UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: CC#11952: A Phase I/II Trial of BKM120 Combined with Vemurafenib (PLX4032) in BRAF$^{V600E/K}$ Mutant Advanced Melanoma

This is a clinical trial, a type of research study. Your study doctor, Alain Algazi, MD, will explain the clinical trial to you. The study team from the UCSF Melanoma Program,can also help if you have questions.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have metastatic melanoma. Melanoma is a serious form of skin cancer. The people in this study will be divided into two groups. There are a few differences in what people in each group will be asked to do.

Why is this study being done?
This study is being done in two phases called Phase I and Phase II. There will be two parts to Phase I, Part A and Part B. Part A will be for patients with no prior treatment of a BRAF inhibitor and Part B is for patients with prior treatment of a BRAF inhibitor. The purpose of Phase I is to test the safety of BKM120 at different dose levels when it is taken with the drug Vemurafenib.This will be done separately in two groups: patients who have not previously been treated with a BRAF inhibitor (Part A) with patients who have (Part B). The purpose of Phase II is to find out if combining BKM120 with Vemurafenib works better than Vemurafenib alone. We want to find out what effects, good and/or bad, BKM120 has on you and your Melanoma.

We know that vemurafenib works for patients with your type of cancer. We want to know if BKM120 is safe to give with vemurafenib and to see if adding BKM120 makes vemurafenib work better. Vemurafenib and BKM120 are both pills that you will take by mouth. BKM120 is an experimental medicine which has not been approved by the US Food and Drug Administration for the treatment of Melanomaor any other form of cancer. Therefore, BKM120 will continue to be tested in patients in research studies such as this one. More than 78 patients with various types of cancer have been treated with BKM120 in clinical studies.

Novartis, the company that makes the study drug BKM120, and the UCSF Helen Diller Family Comprehensive Cancer Center pays for the conduct of this study. Novartis is also providing BKM120 at no charge to the study participants.

How many people will take part in this study?
Up to 61 people will take part in this study at multiple centers around the United States. About 25 of these people will be enrolled at UCSF.

If you choose to participate in this study

There are many different tests and procedures you will have at each study visit. Some of these procedures are procedures that you would have as part of your regular cancer treatment if you did not participate in this study. You will also have "Study Procedures". These are procedures that are only being done because you're in the study or are being done more often than is standard for your type of cancer. All "Study Procedures" are labeled.

-You need to read and understand this Informed Consent Form. You can also ask your family and friends to help you to choose whether this study is right for you.

-You will need to sign this form saying that you want to participate in this study.

-You will need to have the following tests to find out if you can be in the main part of the study. These are called screening tests. If you have had some of them recently, you may not need to do them again. This will be up to your study doctor.

Screening tests and procedures to be done in the 2 weeks before starting the study treatments:

- A doctor will ask you questions about your health and examine you. This includes checking your vital signs and how well you are able to perform daily activities
- You will be given a questionnaire to examine your emotional health. (study procedure)
- A CT scan of your body
  - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally, intravenously, or rectally (less likely). Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. A rectal contrast fills up the loops of your lower bowel so the doctors can see your tumor better. After you have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the radiology department and takes about half an hour.
- Dermatology Exam: A visit with a dermatologist (a skin specialist) who will look at all of your skin. This doctor may also take pictures of your skin.
- About 1 teaspoon of your blood will be taken to see how well your blood, liver, kidneys are working. If you are a woman who can have children, another blood test will be done to make sure that you are not pregnant.

- ½ teaspoon of blood will be collected to test how much sugar is in your blood. You cannot eat or drink anything other than water for 8 hours before this test. (study procedure).

- We will also test your urine to see how well your liver, kidneys and other organs are working.
- You will have an EKG
    - An EKG records the electrical activity of your heart. Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity. This takes about 15-30 minutes.

