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

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Protocol Title: A PHASE II TRIAL OF IPILIMUMAB WITH AND WITHOUT NIVOLUMAB IN PATIENTS WITH RELAPSED/REFRACTORY CLASSIC HODGKIN LYMPHOMA

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INTRODUCTION AND KEY INFORMATION

All research is voluntary. It is your choice whether you take part in this research or not. If you decide to participate, please sign and date at the end of this form. We will give you a copy and you can refer to this consent form at any time.

The following is a short summary of this research study to help you decide whether you would like to be a part of this study. More detailed information is provided later in this form.

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

1. Why am I being invited to take part in a research study?

You are invited to take part in this research study, because you have Hodgkin's lymphoma (HL) that has not improved or gotten worse despite the treatments you have already received, did not respond to previous treatment(s), or for which previous treatment(s) was stopped because the side effects were not tolerable and for which other approved therapies are not indicated.

2. Why is this research being done?

This study is being done to answer the following questions:

What are the effects, both good and bad, when Ipilimumab is given to patients with HL?

What are the effects, both good and bad, when Ipilimumab is given in combination with Nivolumab to patients with HL whose tumor did not shrink when treated with ipilimumab alone?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your cancer. In this study, we will learn about an immunotherapy drug called, Ipilimumab, given alone and Ipilimumab given in combination with Nivolumab. Ipilimumab and Nivolumab will be called “the study drug(s)” throughout this form.

Ipilimumab has been approved by the FDA for the treatment of metastatic melanoma (a type of skin cancer), and specific types of previously treated advanced kidney cancers. It has not been approved for your condition by the Food and Drug Administration (FDA). Nivolumab is a drug which is approved by the United States Food and Drug Administration (FDA) for the treatment of adult patients experiencing relapsed HL who have received at least two prior systemic therapies. We do not know if the study drugs will work on your cancer.

This study is for participants that progressed after previous therapy and will receive Ipilimumab, followed by either continued Ipilimumab or a combination of Nivolumab and Ipilimumab (followed again by a maintenance regimen of Ipilimumab) depending on their response to the initial Ipilimumab treatment.

We are asking you to provide blood for a tissue bank, also called a repository. These samples will be stored indefinitely and may be used and disclosed in the future for research.

3. Who is supporting this research?

The Principal Investigator of this study and Dana-Farber Cancer Institute are the primary sponsors of this study.

Bristol Myers Squibb (BMS) is supporting this research study by providing the study drugs and funding for the study.

4. What does this research study involve and how long will it last?

This research study involves receiving study drugs. After you finish the study drugs, the investigator will continue to follow your condition and watch you for side effects. You will be asked to return to the clinic for follow-up visits.

The names of the study drugs involved in this study are:
- Ipilimumab
- Nivolumab

The research study procedures include screening for eligibility and study treatment including evaluations and follow up visits.
- Participants will initially receive 4 doses of ipilimumab over 12 weeks. Participants who respond (have tumor shrinkage) will continue ipilimumab alone. Participants who do not respond to ipilimumab will have nivolumab added to their treatment regimen for the next 12 weeks.
- You will receive study treatment for up to 27 months and will be followed every 3 months for 2 years after completion of therapy and then every 6 months for the next 5 years.

It is expected that about 10-15 people will participate in this research study.

Information about you and your health is personal and private. Generally, it cannot be obtained without your written permission. By signing this form, you are providing that permission and your information may be obtained and used in accordance with this informed consent and as required or allowed by law. This means that researchers may obtain information regarding your past medical history, as well as specimens and samples from previous health care providers such as hospitals and labs.

5. What are the risks to participating in this study?

There are risks to taking part in any research study. We want to make sure you know about a few key risks right now. There may also be rare, serious and potentially life-threatening side effects. More detailed information is provided in the “What are the risks or discomforts of the research study?” section.

There is a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with other approaches for your cancer.

