Informed Consent Form

Phase II trial of IXAZOMIB and Dexamethasone versus IXAZOMIB, Dexamethasone and Lenalidomide, Randomized with NFKB2 rearrangement. (Proteasome Inhibitor NFKB2 Rearrangement Driven Trial, PINR)

NCT Number: NCT02765854

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EMORY | WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

You Are Being Asked to Be in a Research Study

What Is a Research Study?

The main purpose of research studies is to gain knowledge. This knowledge may be used to help others. Research studies are not intended to benefit you directly, though some might.

Do I Have to Do This?

No. Being in this study is entirely your choice. If you decide to join this study, you can change your mind later on and withdraw from the research study.

Taking part in a study is separate from medical care. The decision to join or not join the research study will not affect your status as a patient.

What Is This Document?

This form is an informed consent document. It will describe the study risks, procedures, and any costs to you.

This form is also a HIPAA Authorization document. It will describe how your health information will be used and by whom.

Signing this form indicates you are willing to take part in the study and allow your health information to be used.

What Should I Do Next?

1. Read this form, or have it read to you.
2. Make sure the study doctor or study staff explains the study to you.
3. Ask questions (e.g., time commitment, unfamiliar words, specific procedures, etc.)
4. If there will be medical treatment, know which parts are research and which are standard care.
5. Take time to consider this, and talk about it with your family and friends.

Emory University and Grady Health System
Consent to be a Research Subject / HIPAA Authorization

Title: MMRC060: Phase II trial of IXAZOMIB and Dexamethasone versus IXAZOMIB, Dexamethasone and Lenalidomide, Randomized with NFKB2 rearrangement

Principal Investigator: Leon Bernal-Mizrachi, MD

Study-Supporter: Millennium: The Takeda Oncology Company

Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

You are being asked to participate in a research study of an investigational genetic test and an investigational drug combination of ixazomib (MLN9708) and dexamethasone. Based on the results of the genetic test, you will be selected to receive Ixazomib in either a 2 drug combination of ixazomib and dexamethasone or in a 3 drug combination of Ixazomib, dexamethasone and lenalidomide. The study will evaluate which drug combination is better for the treatment of patients with the particular genetic characteristic called “NF-kB2 rearrangement” identified by the test. The test will be done on both your blood and your bone marrow. It will then evaluate if the test will be useful to choose the best treatment for patients in the future that have the same genetic characteristics. “Investigational” means the test and the drugs, ixazomib in combination of dexamethasone, have not been approved by any authority that regulates new medicines, including the US Food and Drug Administration (FDA). Ixazomib, lenalidomide and dexamethasone in combination are approved by the US FDA and are commercially available for the treatment of multiple myeloma. The brand name for lenalidomide is Revlimid®.

Ixazomib is a type of drug called a proteasome inhibitor. Proteasome inhibitors block the action of proteasomes which are found inside all cells, normal and cancerous. They have the important role of identifying and marking damaged proteins so they can be broken down. By blocking the action of proteasomes, damaged protein will accumulate within the cells and cause them to die. Cancer cells are more susceptible to this effect than normal cells. Ixazomib in combination of dexamethasone is considered “investigational” because it has not received approval from the FDA, although it has been

previously tested in humans and there are many ongoing studies using ixazomib for the treatment of multiple myeloma.

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.

What is the purpose of this study?

The purpose of this study is to evaluate the benefit of the 2 drug combination of Ixazomib and dexamethasone and the three drug combination of ixazomib, dexamethasone and lenalidomide in patients with the NF-kB2 rearrangement identified by the genetic test. The study will evaluate the side effects of ixazomib when given with dexamethasone and of ixazomib when given with lenalidomide and dexamethasone. It will also evaluate the effect the 2 drug or the three drug combination has on your cancer.

People invited to participate in this study must be 18 years of age or older and, if female, cannot be pregnant. They must have a diagnosis of multiple myeloma that has not responded or has come back after prior therapy. About 90 subjects will be enrolled in this study overall.

About 90 patients will take part in this study. We plan to enroll 60 patients at Emory and Grady.

What will I be asked to do?