- You will have an Echocardiogram or a MUGA (Multigated Acquisition) scan.
    - An Echocardiogram uses sound waves to make pictures of your heart, which helps determine how well your heart squeezes blood. You will be asked to lie on your left side while a technician places a probe with gel on your chest to create images of your heart to determine the function and size. The procedure is done in the cardiology department and will take approximately 45-60 minutes.
    - A MUGA scan is a test that makes a motion picture that shows how well your heart pumps blood. The scan is performed by taking a small sample of your own blood that is then "labeled" with a radioactive substance. The labeled blood sample is then re-injected into a vein in your arm and allowed to circulate in your body. Once the labeled blood has circulated around your body, a series of images (similar to a movie) are taken of your heart. You will be asked to lie flat on a table and remain still for about 10-20 minutes while the pictures of your heart are being taken. This test is done in the Nuclear Medicine department and takes about 90 minutes.

- A piece of one of your tumors will be tested to find out what may be making the cancer grow. When possible a sample of your tumor left over from a previous biopsy will be used. If there isn't enough tissue available for testing you will have another biopsy. This will either be a skin punch biopsy or a fine needle aspiration (FNA) biopsy. (study procedure)
    - **Fine Needle Aspiration (FNA)** This is a special type of biopsy. The doctor will insert a fine (very thin) needle through your skin and into your tumor and will remove a very small sample (less than a thimble-full) of your tumor. Either an ultrasound or CT scan will be used to guide the placement of the needle. You will sign a separate consent form for this procedure. This procedure will take about 15-30 minutes.
    - **SKIN punch BIOPSY** In this procedure, your doctor will remove a small piece of skin (the size of a pencil eraser). The area of the biopsy will be numbed with local anesthesia before this biopsy is taken. You may get stitches in the area where the biopsy is taken from. The biopsy will take about 20 minutes to complete.

- An MRI scan of your brain may be done during screening if your study doctor thinks it is necessary to check your brain for signs of melanoma tumors.
    - An MRI scan takes an image of your skull or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). Gadolinium is contrast material that causes some tumors to appear much brighter than normal tissue on MRI scans (these tumors may not be visible without gadolinium). The contrast material will be given to you in your arm through an intravenous catheter (a tiny tube inserted into a vein). You will then lie down on a narrow bed which will be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will lie there quietly for about one hour, during which time you will hear a loud machine-like noise. The MRI scan is done in the radiology department and takes approximately an hour and a half to complete.

After these tests are done, your study doctor will tell you if you can take part in this study.

What will happen if I take part in this research study?
If you agree to take part in this study, you will receive vemurafenib and the study drug BKM120 as indicated by the following schedule:

Phase I participants:

Part A

- Seven days before you begin taking both drugs together (this is called treatment day "-7") you will receive a single dose of BKM120 alone.
- After the first week, you will start taking both drugs every day.

Part B

- You will not receive a single dose of BKM120 at Day -7. You will be required to stop any BRAF therapy 2 weeks before starting on this study.

Part A and B

- We will collect blood samples from you to check how much of the drug is in your blood before this dose, and 1, 2, and 6 hours after this dose, these are considered study procedures. We will also test your blood for the drug 3 days (72 hours) after this first dose. We will need about ½ teaspoon of blood each time that we take your blood.

- You will take vemurafenib twice daily and you will take BKM120 once daily. You will continue taking these drugs as long as your doctor thinks that they are helping you. You can also decide to stop taking the drugs at any time for any reason. Please tell the study doctor if you decided to do this.

Phase II participants:

- On treatment day 1, you will start taking both drugs every day. You will take vemurafenib twice a day and you will take BKM120 once a day. You will continue taking these drugs as long as your doctor thinks that they are helping you. You can also

decide to stop taking the drugs at any time for any reason. Please tell the study doctor if you decided to do this.

Phase I and II participants:

- Follow-up. You will be asked to come to the clinic 1 month after your last dose of the study drugs. At this visit, we will ask you about your health and test your blood. You will also have a physical exam.

Study visits schedule

The study is conducted in cycles. Each cycle is 28 days long. During the first cycle, study visits will take place on days 1, 8, and 15. You may have a visit on day 22 if your doctor feels it is necessary. During the second cycle, study visits will take place on days 1 and 15. For each cycle after Cycle 2 study visits will take place on Day 1 only.

During the main part of the study...

