Research Study Informed Consent Document

Study Title for Participants: Testing the Addition of Ixazomib/Placebo to Lenalidomide in Patients with Evidence of Residual Multiple Myeloma

Rev. Add3

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol EAA171: Optimizing Prolonged Treatment In Myeloma Using MRD Assessment (OPTIMUM) (NCT03941860)

Version Date: January 4, 2023

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have multiple myeloma.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is This Study Being Done?

This study is being done to answer the following question:

What are the good and bad effects of adding the study drug ixazomib to the usual approach

for patients with multiple myeloma?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your multiple myeloma. The usual approach is defined as care most people get for multiple myeloma.

What is the usual approach to my multiple myeloma?

The usual approach for patients with multiple myeloma who are not in a study, at your stage of treatment, is treatment with lenalidomide after stem cell transplantation. This approach is approved by the Food and Drug Administration (FDA).

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get lenalidomide and the study drug called ixazomib, or you will get lenalidomide and a placebo, until your disease gets worse or the side effects become too severe. A placebo looks like the study drug, but contains no medication. You and your doctor will not know if you are getting the study drug or placebo.

Rev. Add3

After you finish your study treatment, your doctor will continue to follow your condition for up to 10 years from the date you were randomly assigned to a treatment on study and watch you for side effects as well as your overall health. Your doctor will check on you every 3 months after treatment if you stop the study within the first 2 years from the date you were randomly assigned to treatment, every 6 months after treatment if you stop the study between 2 and 5 years after starting, and every 12 months after treatment if you stop the study after more than 5 years.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your cancer.

There is also 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 the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Development of numbness and tingling in the hands and feet
- Fatigue
- Decrease in blood counts
- Increased risk of infection
- Nausea and diarrhea
- Skin rash

There may be some risks that the study doctors do not yet know about.

Benefits

If you agree to take part in this study, there may or may not be direct medical benefit to you. However, it may help the study doctors understand how this study drug works. This study may help the study doctors learn things that may help other people in the future.

There is evidence that ixazomib and lenalidomide are effective in shrinking your cancer or preventing it from returning. It is not possible to know now if the study drugs will extend your life compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

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

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (ECOG-ACRIN). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the effectiveness using lenalidomide and ixazomib to treat your cancer to using lenalidomide and placebo. The addition of ixazomib to the lenalidomide you are already taking could shrink your cancer or prevent it from returning. But, it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better than the usual approach. To determine if it is better, the study doctors will be looking to see if the study drugs lengthen the life of patients compared to the usual approach.

Ixazomib is already approved by the FDA for use in combination with lenalidomide for patients with multiple myeloma that came back after initial treatment. Lenalidomide has also been approved by the FDA for treatment of multiple myeloma that has relapsed after other therapies. There will be about 510 people taking part in this study.

Rev. Add3

What are the study groups?

This study has a screening step that requires a bone marrow biopsy and aspirate.

This study has 2 study groups. You will not be told which group you are in.

- **Group 1**

  If you are in this group, you will get the usual drug used to treat your multiple myeloma, lenalidomide, plus a study drug called ixazomib. You will get these drugs as a capsule you take by mouth with water on an empty stomach. You will take lenalidomide on days 1 to 28 of each cycle and ixazomib on days 1, 8, and 15 of each cycle. Each cycle lasts 28 days.

  There will be about 255 people in this group.

