Research Consent Form
for Biomedical Research
Dana-Farber/ Harvard Cancer Center
BIDMC/BCH/BWH/DFCI/MGH/Partners Network Affiliates OHRS 07.17.15

Protocol Title:

Phase II Trial of the PD-1 Antibody Nivolumab in Combination with Lenalidomide and Low Dose Dexamethasone in Patients with High-Risk Smoldering Multiple Myeloma

DF/HCC Principal Research Doctor / Institution:

Irene Ghobrial, MD/ Dana-Farber Cancer Institute

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study because you have smoldering multiple myeloma (SMM). Patients with smoldering multiple myeloma do not have symptoms but are at risk for progressing to active multiple myeloma. Multiple myeloma is a cancer of the plasma cell, which is an important part of the immune system. Patients with active multiple myeloma generally require treatment. There are currently no approved therapies for smoldering multiple myeloma. This research study is evaluating a new drug called "nivolumab" as a possible treatment for smoldering multiple myeloma in order to prevent or postpone development of active multiple myeloma.

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

It is expected that about 41 people will take part in this research study.

Dana-Farber Cancer Institute has a financial interest in the investigational agent used in this trial (Nivolumab) which may be affected by the outcome of this research. The Institute has taken steps to manage any actual or potential conflict of interest created by this financial interest, which are more fully described in the Information Sheet available to all participants

Bristol Myers-Squibb, a pharmaceutical company, is supporting this research study by providing funding for the research study and the study drug.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you

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can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.
We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial, which tests the effectiveness of an investigational drug(s). The investigational drugs used in this research study are nivolumab, lenalidomide, and dexamethasone. Preliminary experience suggests that the combination of lenalidomide and dexamethasone may prevent or postpone SMM from becoming active multiple myeloma. The purpose of this research study is to determine if the addition of nivolumab may improve the rate of prevention in combination with lenalidomide and dexamethasone.

"Investigational" means that the FDA (the U.S. Food and Drug Administration) has not approved the combination of nivolumab, lenalidomide and dexamethasone as a treatment regimen for your specific disease.

Lenalidomide is an immunomodulatory drug derived from thalidomide. Lenalidomide works by stopping blood flow to your cancer cells and signaling your cancer cells to die off. The FDA has approved lenalidomide for the treatment of many types of cancer including multiple myeloma, and myelodysplastic syndromes.

Dexamethasone, also FDA approved, is a type of steroid and is usually combined with other chemotherapy for the treatment of blood cancers, such as myeloma and leukemias.

Nivolumab is approved by the FDA for some lung cancers, some skin cancers, some kidney cancers, and Hodgkin lymphoma. It is currently being evaluated for use in the treatment of several other types of cancers. Nivolumab may kill or stop cancer cells from growing by blocking a signal in your cells allowing your immune system to fight your cancer. This drug is a human monoclonal antibody, which is a molecule that is made in a laboratory that is designed to act identically to cells in your immune system.

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:

- Take part in another research study.
- Observation, meaning no therapy at this time specific to your smoldering Multiple Myeloma

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.

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.

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.

- **Medical History and Physical Exam** will be performed and you will be asked questions about your general health and specific questions about any problems that you might be having and any medication changes.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood Tests** will be done to check your overall health (1-2 tablespoons).
- **24 hour Urine Sample** will be done to test for signs of disease that sometimes does not show in blood or marrow

- **Scans (or Imaging Tests)** will assess your tumor by X-Ray, MRI or PET/CT
- **Electrocardiogram (ECG)** will be conducted to measure the electrical activity and health of the heart (Only required at screening, at end of treatment or if clinically indicated).
- **Blood Pregnancy Test is required if you are** a woman who is able to get pregnant. The test will need to be negative prior to starting Cycle 1.
- **Bone Marrow Aspirate and Biopsy** will be done to evaluate your disease. For the bone marrow aspirate, a sample of bone marrow cells is taken by a needle and inserted into a bone in your body. For the biopsy, a small piece of bone is removed. These tests are done under local anesthesia. Your physician may require this procedure more often to assess your disease.