You should take both drugs in the morning, at least 2 hours after a breakfast. Both drugs should be swallowed whole (not chewed, broken or crushed) with a glass of water. Do not eat for 2 hours after taking the drugs. You will be asked to fill out a drug diary to document your doses. You should not miss taking any tablets. If you vomit, do not take another tablet that day. If you forget to take the medication one morning, do not take it in the afternoon and do not take any extra doses the next day but instead call your doctor and ask for advice.

Several drugs and foods may interfere with the study drugs being tested. You should avoid Seville oranges, grapefruit or grapefruit juice, grapefruit hybrids, grapefruit products, pomelos or star fruit and the juices of these fruits while on this study as they cause an interaction with the study drug. You should also avoid St. John's Wortas it they can cause an interaction with the study drug.
Tell your study doctor before you take any new medications while you are on this study.

You may continue to get BKM120 until your disease gets worse, you decide not to take part in this study any longer, or your doctor has decided it is in your best interest to stop treatment.

At all study appointments

- A doctor will ask you questions about your health and examine you. This includes checking your vital signs and how well you are able to perform daily activities
- You will have a dermatology exam on Day 1 of Cycle 3 and every 8 weeks (every other cycle) after that ,this may include taking pictures of your skin and removing any spots that could be cancer
- Will be given a questionnaire to examine your emotional health (study procedure)
- You will be asked about any side effects or symptoms you have had since your last visit (study procedure)
- 1 teaspoon of your blood will be taken to see how well your liver, kidneys and other organs are working.
- ½ teaspoon of blood will be collected to test how much sugar is in your blood. You cannot eat or drink anything other than water for 8 hours before this test. (study procedure).
- A sample of your urine may be taken depending on the results of your blood tests

- An EKG will be done at Day 15 of Cycle 1, Day 1 of Cycles 2 through 4, and and Day 1 of every third cycle after that
- An ECHO/MUGA scan will be done every 4 cycles
- A small piece of your melanoma may be taken out after 2 weeks of treatment (study procedure)
- A CT scan will be done after every 2 months of treatment
- If you are a phase I participant, blood samples may be taken to measure how much of each drug is in your body- these samples (about a ½ teaspoon each) will be collected on Cycle 1 Days 1 and 15 and on cycle 2 Day 1 (study procedure)

If you choose to stop taking the study drug or if the doctor thinks that it isn't helping you anymore, we will need to:

- Examine you and ask you questions about your health and medications.
- Take about 1 teaspoon of your blood to see how well your liver, kidneys and other organs are working.
- A sample of your urine may be taken to see how well your liver, kidneys and other organs are working.
- You may have another EKG depending on how recently you've had one and at your doctor's discretion.
- Get a CT scan of your body if you haven't had one recently.

When you are finished receiving treatment on study

You will be asked to come to the clinic one month after you are done with treatment on this study. At that time we will:

- Examine you and ask you questions about your health and medications
- You will be given questionnaires to complete, the questionnaires will ask about your mood and your health
- Take about 1 teaspoon of your blood to see how well your liver, kidneys and other organs are working
- Take a sample of your urine to see how well your liver, kidneys and other organs are working.
- You may have another EKG depending on how recently you've had one and at your doctor's discretion
- Get a CT scan of your body if you haven't had one recently
- Take out another small piece of your melanoma if the study doctor thinks that this is safe(study procedure)
- You will have a dermatology exam, this may include taking pictures of your skin and removing any spots that could be cancer

Where will I go for my study visits?

Most study visits will be at UCSF Mount Zion campus. Some parts of the study will be done at other UCSF locations in San Francisco.

How long will I be in the study?
You will be in the study as long as your doctor thinks that the study drugs are helping you. Each study visit will last 2-4 hours depending on what tests are being done. You can also decide to stop being in the study at anytime for any reason. One month after you are finished taking the study drugs, the study doctor will ask you to come in for a follow-up visit.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.
It is important to tell the study doctor if you are thinking about stopping so any risks from the BKM120 and Vemurafenib can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?
Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your doctor may give you medicines to make any side effects better. Many side effects go away soon after you stop taking the study drugs. Sometimes, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

You should talk to your study doctor about any side effects you experience while taking part in the study.