Risks associated with Ipilimumab:

Common (>20% incidence)

- Diarrhea, nausea
- Tiredness

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Skin: itching; rash, blisters including inside the mouth (can be severe); hives

Risks associated with Ipilimumab in combination with Nivolumab:

Common side effects - Greater than 10% chance this will happen

- ALT increased: lab test result associated with abnormal liver function
- AST increased: lab test result associated with abnormal liver function
- Diarrhea
- Fatigue
- Itching
- Nausea
- Rash

6. Will being in this study benefit me in any way?

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

7. What are my options?

Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment including chemotherapy.
- Decide not to participate in this research study
- Participate in another research study.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to

reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

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.
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 at any time.

A. WHY IS THIS RESEARCH STUDY BEING DONE?

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

In this research study, we are:

- Trying to understand what effects, good or bad, treatment with Ipilimumab, and treatment with ipilimumab in combination with Nivolumab, has on patients with Hodgkin lymphoma. Ipilimumab and Nivolumab are immunotherapy drugs that work by activating your immune system to hopefully kill tumor cells. Prior studies have shown that combining these study drugs can successfully treat other types of cancer.
- Hoping to find out if this approach is better or worse than the usual approach for this type of cancer.

B. WHAT IS INVOLVED IN THE RESEARCH STUDY?

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

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

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Demographic information,** which includes your age, gender, race, and
- ethnicity.
- **A complete physical exam**, including height, weight, and vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- **Performance status**, which evaluates how you are able to carry on with your usual activities.

- **An assessment of your tumor** by PET/CT (Positron Emission Tomography/Computerized Tomography) scan. This is a tumor assessment to measure the degree of your disease.
- **Blood tests**, approximately 2 ½ tablespoons of blood will be drawn for the following tests:
    - Standard laboratory tests including blood cell counts, liver and kidney functions, and blood clotting ability
    - Tests for the number and type of immune cells in your blood
    - Laboratory tests for previous or current viral infection including hepatitis B virus and hepatitis C virus. If you have positive test results for hepatitis B or C, you will be notified. Positive results may need to be reported to health authorities according to local regulations. If you do not want to be tested, you should not take part in this research study.
    - If you are a woman who can become pregnant (even if you have had your tubes tied), a urine and/or blood pregnancy test will be performed. The date of your last menstrual period will be recorded.
- **Electrocardiogram** (ECG), a tracing of your heart's rhythm
- **Urine test,** the research personnel will collect a urine sample for standard laboratory tests.

Your previously collected and stored tissue (archival tissue) may be obtained for tests.

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

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

- **Research blood** sample, will be drawn for research to assess your disease status and to assess the proteins within your cancer cells (approximately 2-3 tablespoons)
- **Tumor Biopsy**, you will be asked to undergo a biopsy of your tumor if your study doctor determines that the procedure can be performed safely. You can still take part in this research study, even if you do not agree to donate this sample.

Study Treatment Overview:

- **Infused Study Drug(s):** You will be given the study treatment(s) once every 3 weeks into your vein (by intravenous infusion) over a period of about 1.5 - 2.5 hours. This will continue for 12-24 weeks. Afterwards, you will receive an infusion of a single study drug (Ipilimumab) every 12 weeks for up to 96 weeks.

Study Visit: Day 1 of Cycles 1-4 (each cycle is 3 weeks), Day 1 of re-induction Cycles 1-4 (each cycles is 3 weeks) only for patients who do not achieve a response to ipilimumab alone, and Day 1 of maintenance cycles (up to 8 cycles, each cycle is 12 weeks).

These visits will involve the following:

- **Infused Study Drugs**
- **Physical Exams,** including medical history
- **Vital Signs:** Blood pressure, heart rate, temperature, respiration rate, oxygen saturation, height, and weight
- **Performance status**, which evaluates how you are able to carry on with your usual activities
- **Scans (or Imaging tests)**, by CT or PET/CT after 12, 24, and 36 weeks of therapy. Afterwards, participants will have imaging tests every 24 weeks while receiving study treatment.
- **Blood tests**, (up to 2 teaspoons) from your vein for routine lab tests to check your health
- **Pregnancy test**, if you are a woman of child-bearing potential
- **Biobanking**, biological specimens (blood) will be collected and banked for future use. The specimens will not be identifiable.