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

Additional research procedures to be performed at the time of screening but not required to determine eligibility:

- **Blood Sample:** Approximately 2 tablespoons of blood will be drawn for research to assess your disease status by looking at your DNA and RNA (the information in your cells that makes you unique)
- **Bone Marrow Aspirate Sample:** For bone marrow procedures that are done as standard of care, a small amount of extra bone marrow cells will be taken for research tests. This additional sample will be taken at the same time as the other sample; you will not need an additional procedure. The research tests will help determine how nivolumab affects your disease.
- **Buccal Swab** will be collected when you are in clinic at the beginning of the study (or at any time during the trial). The purpose is to harvest your normal DNA. You will not be provided with results about the genetic tests, nor will the information be placed in your medical record.

Study Drug Dosing Table:

Each cycle is 28 days in length.

Cycles 1-6

Drug	Route	Schedule
Nivolumab	Intravenous	Days 1 and 15
Lenalidomide	Oral	Days 1-21
Dexamethasone	Oral	Days 1, 8, and 15

Cycles 7-12 (Maintenance)*

Drug	Route	Schedule
Nivolumab	Intravenous	Days 1 and 15
Lenalidomide	Oral	Days 1-21

*Depending on your disease, your doctor may want you to continue to take dexamethasone during the maintenance portion of the trial. If you do continue to take dexamethasone, you will take it on day 1, 8, and 15 of a 28 day cycle

Nivolumab Administration: This drug will be given as a single dose that will be given to you through a vein in your arm (intravenously) over a 60 minute period once daily on the days instructed.

Lenalidomide Administration: This drug will be given as a single dose that you will take orally once daily on the days instructed. You must record all administrations of this drug at home and in clinic in the study drug diary provided to you.

Dexamethasone Administration: This drug will be given as a single dose that you will take orally once daily on the days instructed. You must record all administrations of this drug at home and in clinic in the study drug diary provided to you.

On Study Visits:
Please see the research study plan below for a full list of tests required at each timepoint on the study. If specified, visits will involve the following:

- **Medical History and Physical Exam** will be performed and you will be asked questions about your general health and specific questions about any problems that you might be having and any medication changes.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood Tests** will be done to check your overall health (1-2 tablespoons).
- **24 hour Urine Sample** will be required, which you will return to clinic on Day 1 of each cycle for some patients whose disease is assessed by their urine result. This is to perform a specific test that shows signs of disease that sometimes does not show in blood or marrow.
- **Scans (or Imaging Tests)** will assess your tumor by X-Ray, MRI or PET/CT at the end of your treatment.
- **Electrocardiogram (ECG)** will be done to measure the electrical activity and health of the heart (Only required at screening, at end of treatment or if your doctor thinks that it is necessary).
- **Blood Pregnancy Test** is required if you are a woman who is able to get pregnant. The test will need to be negative within 24 hours of starting Cycle 1 and then again every cycle thereafter on Day 1.
- **Bone Marrow Aspirate and Biopsy** will be done to look more closely at your disease. For the bone marrow aspirate, a thin needle is inserted into a bone in your body and a sample of your bone marrow cells is taken out. For the biopsy, a small piece of bone is removed during the same procedure. These tests are done under local anesthesia. Your physician may require this procedure more often to assess your disease.
- **Side Effects** will be assessed by your research doctor

Research Study Plan:

Tests and Procedures	Screening	Cycles 1-12 Day 1	Cycle 7 Day 1 or to Confirm CR	End of Treatment	Follow-Up Every 3 Months

Medical History and Physical Exam	X	X		X	X
Blood Tests	X	X		X	X
Urine Test	X	X		X	X
X-Ray/ PET-CT/ MRI[3]	X			X	
EKG	X			X	
Pregnancy Test (if applicable)	X	X			
Bone Marrow Aspirate and Biopsy	X		X	X	
Research Bone Marrow Aspirate[2]	X		X	X	
Research Blood Sample[2]	X	X	X	X	
Research Buccal Swab[1]	X				

1 Can be obtained at any time during the study
2 Research samples are mandatory on this trial
3 You will be required to either get an X-Ray and an MRI of your spine, or a PET/CT for this trial

Planned Follow-up:

We would like to keep track of your medical condition every three months for up to three years after you have completed the research study. We would like to do this by seeing you and completing routine blood and urine tests. Keeping in touch with you and checking your condition every three months helps us look at the long-term effects of the research study.