<u>Side effects from vemurafenib include:</u>

<u>Healthy Volunteers</u>

The study drug has been given to 18 healthy volunteers and the risks found in this population are summarized below:

- Headache
- Dizziness
- Itchy rash
- Decreased blood cells that fight infection
- Nausea
- Sleepiness

Cancer patients

More than 800cancer patients are either taking or have been treated with vemurafenib in clinical trials, and the safety information is currently being reviewed. When additional information on side effects is received from these studies, you will be notified of any further study drug–related effects that are not already included in the list below.

In cancer patients, the most common side effects that have occurred in at least 10% of patients and were thought to be related to the study drug are as follows:

Likely

- Tiredness
- Pain in joints (arthralgia)
- Nausea
- Diarrhea
- Changes in blood tests from kidney, blood or liver problems
- Rash
- Itching
- Hair loss
- Sensitivity to light
- Sunburn
- Dry skin
- Joint or muscle pain
- Change in sense of taste
- Headache
- Scaly skin
- Tingling or burning feelings in hands and feet
- Loss of appetite and weight loss
- Skin papilloma (skin growth)
- Hyperkeratosis (thickening of the outer layer of the skin)

Rare but serious

- A curable cancer of the skin called basal cell carcinoma
- Inflammation in the eye that can cause pain or vision problems
- Kidneys stop working suddenly
- Retinal vein occlusion (blockage in the blood supply from the retina - the light-sensitive tissue in the back of the eye)
- Peripheral neuropathy (problem with the nerves that can produce pain, loss of sensation and/or muscle weakness)
- Abnormal liver blood tests, (which may indicate that your liver is not working properly)
- Arthritis (joint inflammation)
- Pancytopenia (reduction in the number of red and white blood cells and platelets)
- Cellulitis (inflammation/infection of skin)
- Delirium (confusion)
- Prolongation of the QTc interval on ECG (an abnormal change to the conduction of electrical impulses that control your heart rate and rhythm) that may lead to life-threatening heart rhythm abnormalities

Other Rare but related adverse events

- Pyrexia (fever)
- Erythema nodosum (tender red skin bumps or lumps)

Because this drug may lead to a prolongation of the QTc interval, you will not be able to participate in this study if you have a condition called "congenital long QT syndrome" or if key electrolytes (salts) in your blood are not balanced and the imbalance cannot be corrected. These conditions may put you at an increased risk for a life-threatening heart rhythm abnormality called "torsade de pointes." While under treatment, we will closely monitor your ECG to determine if your QTc interval becomes prolonged while on study treatment. Additional monitoring and treatment may be required to ensure proper balance of key electrolytes (salts) in your blood and to avoid interaction between your study treatment and other drugs that are known to cause QTc interval prolongation. If your QTc interval becomes abnormally prolonged on ECG, you may be required to interrupt treatment with vemurafenib, have your dose reduced, or you may be required to permanently discontinuevemurafenib.

In studies of melanoma patients, approximately 25% of patients experienced a serious side effect called SCC *of the skin (cutaneous SCC)*. SCC is a common type of skin cancer that is usually treated and cured by a minor procedure (most often by either surgical removal or laser). These were managed with excision,and patients continued treatment with vemurafenib without dose adjustment.If you notice changes in your skin, you should tell the study doctor right away.

Because of mild to severe photosensitivity (predisposition to sunburn) reported in several patients, you should avoid prolonged sun exposure while taking Vemurafenib and for at least 5 days after study drug discontinuation.

You should also use a broad spectrum sunscreen and lip balm of at least SPF 30 or higher to help protect against sunburn.

Other risks
In another study for patients with melanoma, less than 3% of patients treated with vemurafenib developed new primary melanomas that were managed by surgically removing the tumor. These patients continued treatment with vemurafenib prior to and after removal of their new primary melanomas. In this same study, 1 patient (1%) developed a condition known as toxic epidermal necrolysis (a severe skin condition caused by an allergic reaction often resulting in severe blistering and shedding off of skin cells). Two cases of SCC of the head and neck (considered to be malignant head and neck cancer) have been reported in 2 patients treated with vemurafenib who were on study medication more than 300 days while enrolled on a clinical trial. One patient had a history of medical problems that would make them more likely to develop head and neck SCC, and the other patient did not have any medical problems that would have posed any risk in developing this type of cancer. Two cases of intestinal polyps (fleshy benign tumor growths occurring on the lining of the colon or rectum) have been reported in 2 patients who were receiving vemurafenib more than 2 years.