If you decide to take part in this research study, you will undergo the following procedures:

Screening Procedures:

Procedures to determine if you are eligible to take part in a research study are called “screening” procedures. For this research study, the screening procedures include those listed below. These procedures may overlap with procedures you would undergo as part of your routine care, and may be done regardless of whether you join this study. They will be done as an outpatient, and will involve 3-4 hours of your time. You will be seen by a physician, nurse practitioner or physician’s assistant, nurses and medical technicians. All tests must be completed before you receive your first treatment (Cycle 1 Day 1). You must sign this informed consent form before any research procedures may be done.

- A review of your medical history
- A review of any medication(s) you are currently taking; while in the study you should not take St. John’s wort and Ginkgo biloba. Your study doctor will tell you if there are other drugs or dietary supplements you should avoid. Performance status (how well you are able to do your normal activities)
- Vital signs (blood pressure, pulse, and temperature) will be recorded
- A neurologic assessment including a physical evaluation and a questionnaire
- Height and weight will be recorded
- Blood samples (about 3 teaspoons) will be taken for routine tests to check your blood counts (numbers of each type of blood cell), chemistries (to evaluate your overall health status by checking things such as your kidney and liver function). Test to assess your blood clotting will be done.
- An EKG, or electrocardiogram (a test that measures the rhythm of your heart to make sure your heart is functioning properly)

- If you are a woman capable of having children, you will have another blood test to determine if you are pregnant before entering the study (about 1 teaspoon will be collected). This will be done 7-10 days prior to initiation of therapy and again within 24 hours if you are selected to receive lenalidomide
- Blood tests to assess the status of your myeloma.
- Blood test to obtain normal DNA. In this study we will collect about 2 tablespoons of blood during one of your regular lab draws so in that case there will not be an extra needle stick. If you are not scheduled for labs we will ask if you if you are willing to have an extra needle stick to the draw the blood.
- A 24 hour urine collection will be done
- Standard radiologic imaging procedures may be done if you have a plasmacytoma (a solid tumor) to measure the size of your tumor(s) – this can include CT scans (computerized tomography), MRIs (magnetic resonance imaging), and/or other imaging tests
- Skeletal survey - x-rays of the skull, long bones, pelvis and chest. This will be done if it has not been done in the past 4 weeks
- Bone marrow biopsy and aspirate to assess disease status and to perform genetic testing. In addition, we will collect some extra bone marrow for research. We will collect about a half tablespoon of bone marrow, and this will mean at least one extra draw during your regular bone marrow biopsy.

Study Drug Administration:
If you qualify for the study and decide to take part in the study, you will be assigned to one of the treatment groups outlined based on the results of the genetic test

If you **DO NOT have NF-kB2 rearrangement** identified by the genetic test you will receive treatment with the 2 drug combination of Ixazomib and dexamethasone.

If you **DO HAVE NF-kB2 rearrangement** identified by the genetic test, you will be randomly selected (like the flip of a coin) to receive either the 2 drug combination of ixazomib and dexamethasone **or** the 3 drug combination of ixazomib, dexamethasone and lenalidomide.

You and your study doctor will not have a choice in which treatment you will receive. It will be determined by the test and the random selection.

The treatments are described below. Each treatment cycle is 28 days.

Treatment group – Ixazomib and dexamethasone:

- Ixazomib will be given orally at 4.0 mg on days 1, 8 and 15 of each 28 day cycle. Ixazomib capsule should be swallowed whole and not chewed with an 8 oz. /240 ml glass of water on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Ixazomid should be stored refrigerated.

- Dexamethasone will be given orally at 40 mg on Days 1, 8, 15, and 22 of each 28 day cycle.

Treatment group – Ixazomib, dexamethasone and lenalidomide:

- Ixazomib will be given orally at 4.0 mg on days 1, 8 and 15 of each 28 day cycle. Ixazomib capsule should be swallowed whole and not chewed with an 8 oz. /240 ml glass of water on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Ixazomib should be stored refrigerated.

- Dexamethasone will be given orally at 40 mg on Days 1, 8, 15, and 22 of a 28 day cycle.

- Lenalidomide will be given orally at 25 mg on Days 1 through 21 of each 28-day cycle and should be taken once daily at about the same time each day, either with or without food. The capsules should not be opened, broken, or chewed. Lenalidomide should be swallowed whole with water.

All patients will be treated with up to 4 cycles of therapy and then your disease will be re-evaluated. Treatment may continue for 8 cycles or longer, as long as your disease is not getting worse, the side effects are acceptable and you agree to continue treatment.