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

You will be in this research study for about 14 months and be followed for an additional 3 years.

The research doctor may decide to take you off the research study for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens

- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

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

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

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

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

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

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.
Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

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

Additional Safety Information from the Food and Drug Administration and Bristol-Myers Squibb:

In two clinical trials, patients with multiple myeloma were recently stopped from taking pembrolizumab (a drug which destroys cancer cells by working with the immune system) if they were also being treated with lenalidomide (or pomalidomide) and dexamethasone. The treatment was stopped because a higher number of deaths were seen when patients were treated with pembrolizumab together with lenalidomide (or pomalidomide) and dexamethasone.

• Keynote-183 was a randomized trial which evaluated pomalidomide and low-dose dexamethasone with or without pembrolizumab in patients with relapsed and refractory multiple myeloma. This trial showed an overall survival hazard ratio of 1.61 (95% CI: 0.91, 2.85) in the pembrolizumab-containing arm compared to the control arm, which did not contain pembrolizumab. With the current information, on an average it is estimated that the risk of death in the pembrolizumab treated arm is 1.6 times that of the control arm which did not contain pembrolizumab.

• Keynote-185 was a randomized trial which evaluated lenalidomide and low-dose dexamethasone with or without pembrolizumab in patients with newly diagnosed multiple myeloma. This trial showed an overall survival hazard ratio of 2.06 (95% CI: 0.93, 4.55) in the pembrolizumab-containing arm compared to the control arm, which did not contain pembrolizumab. With the current information, on an average it is estimated that pembrolizumab doubles the risk of death compared to the control arm which did not contain pembrolizumab

Some patients in these studies developed fatal, serious side effects, including inflammation of the heart (myocarditis), rash with peeling of skin and/or mucous membranes, heart attack, cardiac arrest, cardiac failure, bleeding of the heart lining, respiratory tract infection, respiratory failure, blood clots in the

lungs, sepsis, multiple organ failure, suicide, and sudden death. Some of the causes of death are unknown at this time.

Although nivolumab is not the same drug, it works in a similar way and these findings may be relevant for your treatment in this study.

Your study doctor may recommend that you stop treatment if he/she thinks the study treatment does not result in benefit or could be unsafe for you.

If your treatment is stopped, you will be asked to return for safety follow-up visits at 28 days after the end of treatment visit and at 90 days after your last dose of nivolumab.

Risks Associated with Nivolumab

Most Common (More than a 50% chance that this will happen)

- Fatigue
- Skin reactions: including rash, itching, hives, redness, and dry skin.
- Diarrhea
- Vomiting
- Nausea
- Decrease in the number of white blood cells that fight infection, which can lead to infections which may be serious or life threatening (neutropenia and eosinophilia)

Less Common (Chance of 1-10% that this will happen)

- Underactive thyroid gland which may be associated with weight gain, heart failure, and or constipation
- Overactive thyroid gland which may cause weight loss, fast heartbeat, and or sweating
- High blood sugar which if severe, may require urgent treatment
- Inflammation of the intestines and colon which could cause fever, abdominal pain, diarrhea, and sometimes blood in the stool (colitis)
- Mouth blisters or sores (stomatitis)
- Abdominal pain
- Weight loss
- Constipation
- Dry mouth
- High body temperature or fever

- Buildup of fluid in the body just under the skin in the limbs or face (fluid retention)
- Infusion reaction which may include fever, dizziness, change in blood pressure, shortness of breath, or pain at the site of the infusion
- Lung and upper respiratory infections (like pneumonia and bronchitis) that can be serious or life threatening. If uncontrolled, it can lead to an infection of the blood stream (sepsis) which can be fatal.
- Other infections of the body including skin infections.
- Liver function abnormalities, which is when there are abnormally high levels of enzymes produced by the liver in your blood, meaning that your liver is not functioning properly and can cause fatigue, and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, this can be serious or life threatening. This can be a sign of liver damage due to inflammation (hepatitis) which could lead to fatigue, jaundice, and mild to severe side effects which could require hospitalization and or surgery.
- Low level of sodium in the blood which may cause confusion, dizziness, or fatigue which may require intervention (hyponatremia)
- Decreased appetite
- Muscle and joint pain
- Inflammation of the joints which can be accompanied by swelling and stiffness (arthritis)
- Inflammation of the joints due to an immune response that can cause tissue and joint damage (rheumatoid arthritis)
- Nerve damage to the arms and feet which may result in numbness, pain and or loss of motor function which can be permanent (peripheral neuropathy)
- Headache
- Dizziness
- Decreased kidney function due to inflammation which could cause a buildup of waste in your blood, and in severe cases, require dialysis
- Shortness of breath (hypoxia)
- Cough
- Condition where patches of your skin turn lighter than the surrounding skin (vitiligo)
- Hair loss
- High blood pressure