Study Visit: End of Treatment

This visit will involve the following:

- **Physical Exam**
- **Vital Signs**,
- **Performance status**
- **Blood tests,** (up to 2 teaspoons) from your vein for routine lab tests to check your health
- **Scans (or Imaging tests)**, by CT (Computerized Tomography) or positron emission topography with CT (PET-CT) will be done to look for the presence of Hodgkin lymphoma

- **Biobanking**, biological specimens (blood) will be collected and banked for future use. The specimens will not be identifiable.

Study Visit: Follow-Up
You will come in every three months for 2 years and then every six months for 3 years thereafter.

These visits will involve the following:
- **Physical Exam**
- **Vital Signs**,
- **Performance status**
- **Blood tests,** (up to 2 teaspoons) from your vein for routine lab tests to check your health
- **Scans (or Imaging tests)**, by CT (Computerized Tomography) or positron emission topography with CT (PET-CT) will be done to look for the presence of Hodgkin lymphoma. After completion of study therapy, participants will have scans every 24 weeks for the first 2 years (up to 4 scans).

C. 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 study drugs 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.

Risk associated with Ipilimumab:

Very Common (More than a 20% chance that this will happen)

- Diarrhea
- Nausea
- Tiredness
- Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:
    - Skin: itching; rash, blisters including inside the mouth (can be severe); hives

Occasional (Between 4-20% chance that this will happen)

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain
- Difficulty swallowing or eating
- Constipation, vomiting
- Weight loss, loss of appetite
- Fever
- Dehydration
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Low blood pressure which may cause feeling faint

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine.
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

Rare and serious (Less than 3% chance that this will happen)

- Bleeding
- Blockage of the bowels which may cause constipation
- Fluid around heart
- Severe illness with multiorgan failure
- Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion
- Confusion

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.

Risks Associated with Nivolumab plus Ipilimumab:

Common (More than a 10% chance that this will happen)

- Abnormal liver tests, which may indicate liver damage.
- Decreased appetite
- Diarrhea
- Fatigue
- Fever
- Decreased thyroid function (hypothyroidism). This may cause fatigue, weight gain, fluid retention, sensitivity to cold & mental apathy. Can be serious or life-threatening
- Itching
- Nausea
- Increased level of lipase in the blood (an enzyme produced by the pancreas in the blood), which may indicate inflammation of the pancreas, and may cause abdominal pain and discomfort and could require hospitalization and intravenous treatment.
- Musculoskeletal pain (pain in the muscles and bones)
- Rash

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

- Abdominal pain
- Adrenal gland function decreased (adrenal insufficiency), which may cause weakness and/or low blood pressure
- Increased amounts of liver and bone enzymes, which may indicate damage to liver or bone. You may experience no symptoms related to this abnormal laboratory finding.
- Allergic reaction/hypersensitivity
- Increased level of amylase in the blood (an enzyme produced by the pancreas), which may indicate inflammation of the pancreas, and may cause abdominal pain and discomfort and could require hospitalization and intravenous treatment.
- Increased level of bilirubin in the blood (hyperbilirubinemia).
- Abnormally high levels of enzymes produced by the liver meaning that your liver is not functioning properly and can cause fatigue, and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, this can be serious or life threatening.
- Chills
- Constipation
- Cough
- Increased level of creatinine in the blood (a substance normally eliminated by the kidneys into the urine), which may indicate decreased kidney function.
- Dehydration
- Dizziness
- Diabetes
- Dry eye
- Dry mouth
- Dry skin
- Hair loss
- Heart rate increased (tachycardia)
- Headache
- Increased blood sugar (hyperglycemia), which if severe may require hospitalization and urgent treatment (diabetes)
- Inflammation of the eye (uveitis), which may cause redness or pain.
- Inflammation of the colon (may also include small intestine) (colitis), which may cause rectal bleeding, bloody diarrhea, abdominal cramps, and pain.