Monitoring / Follow-up Procedures:
During your treatment cycles, you will undergo the procedures listed below. They are considered part of your standard medical care and would be performed whether or not you were participating in a research study. These procedures will all take place at the Winship Cancer Institute. The tests are detailed below.

These procedures will be completed on Day One of each cycle (except Cycle One), unless otherwise indicated. The monitoring/follow-up procedures include:

- A review of any medication(s) you are currently taking
- Performance status (how well you are able to do your normal activities)
- A review of any symptoms or side effects you might be having
- Physical examination and neurologic assessment including the questionnaire
- Vital signs (blood pressure, pulse, and temperature) will be recorded
- Weight will be recorded
- Blood samples (about 3 teaspoons) will be taken for routine tests to check your blood counts (numbers of each type of blood cell) and chemistries (to evaluate your overall health status by checking things such as your kidney and liver function) (This can be done the day prior to each Day One.)
- Pregnancy test for women of child bearing potential on day 1 of each cycle. If you are assigned to take lenalidomide, you will also be required to follow the pregnancy testing guidelines of the Revlimid REMS program.
- The skeletal survey will only be repeated yearly and as needed based on your symptoms.
- X-rays and/or scans to measure a plasmacytoma will be repeated every 12 weeks, to confirm a response or as needed based on your symptoms.
- Blood tests to assess the status of your myeloma will be repeated prior to every cycle
- A 24 hour urine test to assess the status of your myeloma will be repeated prior to each cycle
- A bone marrow aspirate may be repeated to confirm your response to treatment. In the event of relapsed or progression, we will collect one extra draw of about a half tablespoon of bone marrow during your regular bone marrow biopsy for research.

Routine blood tests to check your blood counts will be performed on days 1 and 15 of cycle one, then on day 1 of each cycle. This includes blood counts (numbers of each type of blood cell) and chemistries.

For the visits on Day 1 of each cycle, the procedures will take approximately 2 hours to complete and does not include time needed for the administration of your chemotherapy.

Research –Only procedures for all subjects in this study:
The following research-only procedures apply to all subjects involved in this research study.
Blood tests and bone marrow samples will be obtained prior to initiation of treatment and in the event of relapse or progression. These studies will be done for research purposes to evaluate for genetic alterations that can be associated with response to treatment. The tests are being done for research purposes only, and would not be conducted if you were not participating in this research study.

Blood tests for pharmacodynamics will be drawn on day 1 and day 8 of the first combination cycle and on day 1 of the second cycle.

End of Study Visit:
Once your participation in the study is stopped, for any reason, you will have an end of study visit with the tests noted below. These procedures are part of your standard medical care (routine clinical care) that would be performed whether or not you were participating in a research study. These tests will be performed by your study doctor, or a nurse, physician assistant, nurse practitioner, or lab technician under your study doctor's supervision. The tests will take about 3 to 4 hours, and will include:

- Physical examination and neurologic assessment and questionnaire
- Vital signs (blood pressure, pulse, and temperature) will be recorded
- Weight will be recorded
- Performance status (how well you are able to do your normal activities)
- Blood samples (about 2 teaspoons) will be taken for routine blood tests to check your blood counts (numbers of each type of blood cell) and chemistries (to evaluate your overall health status by checking things such as your kidney and liver function)
- A review of any symptoms or side effects that you may be having
- If you have a plasmacytoma, standard radiologic imaging tests to measure the size of your tumor(s) – this can include CT scans, MRIs, and/or other imaging tests, such as x-rays
- Blood tests to assess the status of your myeloma
- A 24 hour urine test
- Pregnancy test if you are a women of child bearing potential
- Skeletal survey may be repeated based on your symptoms
- Bone marrow aspirate and biopsy
- You will be contacted every three months to check on the status of your health and treatments

Once you come off study for any reason beside disease progression, your condition will be followed monthly until progression or initiation of subsequent therapy. If you are removed from the study for unacceptable side effects, you will be followed until resolution or stabilization of the side effects occurs.

How will my medicine be provided?
Ixazomib that you will take will be dispensed by the pharmacy and delivered to the principal investigator or study team member. The principal investigator or health care providers on his/her research team will provide the medicine to you. If you have questions about the medicine, you should ask the principal investigator or study nurse. You may also call the pharmacy if you have questions about the medicine. The number for the pharmacy is included on your medicine package.

Who owns my study information and samples?
If you join this study, you will be donating your samples and study information. You will not receive any compensation if your samples or information to make a new product. If you withdraw from the study, data and samples that were already collected may be still be used for this study.