Rare (Chance of less than 2% that this will happen)

- Inflammation of the blood vessels that can damage different organs (vasculitis)
- Rash-like bumps on the face (rosacea)
- Red dry scaly patches on the skin (psoriasis)
- Damage to the kidneys causing organ failure which may require dialysis (nephritis and renal failure)
- Damage to nerves due to a problem with your immune system which can cause muscle weakness, pain and numbness (Guillain-Barre Syndrome)
- Weakness in the muscles of your face and other parts of your body
- Muscle pain
- A condition where the lymph nodes swell, and sometimes have a fever and a decrease in white blood cells (histiocytic necrotizing lymphadenitis)
- Lung Inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.
- Allergic reaction to nivolumab or components of nivolumab which could be life threatening
- Intestinal ulcer
- Diabetes mellitus
- Severe high blood sugar caused by uncontrolled diabetes (ketoacidosis)
- Inflammation of the thyroid gland which could cause tenderness in the neck
- Inflammation of the pituitary gland which may cause headaches, changes in eyesight, affect the menstrual cycle of women, increase in thirst, and an increase in urination
- Adrenal insufficiency which results in decrease of hormones in your blood and may cause fatigue, weakness, confusion, weight loss, dizziness, loss of appetite, low blood pressure, nausea or vomiting
- Fast heartbeat (tachycardia)
- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis)
- Problems with the heart, including palpitations, atrial fibrillation, and ventricular arrhythmia and an inflammation of the heart wall (myocarditis)
- Dehydration
- Inflammation of the pancreas that can cause severe stomach pain, nausea, vomiting, and may be life threatening (pancreatitis)
- Inflammation of the optic nerve which can cause pain and temporary vision loss, which usually returns (uveitis)

- Inflammation or loss of the lining of the brain and spinal cord (demyelination) which can cause headaches, fever, nausea, weakness, nerve damage and sometimes paralysis
- Abnormal brain function due to brain inflammation (encephalitis), potentially life-threatening or fatal

Very Rare (Chance of less than 0.1% that this will happen)

- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue. This can include conditions in which the death is skin tissue causes the outer layer of the skin to separate from the middle layer and be serious and life threatening. (Stevens-Johnsons syndrome)

- Toxic epidermal necrolysis: a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe sun burn

Other Risks Associated with Nivolumab

- Solid organ rejection in patients who have previously undergone allogeneic stem cell transplantation and then were treated with nivolumab. Treatment with nivolumab may increase the risk of organ rejection in patients who have received a solid organ or tissue transplant.

- Severe or fatal Graft-Versus-Host Disease, a condition in which immune cells from a tissue transplant donor attacks the organs of its recipient, have been reported in patients who have had a type of bone marrow or stem cell transplant called an allogeneic stem cell transplant that were then treated with nivolumab.

- Patients who have received nivolumab may be at an increased risk of transplant related complications including Graft –Versus-Host Disease, which may be severe or life threatening.

<u>Risks Associated with Lenalidomide</u>

Most Common (More than a 50% chance that this will happen)

- Low number of red blood cells (anemia) which can cause tiredness, shortness of breath, and **m**ay require a blood transfusion
- Constipation or difficult bowel movements
- Diarrhea or loose/frequent bowel movements
- Fatigue

- A serious or life threatening decrease in the number of a type of white blood cell (neutrophil/ granulocyte) that helps to protect against infection which causes an increased risk of infection
- Decreased number of a type of blood cell that help to clot blood (platelet). This may result in bleeding.