- **Group 2**

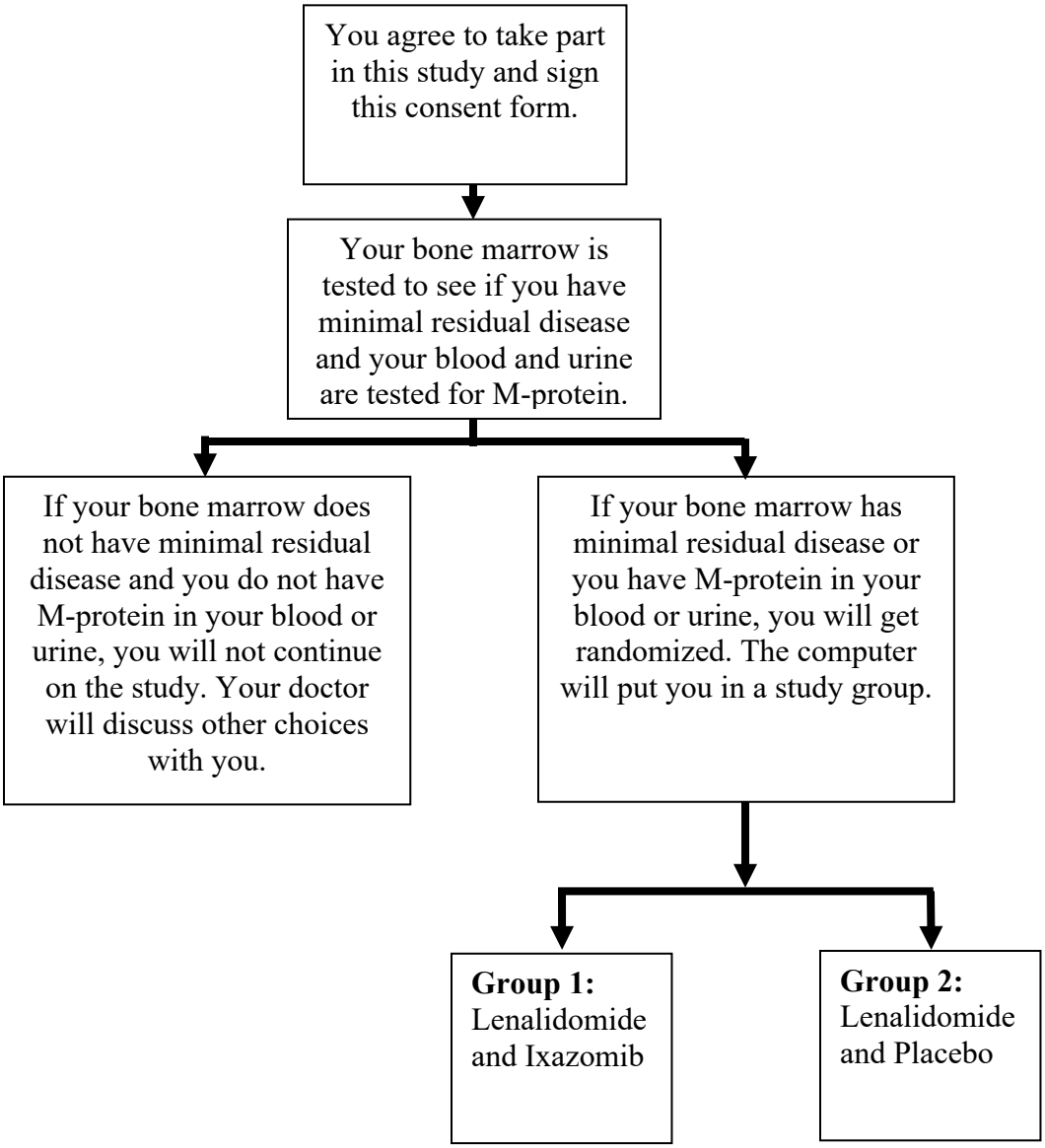
  If you are in this group, you will get the usual drug used to treat your multiple myeloma, lenalidomide, plus a placebo. A placebo is a capsule that looks like the study drug, but contains no medication. You will get these drugs as a capsule you take by mouth with water on an empty stomach. You will take lenalidomide on days 1 to 28 of each cycle and the placebo on days 1, 8, and 15 of each cycle. Each cycle lasts 28 days.

  There will be about 255 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2. Neither you nor your doctor will know which group you are assigned to.

Another way to find out what will happen to you during this study is to read the chart below.