<u>Common risks and side effects related to BKM120 include:</u>

- decreased appetite
- tiredness
- nausea
- constipation

- vomiting and diarrhea that may lead to dehydration
- mouth irritation or inflammation
- abnormal blood test of liver enzymes that may indicate liver dysfunction
- rash
- dry skin
- itching
- high blood pressure
- anxiety
- depression
- headache
- trouble sleeping
- moodchanges- If you or your family notices any mood changes (including anxiety, depression, crying episodes, irritability, and emotional disorder), you should inform your study doctor in order to take the appropriate corrective measures if necessary. In addition, you will be asked to complete two short questionnaires to better follow your mood during the treatment. The origin, nature and impact of those psychiatric mood changes are not entirely documented nor understood. As a result you will be asked to fill out a mood assessment questionnaire during the study. The assessment of this questionnaire can indicate the need to be seen by a psychiatric physician, to initiate concomitant (accompanying) psychiatric medication, as well as treatment changes and the need for other assessments. People living around or with you may observe those mood changes.

Less common side effects of BKM120 include:

- fever
- dizziness
- Changes in how well your heart pumps blood (decreased ejection fraction)
- Decreased blood pressure (hypotension)
- cough
- shortness of breath
- pain in abdomen
- indigestion
- disturbance of taste
- Inflammation, swelling, or irritation of the esophagus or intestines
- pain in hand or foot, back pain, joint pain
- swelling of face, hands, arms, feet, ankles, and other parts of the body
- involuntary muscle contraction
- Inflammation of your skeletal muscles
- bleeding (including nose bleeding) – this may be linked in some cases to decreased number of platelets in your blood
- abnormal blood tests including decreased blood potassium, phosphorous, and sodium levels
- kidneys stop working
- sleepiness
- Changes to your blood's ability to clot (prolonged aPTT)

- Elevated levels of triglycerides
- Skin disorders such as skin inflammation with redness, scaly skin, skin infection (erysipelas), acne, pustular rash
- Low levels of albumin, a protein in blood plasma, which may call swelling
- Restlessness

Rare but serious side effects of BKM120 include:

- Dehydration and low blood pressure that could be life threatening
- Cataract (clouding of the eye's lens), vision blurred
- Breathing problems from inflammation of the lungs, tightening of the airways, infection, or scarring of the lungs
- Sudden stoppage of breathing which may be life threatening (cardio-respiratory arrest)
- Blockage of the lung from a clot or substance in the bloodstream which may be life threatening (pulmonary embolism)
- Pain in the abdomen caused by inflammation of parts of the gut wall
- Disturbances of a pancreatic enzyme called lipase were observed in patients and previously in animal studies
- Reversible swelling in a part of the brain than can be associated with altered consciousness and epilepsy (also called encephalopathy)
- Changes in bone marrow, including low white blood cells (which can increase the risk of infection), a decreased number of red blood cells (which can lead to anemia) and lymphatic system (thymus, lymph nodes, spleen) were also observed in patients who received the drug in combination with other anticancer agents and previously in animal studies.
- Depression or mood changes. Suicide may be a very rare complication of such a condition. Inability to produce enough insulin which leads to a buildup of toxic acids in the bloodstream (diabetic ketoacidosis)
- Insufficient blood flow to the brain which may lead to death of brain tissue or stroke
- Deterioration of the brain's white matter which can affect the covering of nerve cells (leukoencephalopathy)
- Severe, whole-body allergic reaction which may be life threatening (anaphylaxis)
- Severe burning, redness, swelling, blistering, itching, or rash after exposure to sunlight.
- Skin reaction associated with liver and kidney damage and life threatening low blood pressure (DRESS)
- Hallucination

Treatment with BKM120 was also associated with an increase of the upper (systolic) and lower (diastolic) blood pressure in dogs. Your blood pressure and cardiac function will regularly be monitored while you are participating in the study.