Somewhat Common (Chance of 10-50% that this will happen)

- Abnormally low level of thyroid hormones. This may cause fatigue, weight gain, fluid retention, sensitivity to cold and mental apathy. Can be serious or life threatening.
- Nausea or the urge to vomit
- Vomiting
- Chills
- Swelling or tingling of the arms and legs
- Fever
- Infection, which may be serious and life threatening
- A decrease in the number of a type of white blood cell (lymphocyte) and decrease in the total number of white blood cells (leukocytes) which may increase the risk of infection.
- Weight loss
- Loss of appetite
- Back, joint and muscle pain
- Muscle cramps/spasms
- Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Headache or head pain
- Difficulty sleeping or falling asleep
- Cough
- Shortness of breath
- Itching
- Skin rashes that may be flat (macular), raised (papular) or red and irritated.
- Excess sweating
- Formation of a blood clot that may break loose and be carried by the blood stream to plug another blood vessel. May be serious and life threatening. (thromboembolism)

Rare (Chance of less than 1% that this will happen)

- Inflammation of the pancreas. This may cause abdominal pain and require hospitalization and intravenous treatment. It may be accompanied by increased blood levels of a fat-digesting enzyme called lipase.
- Serious life-threatening allergic reaction requiring immediate medical treatment. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Tumor Lysis Syndrome, which is the result of rapid destruction of cancer cells that can occur after treatment of cancer has started and may cause an electrolyte imbalance, increased uric acid buildup (gout), and kidney damage
- Decreased production of blood cells by the bone marrow (marrow aplasia) including cells that fight infection, clot the blood, and carry oxygen to tissue
- Temporary growth in tumor or worsening of tumor-related problems
- Tissue death of a part of the brain without inflammation that may affect different functions of the brain including speech or movement and may be severe or life threatening
- Sudden decrease of kidney function. When the kidneys do not work properly, wastes can build up in your blood, leading to swelling in the arms and legs, tiredness and weakness. This could become severe, requiring hospitalization and dialysis to clean the wastes out of your blood. If the wastes are not removed from your blood, this could cause seizures and be life threatening.
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue. This can include conditions in which the death is skin tissue causes the outer layer of the skin to separate from the middle layer and be serious and life threatening.
- Development of a second cancer including leukemia.

Risks Associated with Dexamethasone

Less Common (Between a 1-10% chance that this will happen):

- Increased blood sugar. If you have diabetes, this may lead to a need to adjust your medications used to treat the diabetes.
- Increased appetite.
- Weight gain.
- Fluid retention (edema), which can cause a buildup of fluid in the body or extremities causing swelling.
- Elevation of blood pressure

- Mood changes (depression, or abnormal feelings of well-being and excitement)
- Difficulty sleeping
- Skin changes leading to thinning and easy bruising
- Gradual changes to bones that may increase their risk of breaking
- Muscle weakness
- Stomach irritation/ulcer
- Increased risk of infection
- Acne

Rare (Less than 1% chance that this will happen):

- Loss of potassium, which may lead to weakness and abnormal heart beats.
- Increased eye pressure in patients with glaucoma which may cause damage to the optic nerve and vision loss
- Gradual development of cataracts, or a clouding of the lens of the eye causing hazy or blurry vision
- If used for a long time, dexamethasone can suppress the function of the normal glands that make steroids. This may cause weakness, confusion, fatigue, listlessness, low blood pressure, dizziness, weight loss, and loss of appetite. May also cause abdominal cramps, nausea, vomiting and diarrhea and changes in electrolytes (body salts). Symptoms may be worse at times of stress, such as high fevers, infection, surgery or a serious accident. If your adrenal glands do not produce enough hormones, you will need to take oral medications to replace the hormones
- Glaucoma, or optic nerve and vision damage which can be caused by an increase in pressure within the eye
- Pancreatitis or an inflammation of the pancreas causing pain in the upper abdomen that can become severe and cause nausea, vomiting, and could require hospitalization and may be life threatening.

Special Considerations

Lenalidomide is a member of a class of drug that causes damage to a fetus (teratogen). It is important that **mandatory** contraceptive measures be used while taking lenalidomide. It also requires special prescription forms (RevAssist) and **frequent counseling.** Your physician will discuss this with you.