What are the possible risks and discomforts?
Drugs for cancer are strong and have side effects. As with any experimental procedure, there may be side effects that are currently unknown. Side effects can go away shortly after drug administration is stopped, but some risks could be long-lasting, permanent, serious, life threatening, or even cause death. You should talk to your study doctor about any side effects you have while taking part in the study. The risks involved with this study are listed below:

Potential discomforts and risk of Ixazomib
Taking part in this study has risks. Some of these risks we know about. There is also a possibility of risks that we do not know about and have not been seen in humans to date. Please call the study doctor if you have any side effects even if you do not think it has anything to do with this study. Many discomforts and risks go away shortly after the study drug is stopped or with treatment for the discomforts and risks, but in some cases, discomforts and risks may be serious, long lasting, or permanent and may even result in hospitalization or death.

Based on studies of ixazomib it is possible to predict some of the discomforts and risks. However, it is possible that ixazomib may cause risks that have not yet been observed in patients. The following risks might be seen:

- Low platelet count which may increase the chance of bleeding (30%)
- Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body (11%)
- Nausea (53%)
- Vomiting (38%)
- Diarrhea (44%)
- Numbness or tingling or pain feelings in hands and feet (10%)
- Swelling or fluid buildup in the arms or legs
- Flu-like symptoms and other upper respiratory tract infections
- Arthralgia or joint pain
- Lung infections including pneumonia or pneumonitis
- Herpes Zoster that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time

Other discomforts and risks reported in studies with Ixazomib, which may have been due to the patient's disease, ixazomib, other medications, or some combination of these include:
- Not feeling like eating
- Electrolyte imbalance (blood chemical imbalance)
- Loss of water from the body (dehydration) because of vomiting and/or loose stools
- High blood creatinine and renal failure which means your kidneys are having trouble working well; Patients who had lost body water (dehydration) because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some

severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney (dialysis)
- Feeling short of breath or difficulty breathing
- Lung infections including pneumonia or pneumonitis
- Chills
- Cough
- Fever
- Pain in the abdomen or back
- Muscle weakness
- Feeling dizzy or dizziness
- Lowered blood pressure that can commonly cause you to feel light headed, faint or pass out when you stand up
- Lowered white blood cells called lymphocytes
- Lowered red cells or anemia which may make you feel tired
- Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever
- Constipation
- Pain (muscular) in extremities
- Distortion of the sense of taste i.e. an abnormal or impaired sense of taste
- Trouble falling asleep, staying asleep or both

Some discomforts and risks occur with lesser frequency than those mentioned above, but should be noted because they are severe, life-threatening or fatal. With limited experience and because these events occurred while patients were receiving other drugs as well, we do not know if ixazomib causes such problems. Severe, life-threatening or deadly conditions that may involve rash, blistering, skin peeling and mouth sores including Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute febrile neutrophilic dermatosis (Sweet's syndrome) and pemphigus vulgaris, have been reported in ixazomib studies when given in combination with other drugs. These rashes are disorders of the immune system, which differ from regular skin rashes and are generally more severe.

In addition, two rare neurological conditions have been reported in patients on ixazomib. Posterior reversible encephalopathy syndrome (PRES) which affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible. Transverse myelitis, also a rare condition is an inflammatory disease-causing injury to the spinal cord which has been reported in a patient receiving ixazomib. This condition may cause varying degrees of muscle weakness, reduced movement in legs, changes in the feelings of the toes and feet unusual muscle tightness, feelings of pain, changes in bowel (constipation) or urinary (loss of control) function or loss of leg movement. In general, recovery may be partial, complete, or not at all but most patients experiencing transverse myelitis have good to fair recovery of symptoms. We do not know whether ixazomib causes transverse myelitis, however, as it happened to a patient receiving ixazomib, we are not able to exclude the possibility that ixazomib may have contributed to transverse myelitis.

Progressive multifocal leukoencephalopathy (PML) is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or

severe disability. PML has been observed rarely in patients taking ixazomib. It is not known whether ixazomib may contribute to the development of PML

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS), are rare, serious blood disorders that cause low levels of platelets and red blood cells, and result in blood clots in small vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders can occasionally be fatal. TMA, TTP, and HUS have been seen rarely (<0.1%) in patients treated with ixazomib.