If you experience rash during the study, you may be asked to provide a blood sample to measure the concentration of BKM120 and paired skin biopsies (one each from an affected and an unaffected area) for a better assessment of the rash. You should call your study doctor immediately if you experience one of these symptoms: severe burning, redness, swelling,

blistering, itching, or rash after exposure to sunlight. No one can tell what side effects you may have or how severe they will be. Most side effects are expected to go away in most of the cases shortly after BKM120 treatment is stopped; however, in some cases, the side effects may be serious, long-lasting, permanent, or lead eventually to death. Therefore all problems need to be reported to the doctors or study nurses looking after you at your next visit, or by calling your study doctor immediately.

At each visit, the study doctor will ask you about any unusual symptoms and other treatments you may have started. Should a serious side effect occur, the study medication will be stopped. You will be checked regularly for the improvement of the side effects. This may require extra visits and examinations including blood and urine tests as well as cardiac function tests. The study medication may be restarted at the same or a lower dose after the side effects improve or disappear, depending on the severity and the duration of the events.

You will be told if any new side effect is found as a result of this study or any other study using BKM120 that could affect your participation in this study. If you are concerned about your health between visits and because of the trial, then emergency telephone numbers are provided at the end of this document.

Additionally, you must not drink grapefruit juice; eat grapefruit or grapefruit products while taking BKM120. You must not eat Seville oranges and star fruit or their products, or drink the juice of these fruits, while taking BKM120.

At each visit, the Study Doctor will ask you about any unusual symptoms and other treatments you may have started. Should a serious side effect occur, the study medication will be stopped. You will be checked regularly for the improvement of the side effects. This may require extra visits and examinations including blood and urine tests as well as cardiac function tests. The study medication may be restarted at the same or a lower dose after the side effects improve or disappear, depending on the severity and the duration of the events.

You will be given any new information on BKM120 that may affect your willingness to start or continue in the study as it becomes available.

Study drug combination risks: The side effects of the combination of vemurafenib and BKM120 are not yet known. It is possible that this combination of drugs will cause new or more serious side effects than taking these drugs separately. You will be monitored closely for side effects and your doctor may change your medications if it appears that this combination is causing serious side effects. You should tell your doctor about any side effects you experience while on this study. When additional information about side effects is known, you will be notified of any further study drug related effects.

A patient at UCSF experienced dehydration and low blood pressure (hypotension) while participating in this study. Another patient at UCSF experienced a severe adverse reaction to the study treatment which involved a skin rash, elevated counts of disease fighting white blood cells, fever, enlargement of lymph node, and internal organs.

Risks from study tests

Dose Escalation: Since patients will be assigned to different doses of study drug, some patients may receive a dose of the drug that is too small to be effective (this may include a dose of vemurafenib that is lower than the dose currently approved) while others may receive a higher dose that may cause increased side effects. You can ask your study doctor what dose you will be given.

Blood tests: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and rarely, infection.

Echocardiogram: The cardiac echogram might cause you to be uncomfortable from the pressure of the probe on your chest or lying still for the examination.

MUGA scan: MUGA scans involve the risks of radiation. You may develop bruising where the needle is placed in your veins to administer the radioactive substance. You may have an allergic reaction to the radioactive substance. You may be uncomfortable lying flat.

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

Radiation: The amount of radiation you will be exposed to is relatively small. Such doses of radiation may be potentially harmful, but the risks are so small that they are difficult to measure. If you have had many x-rays, or if you might be pregnant, you should discuss this with the researchers before agreeing to be in this study.

CT scan risks: CT scans involve the risks of radiation. In addition, if contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan with contrast. If you are taking metformin (or similar drugs by mouth to treat high blood sugar), such treatment will be stopped for 2-3 days around the time a scan is planned in order to avoid kidney side effects. Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. If contrast material is used, you may feel discomfort when it is injected by vein. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.

MRI risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve

stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenicsystemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

Punch/ Skin Biopsy: There will be some discomfort with this procedure, and there may be bleeding as well. One or two stitches at the biopsy site may be required, which would need to be removed one week later. This procedure may result in temporary pain and bruising. In addition, scarring may occur at the biopsy site. Infection at the skin biopsy site occurs rarely.