- Inflammation of the mouth (stomatitis), which may cause blisters or sores in or around the mouth.
- Inflammation of the pancreas (pancreatitis), which may cause pain in the upper abdomen. This could become severe and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening.
- Inflammation of the pituitary gland (hypophysitis), which may cause headaches, change in eyesight, few to no menstrual cycles (for women), increased thirst, and increased frequency passing urine.
- Inflammation of thyroid gland (thyroiditis), which may cause fatigue, weight gain, constipation, dry skin.
- Infusion-related reaction, which may cause dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sickness to your stomach, or pain at the site of infusion. Although usually reversible with treatment, it can be severe or life threatening.
- Inflammation of the liver (hepatitis), which may cause you to feel not hungry, tired, have a mild fever, muscle or joint aches, nausea and vomiting and stomach pain.
- Joint pain or stiffness
- Loss of color (pigment) from areas of skin (vitiligo)
- Low blood pressure (hypotension), which may cause dizziness, lightheadedness or fainting.
- Inflammation of the lung (such as pneumonitis), which may cause shortness of breath and difficulty breathing. If severe, this can be life threatening.
- Redness (of the skin)
- Kidney problems or failure
- Shortness of breath (dyspnea)
- Decreased sodium levels in the blood (hyponatremia). This can cause confusion, seizures, fatigue and low levels of consciousness
- Swelling, including face, arms, and legs
- Overactive thyroid gland (hyperthyroidism). This may cause weight loss, rapid heartbeat, sweating, trouble with heat, nervousness. May require medical intervention to resolve symptoms
- Thyroid stimulating hormone increased (lab test associated with abnormal thyroid function)
- Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet

- Vision blurred
- Vomiting

Rare (Between a 0.1-1% chance that this will happen)

- Inflammation of the lining of the bronchial tubes (bronchitis), which may cause chest congestion (where your chest feels full or clogged), cough that may bring up a lot of mucus or shortness of breath.
- Cranial nerve disorder (when one or many of the nerves in your nervous system and brain are not functioning properly), which may cause facial pain, dizziness (vertigo), hearing loss, weakness or paralysis.
- Diabetes complications resulting in excess blood acids
- Disease caused by the body's immune system attacking healthy organs
- Double-vision
- Drug-induced liver injury
- Erythema multiforme (a type of self-limiting allergic skin reaction which in most cases can occur in response to an infection or sometimes by certain medicines)
- Guillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
- Heart rhythm abnormal (arrhythmia), which may be serious or life threatening.
- High blood pressure (hypertension)
- Hives
- Inflammation of the brain (encephalitis), which may cause headache, confusion, problems with speech or hearing, paralysis, loss of sensation, seizures, and/or coma and may be serious, life threatening, or fatal
- Inflammation of the heart muscle (myocarditis), which may cause shortness of breath, fatigue, decreased exercise tolerance, chest pain, swelling in the ankles or legs, irregular heartbeat and fainting. This may be serious and require hospitalization
- Inflammation of the kidney (nephritis); symptoms may include frequent urination, pain in pelvis, and swelling of the body and may lead to failure of the kidneys.
- Inflammation of the stomach (gastritis), which may cause abdominal pain, nausea, and vomiting. Sometimes, there are no symptoms.
- Lung infiltrates associated with infection or inflammation
- Muscle inflammation

- Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles.
- Pemphigoid: blistering of the skin or mouth caused by the immune system attacking healthy tissue
- Hypophysitis, which could lead to headache, visual disturbance, and hormone deficiencies
- Psoriasis: characterized by patches of abnormal, scaly skin
- Rhabdomyolysis: muscle fiber released into the blood stream which could damage your kidneys
- Respiratory failure or distress
- Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes
- Upper respiratory infection

Very Rare (Less than a 0.1% chance that this will happen)