Overdose has been reported in patients taking ixazomib. Reports of accidental overdose have been associated with risks such as nausea, lung infections including aspiration pneumonia, multiple organ failure, and death. It is important to take only one dose of ixazomib at a time, and only at the prescribed interval.

In addition, posterior reversible encephalopathy syndrome has also been reported with Ixazomib with lesser frequency (<1%). This condition affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible.

Additionally, it is worth noting that:
- Ixazomib is similar to the drug known as VELCADE ® (bortezomib) for Injection which is approved for the treatment of multiple myeloma (a cancer of the plasma cell), as well as mantle cell lymphoma (a cancer of the lymph nodes) in patients who have received at least one prior therapy.
- Ixazomib, like VELCADE, should not be taken if you have ever had an allergic reaction to the active substance or any of the inactive ingredients used in its formulation.

The following side effects have been reported with VELCADE use and therefore may also be a risk with Ixazomib:
- Rapid death of cancer cells that may let large amounts of the cells into the blood that injure organs, such as kidneys (this is referred to as tumor lysis syndrome). Your study doctor can talk with you about other common side effects with VELCADE use.
- The more severe but rare side effects seen with VELCADE, include but are not limited to, worsening of your heart function (congestive heart failure), disorders that could affect the function of your lung that could be serious enough to result in death, and liver failure. Your study doctor can talk to you further about the risks of VELCADE.
- Other drugs and supplements may affect the way Ixazomib works. Tell your study doctor about all drugs and supplements you are taking while you are in this study.

One fatal case of progressive multifocal leukoencephalopathy (PML) has been reported with MLN9708 in an oncology patient who had previously received a medication associated with PML. PML is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. It is not known whether MLN9708 may have contributed to the development PML in this patient.

Risk to the unborn child (Men and Women)

Female subjects: We do not know if the study drug combination will affect mother's milk or an unborn child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to

unknown risks and potential harm to the unborn child/ infant, you should not become pregnant or nurse a baby while on this study and for at least 90 days after you have been discontinued from treatment.

If you are a woman who is able to have children, you must have two negative pregnancy tests prior to enrolling in the study and agree to the pregnancy testing requirements and if randomized to receive lenalidomide, adhere to the appropriate guidelines per the Revlimid® Patient-Physician Agreement that will be provided to you by your physician. You must also use two effective methods of birth control as noted in the Revlimid® Patient Physician Agreement form for at least 28 days before starting study treatment, for the entire study drug treatment period (including interruptions in treatment), and for 90 days after treatment has been stopped.

Please be aware that some of the follow up and contraception requirements for this protocol extend past those required in the Revlimid Patient-Physician Agreement and need to be followed as part of this study.

If you are unable to have children, you must still adhere to the appropriate guidelines of the Revlimid® Patient-Physician Agreement that will be provided to you by your physician.

Male subjects: We do not know if using the study drug combination will affect sperm. Therefore, due to potential risk, you should not get your partner pregnant during the study drug treatment period. Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex or synthetic condom with or without a spermicidal agent) during the entire study drug treatment period (including interruptions in treatment), and for 90 days after completing study drug treatment. Or, you should completely avoid having heterosexual intercourse. You must also adhere to the appropriate guidelines of the Revlimid® Patient-Physician Agreement form that will be provided to you by your physician.

Please be aware that some of the follow up and contraception requirements for this protocol extend past those required in the Revlimid Patient-Physician Agreement and need to be followed as part of this study.

All subjects (male or female): If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The study doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female subjects who become pregnant while on this study, the study drug will be stopped immediately and the pregnancy will be followed until conclusion.

If you do not understand what any of these discomforts and risks mean, please ask the study doctor or study staff to explain these terms to you.

Study Drug risks

If you take home the study drug, you will be given complete instructions about dosing, storage, safe handling of the drug, and how to use the patient diary given to you. Notify your study doctor immediately if the study drug capsule is broken or you are in contact with the capsule contents.

Possible discomforts and risk of Lenalidomide and Dexamethasone

- Your study doctor will discuss with you the possible risks involved with the other medicines that you are required to take in this study, lenalidomide and dexamethasone, as they are commonly used to treat your type of cancer. Lenalidomide increases the risk of deep vein thrombosis and may require use of aspirin or alternate anti-coagulation. Your study doctor has a listing of the risks associated with lenalidomide and will review this with you.

