 years.

If you take part in this research study you will be given a drug diary. You will be asked to document information in the drug diary about the study treatment you are being asked to take.

Research Study Plan:

	Pre-Study	Targeted Therapy Lead-In		Combined Targeted Therapy plus Immune		Single-Agent pembrolizumab	
		Week 1	Week 2	Week 3	Week 6	Week 9	Week 12
Medical History	X	X		X	X	X	X
Dermatology Exam	X					X	
Eye Exam	X					X	
Physical exam	X	X		X	X	X	X
ECG	X			X	X		
Performance Status	X	X		X	X	X	X
Blood Tests	X	X		X	X	X	X
Tumor Assessments	X					X	
ECHO/MUGA	X					X	
Tumor Biopsies*	X			X		X	
Oral Drugs		X	X	X	X		
Infused Drug				X	X	X	X

	Single-Agent pembrolizumab					Off-Study
	Week 15	Week 18	Week 21	Week 24	Weeks 21-107	
Medical History	X	X	X	X	X	
Dermatology Exam						
Eye Exam						
Physical exam	X	X	X	X	X	X
ECG						
Performance Status	X	X	X	X	X	X
Blood Tests	X	X	X	X	X	X
Tumor Assessment	X		X		X	
ECHO/MUGA						

Tumor Biopsies						
Oral Drugs						
Infused Drug	X	X	X	X	X	

*If the cancer should continue to grow despite treatment (recur), you might be asked to complete another biopsy at that time.

Planned Follow-up:

We would like to keep track of your medical condition. We would like to do this by planning follow-up appointments. Your doctor will recommend a schedule of follow up appointments that will initially involve every three to six month visits. Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study. If you are not followed at this study center, then we will plan to call you every three to six months.

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

You will be in this research study for up to 2 years.

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 (at least a 20% chance that this will happen):

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

Common (between a 5% - 20% chance that this will happen):

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

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

Uncommon (between 1%to 5% chance that this will happen):

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

Rare (less than a 1% chance that this will happen)*:*

- Inflammation of the nerves that may cause pain, weakness, or tingling in your hands and feet and may spread to your legs, arms, and upper body leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome)
- Inflammation of the muscles so you may feel weak or have pain in your muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)

- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, 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 your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- Type 1 diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination, and weight loss. You are likely to need regular insulin shots
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting (myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to a 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 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)

- The immune system can attack normal organs and tissues in your body and can affect the way they work, which can result in side effects that may become serious (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.
- 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 that can lead to damage of different organs

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 or skin, feeling tired, and itching (sclerosing cholangitis).

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.

Risks Associated with trametinib:

Frequent: Between a 10-50% chance that this will happen

- Skin rash which may cause redness and itching
- Diarrhea, which may cause dehydration. Hospitalization and treatment with intravenous fluids may be required. Severe and prolonged diarrhea can be life threatening.
- Swelling of the hands and feet (peripheral edema)
- Increase of blood pressure, which can cause headaches, lightheadedness, dizziness, ringing in the ears, altered vision, or fainting.
- Stomach pain
- An abnormal liver enzyme result may suggest damage to the liver causing the liver to not function properly
- Low blood levels of albumin (possible swelling, weakness, and or fatigue)
- Anemia (decreased red blood cells): can cause tiredness and shortness of breath. May require a blood transfusion.
- Localized tissue swelling due to fluid accumulation (lymphedema)
- Redness, chapping or cracking of the skin
- Bleeding (gums, uterus, vagina, hemorrhoids, and/or eye)

Occasional: Between a 1-10% chance that this will happen

- Hypersensitivity / allergic reaction – may present with symptoms like fever, rash, abnormal liver enzymes and visual changes
- Visual problems - such as blurry vision, color dots, and halo. These symptoms go away in most cases.
    - It is important that you do not drive a car or work with machinery if you are experiencing any visual changes.

- Swelling on face or around the eyes
- Dry or itching skin
- Dry mouth
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles
- Dry eyes
- Enlarged Heart due to damaged heart muscles, this may cause shortness of breath, an abnormal heart rhythm, and swelling
- Weakening of your heart muscle which can affect the heart's ability to pump blood.—this may cause an irregular heartbeat, shortness of breath, swelling in your legs and/or tiredness.
- Dizziness
- Abnormal taste in mouth
- Increased risk of infection (may include fever, pain, redness, difficulty breathing, and may become life threatening).
- Inflammation of the lung (pneumonitis) symptoms may include shortness of breath, or changes in chest CT scan.
- Breakdown of muscle tissue (possibly kidney failure), which may cause muscle weakness, fatigue, soreness, bruising, dark tea-colored urine, infrequent urination, fever, feeling sick, nausea, vomiting, confusion, and agitation (anxiety/nervousness)

Rare: Less than a 1% chance that this will happen

- Heart pumping less efficiently (cardiac failure) - may present with symptoms like shortness of breath, extreme tiredness and swelling in ankles and legs
- Visual problems (different from above) including:
    - Separation of the light-sensitive membrane in the back of the eye (the retina) from its supporting layers (retinal pigment epithelial detachment) which can result in blurry vision
    - Swelling in the eye caused by fluid leakage (chorioretinopathy), which may result in loss of vision
    - Swelling of the optic nerve (papilloedema) – may present with symptoms like headache, nausea and vomiting, vision problems
    - Blockage of the vein draining the eye which in severe cases can lead to vision loss (retinal vein occlusion)
        - While these types of visual problems often improve, there is a risk that they may not improve.