- Anaphylactic reaction (severe allergic reaction), which may cause difficulty breathing, low blood pressure, and/or organ failure. This can be life-threatening.
- Diabetes complications resulting in diabetic coma
- Rupture of the intestine/hole in the intestine
- Inflammation of the lining of the brain and spinal cord (meningoencephalitis), which may cause headaches, seizures, and/or coma
- Inflammation of blood vessels
- Polymyalgia rheumatica (an inflammatory disorder causing muscle pain and stiffness)
- Rosacea: acne-like skin condition resulting in redness of face
- Syndrome associated with fever, white blood cell activation and abnormal function (including destruction of other blood cells by certain white blood cells), low blood cell counts, rash, and enlargement of the spleen
- Stevens Johnson Syndrome (SJS): inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin.
- Toxic Epidermal Necrolysis (TEN): a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn.

Lung Inflammation (pneumonitis): It is possible that nivolumab may cause

inflammation of the tissues of the lung. This adverse effect has been reported in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. 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.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms. Monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body’s ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Complications, including fatal events, have occurred in patients who received allogeneic hematopoietic stem cell transplantation (HSCT) before or after nivolumab. Complications, including rejection, have also been reported in patients who have received an organ or tissue transplant. Treatment with nivolumab may increase the risk of rejection of the organ or tissue transplant.

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

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

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

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

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

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the CT or PET scan. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.
Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
The drugs used in this research study may affect a fetus.

While participating in this research study and for 2 months after your last dose of a study drug, you should not:

- become pregnant
- nurse a baby
- father a baby
- donate eggs or sperm

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.

If your partner becomes pregnant while you are on the study, 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.

Risks of Tissue Collection for Biobanking:
Generally, hospitals will keep some of your tissue. There is a small risk that when this tissue is collected and the sample is submitted to the biobank, your tissue could be used up and unavailable for use in the future.

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.

D. WHAT WILL HAPPEN IF I AM REMOVED FROM THE STUDY OR DECIDE TO END MY PARTICIPATION IN THE RESEARCH?

You may be taken off the research study for any reason including:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- You are a female and become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to end the study

- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

You can also choose to stop participating 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.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the study drugs.

In some cases, the abrupt stopping of a drug can have risks in itself. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

It is important to note that although you may withdraw from study participation, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from study records. Additionally, the research doctor may consult public records after you have withdrawn from the study.

If you agree to allow your tissue/blood to be kept for future research with identifying information that could link your sample to you, you may withdraw your permission at any time. We ask that you contact your study doctor and let them know you are withdrawing your permission for your identifiable tissue/blood to be used for future research.

If you decide to withdraw from a study that involves de-identified samples, it will not be possible to remove the samples that have already been submitted to a biobank.

E. WHAT ARE THE BENEFITS OF THIS RESEARCH STUDY?

Taking part in this research study may or may not benefit you. We hope the information learned from this research study will provide more information about how best to treat your cancer.

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

You will not be paid for participating in this study.

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

G. WHAT ARE YOUR COSTS?

Taking part in this research study may lead to added costs to you or your insurance company. This may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your disease. You may:

- Have more travel costs
- Need to take more time off work
- Have other additional personal costs

You will not be charged for the study drugs while you are participating in this study.

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

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. Standard of care is the care that you would receive regardless of whether you were enrolled in the study or not. You may be responsible for co-payments, co-insurance, premiums and deductibles that are typical for your insurance coverage. This includes the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests, done for research only, are supplied at no charge.

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

- Brigham and Women's Hospital: (617) 732-5524 or (617) 732-7485

- Dana-Farber Cancer Institute: (617) 632-3455

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)

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

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

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments may be billed to you or your insurance company. You will be responsible for deductibles, co-payments and co-insurance. There are no plans to pay you or give you other compensation for the injury.

You do not give up your legal rights by signing this form.

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

If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in this research. If possible, you should give them a copy of this consent form.

The study sponsor BMS may pay for the cost of medical treatment. The treating institution and the study sponsor will be responsible for determining what costs may be covered by the study sponsor. You or your insurance company will still be responsible for costs that are not covered by the study sponsor.