- All possible adverse effects from the combination therapy of lenalidomide, dexamethasone, and Ixazomib are unknown at this time.

- In order to participate in this study you must register in and follow the requirements of the Revlimid Risk Evaluation and Mitigation Strategy (REMS)™ program (formerly known as RevAssist® program) of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts due to use of lenalidomide.

Risks and Side Effects of venipuncture/ intravenous needle insertion:

Infrequent (occurs in 1% to 10% of people - from 1 to 10 out of 100 people): mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

Rare (occurs in less than 1% or people - less than 1 out of 100 people): severe pain, swelling, infection from the actual injection, and fainting.

Risks and Side Effects of EKG (Electrocardiogram):

Rare – Occurs in less than 1% of people (less than 1 out of 100 people):
Side effects that may be associated with the EKG electrode placement are skin irritation, redness, and chafing of the skin at the placement site.

Risks and Side Effects of Bone Marrow Aspirate and Biopsy

Possible side effects of a bone marrow aspirate and biopsy include bleeding, infection, bruising, pain or discomfort at the biopsy site and possible side effects from the local anesthetic (pain or bruising at the injection site).

The bone marrow test is performed by using a needle to obtain a small sample of bone marrow from the pelvic bone. The main discomfort associated with this test is pain when the bone marrow is being withdrawn. In order to make the procedure more comfortable, you will get a local anesthetic to numb the area. A mild sedative may also be given to you. While you are sedated, you will be able to respond to commands.

Radiation Risks and Side Effects (CT Scan/X-ray):

You will be exposed to radiation from CT scans and other x-rays. These procedures are necessary for your medical care and will occur even if you do not participate in this study. The estimated radiation dose that you will receive is equal to or less than the annual radiation exposure limit allowed for persons who are occupationally exposed to radiation (for example, x-ray technologist, radiologist). The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk for radiation-induced cancer from this study is minimal.

Risks and Side Effects of MRI:
Rare – Occurs in less than 1% of subjects (less than 1 out of 100 subjects):
Possible anxiety and claustrophobia related to being placed in the large body scanner; temporary discomfort related to having to lie still during the procedure; and possible pain, infection and bleeding related to venipuncture if contrast dye is used. Because MRI works through a powerful magnetic field, it cannot be done if subjects have a pacemaker, intracranial aneurysm clips or other metal implants (for example, types of implants used in eye surgery or orthopedic [bone] surgery). You will be questioned and examined, if necessary, to confirm that you may undergo MRI scanning without additional risk. An x-ray may be performed to rule out the presence of a suspected foreign body prior to the MRI.

If you will be taking the study drug home, keep it out of the reach of children or anyone else who may not be able to read or understand the label. Do not let anyone else take the study drug besides you.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Will I benefit directly from the study?
This study is not designed to benefit you directly. Your condition may improve while you are in this study but it may not, and it may even get worse. This study is designed to learn more about how to select patients that will benefit the most from specific drug combination to treat their multiple myeloma. This information could help future myeloma patients.

Will I be compensated for my time and effort?
You will not be paid for taking part in this research study. However, you may receive reimbursement of travel expenses for participating in the study. Your participation in this research study may contribute to the development of commercial products from which Millennium Pharmaceuticals, Inc., or others, may derive an economic benefit. You have no rights to and will not receive payments of any kind for discoveries, patents or products that may be developed from this study.

What are my other options?
Your study doctor will discuss with you any other treatments or other clinical trials, which may be available for the treatment of your disease and their risks and benefits. Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Receiving other standard therapies for newly diagnosed multiple myeloma
- Other clinical trials may be available that might have fewer side effects or might be better for your health.

Talk to your study doctor about your choices before you decide if you will take part in this study.

Taking part in this study, however, may make you unable to participate in some other research studies, if they exclude people who have taken certain treatments. You should discuss this with the

researchers if you have concerns. You may wish to research other study options at websites like clinicaltrials.gov and ResearchMatch.org.

How will you protect my private information that you collect in this study?
Emory **and** Grady Health System will keep any research records that it creates private to the extent that this is required to do so by law. Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Study records can be opened by court order. They also may be provided in response to a subpoena or a request for the production of documents.

How is my Genetic Information Protected? What are the Risks?
The Genetic Information Nondiscrimination Act (GINA) is a federal law that generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that GINA does **not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, and does not apply to employers with less than 15 employees.