Lenalidomide has been shown to increase the level of digoxin in the blood in some patients. Please tell your doctor immediately if you are taking digoxin.

The use of lenalidomide therapy has been known to hinder the collection of your own stem cells in patients with multiple myeloma. If your disease progresses to multiple myeloma and you are deemed a candidate for autologous (using your own cells) stem cell transplant, it is unknown if the long term use of lenalidomide therapy will rule out stem cell collection from your peripheral blood.

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 Bone Marrow Aspiration:

For this procedure, a numbing drug is injected into the skin over one of your hipbones. A needle is then inserted into the hipbone and a sample of bone marrow fluid is removed. Risks of this procedure are small, but may include:

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

Risks Associated with Bone Marrow Biopsies:

For this procedure, a numbing drug is injected into the skin over the same hipbone. A needle is then inserted into the hipbones and a small piece of bone is removed. The risks may include:

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

Radiation Risks Associated with Scans and X-Rays:

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

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

Reproductive Risks:

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

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

Lenalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Findings from a laboratory study indicate that lenalidomide caused birth defects in the offspring of females who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females should not become pregnant while taking lenalidomide. You have been informed that the risk of birth defects is unknown. If you are female, you agree not to become pregnant while taking lenalidomide

Patients with blood cancers who take lenalidomide and dexamethasone have a greater chance of having blood clots. Because of this, it is recommended patients discuss the use of birth control pills or hormone replacement therapy with the study doctor to better understand the risks and benefits of these choices

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?

This study may or may not help you. Taking part in this research study may help researchers learn things that may help people in the future

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

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

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

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

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the nivolumab/ lenalidomide/ dexamethasone. 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?

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

Your participation in this research study may contribute to the development of commercial products from which Bristol-Myers Squibb, Inc or others, may derive

an economic benefit. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit.

You will not be paid to take part in this research study.

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 nivolumab. 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 lenalidomide and dexamethasone. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.
Lenalidomide and dexamethasone are commercially available which means that the FDA has approved them for use in patients with another type of cancer. Because there is evidence that supports using this drug in patients with your type of cancer, you or your insurance company will be billed for the cost of both lenalidomide and dexamethasone.

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

- 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 SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

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

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. The treating hospital may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

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

L. WHAT ABOUT CONFIDENTIALITY?

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

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

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

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

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

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

Dana-Farber Cancer Institute:

- Irene Ghobrial, MD: Irene_Ghobrial@dfci.harvard.edu; 617-632-4198

If you are experiencing an urgent medical issue, please go to the nearest

emergency medical facility, or contact our site to have your physician paged.

24-hour contact: DFCI: Irene Ghobrial, MD (617) 632-3352 and ask for your physician to be paged at beeper 41651

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

N. PRIVACY OF PROTECTED HEALTH INFORMATION

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

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

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

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

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); 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 for the purpose of this or other research relating the study drug and its use in cancer; 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).
- Adaptive, Inc. in Seattle, WA will receive bone marrow samples that directly identify you. However, your identifiers will only be shared with Adaptive, Inc and will not be shared with Dana Farber. The results of these tests will be shared with Dana Farber in aggregate, meaning; the results will not be linked to any information that identifies you. Your samples and related medical information will not be retained for more than 6 months after your samples have been analyzed.
- Bristol-Myers Squibb, who is supporting this research study by providing funding for the research study and the study drug
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.

- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

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

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

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

6. Statement of privacy rights:

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

O. Safeguards of Confidentiality in Studies Involving Genes (Genetic Studies)

A federal law (Genetic Information Non-Discrimination Act, GINA) will help lower the risk from health insurance or employment discrimination on the basis of genetic information. The federal law does not include other types of misuse by life insurance, long term care or disability insurance. If you want to learn more about the GINA Law, which went into effect in 2009, you can find information about it on the internet or ask the study staff. In addition to the federal law, some states have laws that also help to protect against genetic discrimination. While we believe that the risks to you and your family are very low, we cannot tell you exactly what all of the risks are from taking part in genetic research studies. Your privacy and confidentiality will be protected to the fullest extent possible.

P. DOCUMENTATION OF CONSENT

My signature below indicates:

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

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

Adult Participants

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

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

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

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

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is illiterate

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

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

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

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

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

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