    - Certain medical conditions like uncontrolled glaucoma, hypertension or diabetes are also potential risks factors for this type of vision problems.
- Decreased function of the kidneys which may cause nausea, vomiting, loss of appetite, fatigue, sleep probleems, changes in how much you urinate, and muscle cramps.
- Red, Tender, and possibly painful hands and feet (hand and foot syndrome)
- Shortness of breath

Risks Associated with dabrafenib*:*
Frequent: Between a 10-50% chance that this will happen

- Feeling weak or having no energy (asthenia)
- Pain in extremity
- Cough
- Fatigue
- Diarrhea
- Nausea
- Vomiting
- Decreased appetite
- Skin effects including:
    - Skin papillomas (skin growth)
    - Rash
    - Thickening of the skin
    - Hand-foot syndrome – leakage of anti-cancer drugs from the palms and/ or soles of the feet can result in redness, tenderness, and possibly peeling of the skin of the palms and soles. The redness, also known as palmar-plantar erythema, looks like sunburn. The areas affected can become dry and peel, with numbness or tingling developing. Hand-foot syndrome can be uncomfortable and can interfere with your ability to carry out normal activities.
    - Itching
    - Hair loss
- Headache
- Fever, which may sometimes be associated with low blood pressure and/or dizziness or fainting
- Pain or stiffness of joint(s)

- Muscle pain
- Chills
- Decrease in red blood cells which may cause fatigue, shortness of breath or dizziness (anemia)

Occasional: Between a 1-10% chance that this will happen

- A decrease in white blood cell count which may affect your ability to fight infection. In some cases a severe decrease in white blood cell counts has occurred. (neutropenia or leukopenia)
- Low phosphorous level which may cause muscle weakness, confusion, seizures and/or heart failure (hypophosphatemia)
- Squamous cell carcinoma of the skin (a type of skin cancer)
- Abdominal pain
- Constipation
- Gastrointestinal Ulcer which may cause dull pain in the stomach, weight loss, not wanting to eat because of pain, nausea or vomiting, bloating, burping or acid reflux, or heartburn (burning sensation in the chest)
- Gastrointestinal Bleeding
- Peptic Ulcer which may cause a burning stomach pain, feeling of fullness, bloating or belching, fatty food intolerance, heartburn, and nausea
- Flu-like symptoms (fatigue, low appetite, muscle ache, joint ache, mild fever)
- Skin effects, including noncancerous skin growths:
    - Skin growths that look like a small piece of soft, hanging skin (skin tags)
    - A rough and dry skin lesion (actinic keratosis)
    - A noncancerous skin growth (seborrheic keratosis)
    - Dry or red skin
    - Itchy skin lesions on the body which may last a long time (months)

Rare: Less than a 1% chance that this will happen

- Inflammation of the pancreas, a gland that regulates blood sugar levels and helps digest food. (pancreatitis)
- Kidney damage or failure, which is when your kidneys do not filter waste as will from the blood

- Inflammation of the eye, which can infrequently result in blindness. Tell your doctor about any changes in your vision (uveitis)
- Allergic reaction or hypersensitivity
- New melanoma or other non-skin type malignancies
- Blood clots in veins, usually in the leg. These blood clots can travel through the veins and into the lung, forming a sudden blockage in a lung artery that can be fatal
    - Encephalopathy (disease/ disorder of the brain), symptoms of which include:
        - Severe confusion or disorientation
        - Involuntary twitching or trembling
        - Difficulty speaking or swallowing

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 either will be performed in the office (if your doctor can feel your tumor) or 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.

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, CT scans, PET/CT scans, x-rays, and/or other 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.

Certain types of drugs or combinations of these drugs with radiation may further slightly increase the risk of developing a new cancer. This risk is described above, in the section about the risks associated with dabrafenib.

Risks Associated with MRI Scans:
When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

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 and for 4 months after, 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 combination of drugs/drug. 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 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, including the study drugs dabrafenib and trametinib. 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:

- Beth Israel Deaconess Medical Center: (617) 667-5661
- Massachusetts General Hospital: (617) 726-2191
- Dana-Farber Cancer Institute: (617) 632-3455

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. FINANCIAL DISCLOSURES

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: Merck. 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.

M. 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.

As participation in this study involves providing a specimen of your tissue, please know that if the research doctor leaves the institution, the research and the tissue might remain at the DF/HCC or might be transferred to another institution.

For all Clinical Trials registered on clinicaltrials.gov (DF/HCC SOP REGIST-200) participants must be notified in the informed consent document that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank. The required statement is as follows:

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.

N. 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
- Ryan Sullivan, MD: (617)-643-3614

Beth Israel Deaconess Medical Center
- David McDermott, MD: (617) 632-9250

Dana-Farber Cancer Institute
- Elizabeth Buchbinder, MD: (617)-632-5055

24-hour contact: Please contact Massachusetts General Hospital at 617-724-4000 and ask that your 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.

O. 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 of the study, its subcontractors, representatives, business partners, and its agent(s): Any Co-Investigators, members of the study team, clinic staff, research RNs and fellows under the supervision of study team members.
- The funders of the study, its subcontractors, representatives, business partners, and its agent(s): Merck
- 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?"

P. 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:

You are being asked to provide and optional Biopsy at Time of Disease Progression to see how your tumor reacted to the combination of the study drugs.

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

☐ Not applicable

☐ Yes _____Initials _____Date

☐ No _____ Initials _____Date

Q. 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

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