I. 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
- Reid Merryman, MD: (617) 632-6844

24-hour contact: DFCI: Reid Merryman, MD at 617-632-6844 (business hours) or page at (617) 632-0000 beeper 58741.

Massachusetts General Hospital
- Jeremy Abramson, MD (617-724-4000 or 617-726-8743)

24-hour contact: MGH: Jeremy Abramson, MD at 617-724-4000 or 617-726-8743.

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

J. RETURN OF RESEARCH RESULTS

Tests done on samples in this research study are only for research and have no clear meaning for your health care. For this reason, your study doctor will not share the results with you.

K. CLINICALTRIALS.GOV (CT.GOV)

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.

L. FUTURE USE OF DATA AND SPECIMENS

Your personal information and/or biospecimens collected during this study may be stored and used for future research. Any personal identifiers will be removed, before they are shared, so that the information or samples cannot be linked back to you. As a result, we will no longer be able to identify and destroy them.

Investigators, including investigators from collaborating institutions, can request this data and samples for new research. Samples and data may also be shared with outside non-profit academic investigators as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate.

You will not be asked to provide additional informed consent for the use of your de-identified information or samples in future research.

Future research studies may include genetic research. Your genes are unique to you. At this time, you cannot be identified through this research, if the samples and specimens are de-identified. There is a risk that you might be reidentified in the future as genetic research progresses

M. 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 research database.

Participation in this study involves providing a specimen of your tissue; please know that if the research doctor leaves the institution, the research and the tissue

might remain at the research doctor's current institute or might be transferred to another institution.

The study team plans to publish the results of this research study and when we do, we may be asked to make the data we collect available to other researchers. We will not include information that identifies you in any publications or to the researchers who request the data to do additional research.

Your de-identified specimens or genetic data may also be placed into one or more publicly-accessible scientific databases. Through such databases, researchers from around the world will have access to de-identified samples or data for future research.

There is a risk that de-identified research data that is shared with outside collaborators may be reidentified. When de-identified data and specimens are shared with outside collaborators agreements limit what the outside collaborators can do with the information to help prevent reidentification.

N. FINANCIAL DISCLOSURES

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

O. GENETIC RESEARCH

This research will involve genomic and germline testing.

The Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects Americans from being treated unfairly because of differences in their DNA that may affect their health, and may prevent discrimination by health

insurers and employers based on genetic information. GINA is intended to ease concerns about discrimination that might keep some people from getting genetic tests that could benefit their health, and enable people to take part in research studies such as this without fear that their DNA information might be used against them by health insurers or their workplace. This protection does not extend to disability or life insurance. Additional information can be found at http://www.genome.gov/10002328.

As part of this study, your de-identified specimens or genetic data may be placed into one or more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). Through such databases, researchers from around the world will have access to de-identified samples or data for future research.

P. PRIVACY OF PROTECTED HEALTH INFORMATION (HIPAA AUTHORIZATION)

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

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

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

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

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;

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

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

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

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

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

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, representatives, business partners, and its agent(s): Principal Investigator and Dana-Farber Cancer Institute
- 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?”

Q. CONSENT TO OPTIONAL RESEARCH STUDIES:

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

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

Optional Study #1:

During the study, the study team may want to collect more tumor tissue (biopsy); this is optional. A repeat tumor biopsy will be performed if the biopsy can be performed safely. An effort will be made to sample the same tumor site that was biopsied during the screening phase of the study, but an alternative site of tumor may need to be biopsied. During the study, if you have any medical non-study related procedures that resulted in collecting more tumor tissue, if there are left over tissue, we would like to collect this unused tissue. The tumor tissue obtained will be sent for biomarker testing as described above. This tissue will help researchers better understand why some subjects respond to treatment, while others do not, or to understand why some subjects who respond to treatment, then stop responding after a period of time.

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

☐ Not applicable

☐ Yes _____Initials _____Date

☐ No _____ Initials _____Date

R. DOCUMENTATION OF CONSENT

My signature below indicates:

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

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

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

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

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

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

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

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

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

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

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

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

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