Fine Needle Aspiration (FNA) Biopsy: The general risks associated with this procedure are pain, discomfort, infection, and bleeding. If it is necessary for you to have a biopsy, the exact risks associated with the procedure you will be receiving will be discussed with you.

Reproductive risks: You must not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women must not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. You will stop being on this study if you become pregnant during treatment.

Women on the study:
You must use birth control if there is any chance that you could get pregnant while on this study. Use an effective method of birth control from the time that you sign this form until at least 4

weeks after your last dose of the study drugs. You will be asked to take a pregnancy test within 3 days of starting treatment. We may ask you to take another pregnancy test later in the study if there are any changes to your periods.

You will be asked to use any two of the followingbirth control methods:

- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier method of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

You could get pregnant even if you are using birth control. Tell your doctor if you think that you might be pregnant.

Men on the study:
Youmust use birth control if there is any chance that you could father a child. Use an effective method of birth control from the time that you sign this form until at least 16 weeks after your last dose of the study drugs. You and your female partner will be asked to use any two of the following birth control methods:

- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier method of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Tell the study doctor if your partner gets pregnant during the study or within 6 months after stopping treatment. The risk to your partner and the baby are unknown.

Risks we don't know about yet: The experimental treatments may have side effects that no one knows about yet, as there is limited safety information on the use of BKM120 and /or the combination of BKM120 and vemurafenib in humans. The researchers will let you know if they learn about any new side effects. You can always change your mind about participating in the study if you are worried about these new side effects.

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

Are there benefits to taking part in the study?
Vemurafenib is an approved drug that shrinks melanoma tumors about half of the time. It could also help you to live longer. Doctors hope that adding BKM120 to vemurafenib will make it work better, but there is no proof of this. This study will help doctors to learn more about how to treat your type of cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?
Your other choices may include:

- Getting standard treatment for your cancer without being in a study. This may include Vemurafenib outside of this study, chemotherapy, ipilimumab or Interleukin-2 (IL-2)
- Taking part in another study.
- Getting no treatment.
- Getting treatment for symptoms only.

Please talk to your doctor about your choices before deciding if you will take part in this study.

Will my medical information be kept private?
Your personal information may be given out if required by law. Your name and other personal information will not be used in scientific journals or meetings. Some groups will be able to look at your information including:

- Novartis Corporation, and its authorized agents
- The US Department of Health & Human Services, including the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP), which are involved in keeping research safe for people
- The UCSF committee on Human Research
- Staff of the UCSF Helen Diller Family Comprehensive Cancer Center
- Governmental agencies in other countries where the study drug may be considered for approval
- The University of California

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

What are the costs of taking part in this study?
You or your health insurance company will need to pay for some of the costs of treatment on this study. These are usually the costs that you or your insurance company would have to pay for any standard cancer treatment. These may include office visits, CT and MRI scans, blood tests and EKGs. Some health plans will not pay these costs for taking part in studies. Check with your health plan/insurance company to find out what they will pay for. You will not be charged for any procedureslabeled “study procedures”. This includes tumor biopsies, questionnaires about your emotional health and blood sugar testing and blood tests to measure how much study drug is in your body.Taking part in this study may cost you or your insurance company more than the cost of getting regular cancer treatment.
BKM120 will be supplied to you at no charge.

Vemurafenib will be billed to your health insurance. You will not be billed for any clinic visits or any of the tests that would not usually be covered by your health insurance.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can get a copy of the "Clinical Trials and Insurance Coverage" information from this Web site or by calling **1-800-4-CANCER (1-800-422-6237)**.

Will I be paid for taking part in this study?
You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor, Dr. Alain Algazi, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him at 415-353-9900.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415- 476-1814.

If you are injured, Novartis will not provide payment for any medical expenses which you may incur as a result of your participation in this study.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor Alain Algazi, MDat 415-353-9900.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you want to participate in this study and all of your questions have been answered, you should sign below.