In addition to GINA, the State of Georgia has laws that prohibit insurers from using genetic testing information for any non-treatment purpose. However, like GINA, this state law protection has exclusions: life insurance policies, disability income policies, accidental death or dismemberment policies, Medicare supplement policies, long-term care insurance policies, credit insurance policies, specified disease policies, hospital indemnity policies, blanket accident and sickness policies, franchise policies issued on an insurance policy written as a part of workers' compensation equivalent coverage, or other similar limited accident and sickness policies.

Privilege
In the State of Georgia, in some circumstances your genetic information has may have special legal protections called "privilege." This means that the information cannot be used as evidence in a court. By allowing us to use and disclose your genetic information for this research study along with other information about you that genetic information used in the research may no longer have that legal protection. Other protections described in this form will still apply. There are also other confidentiality protections for research data in general under Georgia state law.

Medical Record
If you have been an Emory Healthcare and Grady Health System patient before, then you already have an Emory Healthcare and Grady Health System medical record. If you have never been an

Emory Healthcare and Grady Health System patient, you do not have one. An Emory Healthcare and Grady Health System medical record will be made for you if an Emory and Grady Health System provider or facility gives you any services or procedures for this study.

Copies of the consent form/HIPAA authorization that you sign will be put in any Emory Healthcare and Grady Health System medical record you have now or any time during the study.

Emory Healthcare and Grady Health System may create study information about you that can help with your care. For example, the results of study tests or procedures. These study results will be put in your Emory Healthcare and Grady Health System medical record. Anyone who has access to your medical records will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA privacy rule. State and federal laws may not protect the research information from disclosure.

The results of some study tests and procedures will be used only for research purposes and will *not* be placed in your medical record. For this study, those items include: None

Tests and procedures done at non-Emory and Grady Health System places may not become part of your Emory medical and Grady Health System record. Also, if you decide to be in this study, it is up to you to let your other health providers know.

In Case of Injury

If you get ill or injured from being in the study, Emory and Grady Health System will help you to get medical treatment. Emory and Grady Health System and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proven that your injury or illness is directly caused by the negligence of an Emory and Grady Health System or sponsor employee. "Negligence" is the failure to follow a standard duty of care.

If you become ill or injured from being in this study, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs. If you believe you have become ill or injured from this research, you should contact Dr. Leon Bernal-Mizrachi at telephone number [redacted]. You should also let any health care provider who treats you know that you are in a research study.

Costs

The study sponsor will pay for certain items and services that you may receive if you take part in this study.

You will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for your regular medical care. If you have insurance, Emory and Grady Health System will submit claims to your insurance for items and services that the sponsor does not cover. Emory and Grady Health System will send in only those claims for items and services that it reasonably believes your insurance will pay and that the sponsor has not paid.

The actual amount that you have to pay depends on whether or not you have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance

companies will not pay for regular medical treatment or treatment for complications if you are in a study. How much you will have to pay for any co-payments, deductibles or co-insurance depends on your plan. Emory and Grady Health System and the sponsor will not pay for these costs.

It is a good idea to contact your insurance provider and tell them you want to be in this research study. Ask them what they will pay for and what they will not pay for. You can also ask the study team for help in figuring out what you will have to pay.

If you do not have insurance, Emory and Grady Health System will review your case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if you have to pay any costs for taking part in the study and what those costs will be.

Withdrawal from the Study
You have the right to leave a study at any time without penalty.

For your safety, however, you should consider the study doctor's advice about how to go off the study treatment. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study

PHI that Will be Used/Disclosed:
The PHI that we will use or share for the main research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for Which Your PHI Will be Used/Disclosed:
We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study,

we may use your PHI to determine your health, vital status or contact information. We will use and disclose your PHI for the administration and payment of any costs relating to subject injury from the study.

Use and Disclosure of Your Information That is Required by Law:
We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults. We will also comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Authorization to Use PHI is Required to Participate:
By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form to authorize the use and disclosure of your PHI. If you do not sign this form, then you may not participate in the research study or receive research-related treatment. You may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory and Grady Health System may use and disclose your PHI to get payment for study related treatment and to run normal business operations.
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- Millennium Pharmaceuticals, Inc., (the makers of ixazomib) the Study Supporter.
- The Multiple Myeloma Research Consortium, Inc. (an organization consortium that provides financial an administrative support for the conduct of clinical trials to member institutions) and its contractors or designees
- Researchers at other institutions which are participating in this study.
- Empire Genomics (the makers of the NFKB2 FISH test evaluated in this study)
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory and Grady Health System offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research.
    - Government agencies that regulate the research including: Food and Drug Administration.
    - Public health agencies.
    - Research monitors and reviewer.
    - Accreditation agencies.

Expiration of Your Authorization
Your PHI will be used until this research study ends.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at:

Leon Bernal-Mizrachi, MD
Winship Cancer Institute, Emory University
1365-C Clifton Road NE
Atlanta, GA 30322

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know about Your Privacy
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them. The Sponsor, and people and companies working with the Sponsor on this study are not covered by the Privacy Rules. They will only use and disclose your information as described in this Consent and Authorization.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

In order to obtain lenalidomide through the **Revlimid Risk Evaluation and Mitigation Strategy (REMS)**™ program **(formerly known as RevAssist® program)**, your name, address, phone, date of birth and the fact that you are participating in this trial will be disclosed to Celgene and its agents or vendors that supply lenalidomide and support the Revlimid REMS™ program. By signing this consent form you agree to this disclosure.

<u>What happens to my blood, samples or tissue?</u>
The following samples will be used up in the testing performed for this study and any remaining sample will be stored for retesting until the study results have been reported:

- Clinical Laboratory Evaluations (disease assessments)
- Hematology and Chemistry
- Urine Samples

The additional blood and bone marrow samples collected for this study will be stored at Emory University, Atlanta, GA, USA, its agents or its affiliated companies for up to 15 years from when the study results are reported or if less, the maximum period permitted under applicable law or until consent is withdrawn. The samples will be sent to Empire Genomics which will process the sample and extracts the DNA, RNA or protein. Samples will then be transferred to Emory University for storage. Emory University, its agents and affiliated companies will have access to the samples collected. All samples collected during the study will be stored securely with limited access and Emory University will require anyone who works with the samples to agree to hold the research information and any individual results in confidence. After that time, the samples will be destroyed.

The study doctor will keep records linking your identity with your samples as required by applicable law. The sample will be labeled with a unique sample identifier. The sample will be used in the analysis of Ixazomib and related disease states. The sample and data are linked to your personal health information with code numbers. This link means that you may be identified but only indirectly. The code numbers will be kept secure by the study doctor at Emory University.

You may also request that your samples and material obtained from your samples be destroyed at any time by contacting your study doctor. As long as the records linking your identity to your samples exist, your samples can still be destroyed. However, Emory University will be entitled to keep and use any study results or information which it obtained from your samples prior to your request.

You will have access to results of blood tests done as part of routine cancer care. However, you will not have access to all your individual sample results from the study.

The samples collected may also be used in the future as part of research related to the development of ixazomib or involving additional biomarkers which may be relevant to your disease or response to ixazomib. The blood samples collected from you and the information and results from tests performed with these samples may be used individually or combined with other data. The tests performed with these samples are not intended to make determinations about your health or the likelihood you will develop any disease, so no test results will be provided to your doctor or put into your medical record. By signing this consent form, you agree that we may store your blood samples and tumor tissue and may use it for studies going on right now, as well as Ixazomib or Multiple Myeloma related studies that are conducted in the future.

Disclosure

This study is evaluating a product manufactured by Celgene pharmaceuticals. Dr. Bernal-Mizrachi serves as a consultant to Celgene and receives compensation for these services. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

Contact Information

Contact Dr. Leon Bernal-Mizrachi at [redacted]:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at [redacted]:

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.
- You may also let the IRB know about your experience as a research participant through our Research Participant Survey at http://www.surveymonkey.com/s/6ZDMW75.

If you are a patient receiving care from the Grady Health System and have a question about your rights, you may contact the Office of Research Administration at research@gmh.edu.

Consent and Authorization

TO BE FILLED OUT BY SUBJECT ONLY

Please **print** your name, **sign**, and **date** below if you agree to be in the main study. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the signed form to keep.

_____
Name of Subject

_____ _____ ____:____ am / pm
Signature of Subject (18 years or older and able to consent) Date Time (please circle)

TO BE FILLED OUT BY STUDY TEAM ONLY

_____
Name of Person Conducting Informed Consent Discussion

_____ _____ ____:____ am / pm
Signature of Person Conducting Informed Consent Discussion Date Time (please circle)