_____ _____

Date Participant's Signature for Consent

_____

Print name

_____ _____

Date Person Obtaining Consent

_____

Print name

_____ _____

Date Witness – Only required if the participant is a non-English speaker

Contact Numbers:

Dr. Alain Algazi, UCSF Melanoma Clinic:	(415) 353-9900
Urgent calls (24 hrs/day, 7 days/week):	(415) 353-9900
Michael Buljan, practice nurse:	(415) 353-9900
UCSF Committee on Human Research:	(415) 476-1814

Timeline to Start Treatment

Phase 1 participants

Sign consent form	2 Weeks Before Start of Daily Treatment - Stop taking BRAF inhibitor **(Part B only)**	Within 14 days - CAT/MRI scans - Blood tests - Heart test -Cancer gene test	Next 7 days - Doctor visit - Tumor sample - Blood tests - 1 dose of BKM120 **(Part A only)**	Start of Daily Treatment - Doctor visit - Blood tests - Start taking both drugs every day - Scans again in 8 weeks

Phase 2 participants

Sign consent form	Within 14 days - CAT/MRI scans - Blood tests - Heart test - Cancer gene test	Start of Treatment - Doctor visit - Blood tests - Start taking both drugs every day - Scans again in 8 weeks

Medications and Foods to Avoid

The following is a list of medications to avoid while you are on this study. If you go to any medical visit, please take this list with you for the doctor's reference. Before you begin treatment, Dr. Algazi or one of his associates will review all medications you are taking. Make sure you talk with Dr. Algazi before you start or stop taking any medications. This list contains only the most common drugs and food that are known to interact with the drugs used in this study. It is very important to discuss all medications that you are taking with your study doctor.

In addition to the listed medications, you should also avoid eating Seville (sour) oranges, grapefruit, starfruit, pomelos, and their juices, and you should avoid using any herbal products.

Generic Name	Brand Names ®	Generic Name	Brand Names ®
Aminoglutethimide	Cytadren	Lapatinib	Tykerb
Amiodarone	Cordarone	Lopinavir	(+Ritonavir = Kaletra)
Amprenavir	Agenerase	Methadone	Methadose, Dolophine
Aprepitant	Emend	Metronidazole	Flagyl
Arsenic Trioxide	Trisenox	Modafinil	Provigil
Atazanavir	Reyataz	Nafcillin	--
Bosentan	Tracleer	Nefazodone	Serzone
Carbamazepine	Carbatrol, Tegretol	Nelfinavir	Viracept
Chloroquine	Aralen	Nevirapine	Viramune
Chlorpromazine	--	Nicardipine	Cardene
Cimetidine	Tagamet	Norfloxacin	Noroxin
Cisapride	Propulsid	Oxcarbazepine	Trileptal
Clarithromycin	Biaxin	Pentamidine	Nebupent
Conivaptan	Vaprisol	Pentobarbital	Nembutal
Cyclosporine	Gengraf, Neoral, Sandimmune	Phenobarbital	Luminal
DHEA	Dehydroepiandrosterone	Phenytoin	Dilantin
Delavirdine	Rescriptor	Pimozide	Orap
Desipramine	Norpramin	Pioglitazone	Actos
Diltiazem	Tiazac, Cartia	Posaconazole	Noxafil
Disopyramide	Norpace	Primidone	Mysoline
Dofetilide	Tikosyn	Procainamide	--
Domperidone	--	Quetiapine	Seroquel
Doxycycline	Vibramycin	Quinidine	--
Efavirenz	Sustiva	Rifabutin	Mycobutin
Ephedra	Ma Huang	Rifampin	Rifadin
Erythromycin	Ery-tab	Rifapentine	Priftin
Etravirine	Intelence	Ritonavir	Norvir
Fluconazole	Diflucan	Saquinavir	Invirase
Fosamprenavir	Lexiva	Saw Palmetto	--
Gingko biloba	--	Sertraline	Zoloft
Ginseng	--	Sotalol	Betapace
Haloperidol	Haldol	St John's Wort	--
Hormonal	Contraceptives	Tacrolimus	Prograf
Ibutilide	Corvert	Telithromycin	Ketek
Imatinib	Gleevec	Tetracycline	Nu-Tetra
Indinavir	Crixivan	Thioridazine	--
Isoniazid	--	Topiramate	Topamax
Itraconazole	Sporanox	Vardenafil	Levitra
Kava	--	Voriconazole	VFend
Ketoconazole	(oral forms only)	Warfarin	Coumadin
		Yohimbe	--