Start reading from the top and read to the bottom, following the lines and arrows.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

Rev. Add3 **Before you begin the study:**

You will need the following extra tests and procedures to find out if you can be in the research study:

- Pregnancy test (if you are a patient of childbearing potential)
  - Once within 14 days of starting study treatment
  - Will be repeated on the first day of treatment, before you take the first dose of
  - study treatment
- Blood tests
- Imaging scan called 18Fluorodeoxyglucose positron emission tomography/computed tomography (abbreviated as 18F-FDG PET/CT)

  This imaging scan is part of the usual care you would get if you were not in a study. As part of this study, a copy of your scan will be sent to a central database to be reviewed for research purposes. Your name and other personal information will not be associated with the scan so you cannot be identified. Neither you nor your study doctor will be given the findings from the research review of your scan.
- Bone marrow biopsy and aspirate

  Mandatory Bone Marrow Biopsy and Aspirate

  You will need to have a bone marrow biopsy and aspirate procedure as part of this study. We will ask you to undergo a bone marrow biopsy to establish the diagnosis of multiple myeloma and ask for a sample (approximately two (2) teaspoons) of the bone marrow aspirate at this time. You and your study doctor will get the results of this special testing in which we are looking for residual myeloma cells, called Minimal Residual Disease (MRD) testing. The MRD testing is being done to look for any remaining traces of myeloma cells. If you do have minimal residual disease (also known as MRD positive) or have M-protein in your blood or urine, and you meet all the study requirements, then we can assign you to treatment. If we find that the bone marrow specimen from your bone marrow biopsy and aspirate procedure does not have minimal residual disease (also known as MRD negative) and you do not have M-protein in your blood or urine, then your doctor will discuss other options for your care.

These results will be placed in your medical record, which may affect your care. If you agree to take part in the study, you may need to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done.

If there are any leftover bone marrow samples that may possibly be stored for bio-banking, this will be discussed in the section under "Optional Studies."

The results of the MRD and immunofixation testing will be used to determine if you can take part in this study.

- If the MRD test results are negative and you do not have M-protein in your blood or urine, you will be taken off study.
- If the MRD test results are positive or you have M-protein in your blood or urine, you will be registered to the study.

NOTE: The MRD test used in this study is considered investigational.

Rev. Add3 **During the study:**

- Pregnancy test during every cycle (if you are a patient of childbearing potential)
- Blood tests during every cycle
- Bone marrow biopsies and/or aspirates at the end of cycles 12, 24, 36, and 60
- Imaging scan called ^{18}Fluorodeoxyglucose positron emission tomography/computed tomography (abbreviated as ^{18}F-FDG PET/CT) at the end of cycles 12 and 24

  These imaging scans are part of the usual care you would get if you were not in a study. As part of this study, a copy of your scans will be sent to a central database to be reviewed for research purposes. Your name and other personal information will not be associated with the scan so you cannot be identified. Neither you nor your study doctor will be given the findings from the research review of your scan.

Patient Reported Outcomes questionnaires

If you are an English speaker and choose to take part in this study, you will be asked to answer questions about your quality of life. Researchers will use this information to learn more about how cancer treatment affects people. There are four types of questionnaires you will be asked to complete. You don't have to answer any question that makes you feel uncomfortable.

The first questionnaire is a question about your health, and it takes about 8-10 minutes to complete. You will be asked to fill out this questionnaire at the times listed below:

- Prior to starting study treatment
- At the end of every 3 cycles for the first 2 years of treatment (before starting cycles 4, 7, 10, 13, 16, 19, 22, and 25)
- At the end of every 6 cycles after the first 2 years of starting treatment up to 4 years (before starting cycles 31, 37, 43, and 49)
- At early discontinuation of treatment prior to 2 years
- 3, 6, 9, and 12 months after the end of treatment

The second questionnaire is about side effects commonly experienced with this study treatment. This questionnaire will take about 10 minutes to complete, and you will be asked to complete this at the times listed below:

- Prior to starting study treatment
- At the end of every cycle for each cycle for the first 2 years of treatments

It is important to know that you are taking your medications properly. Therefore, we will ask you to fill out a third very brief questionnaire at the end of every 6 cycles while you are on study treatment (before starting cycles 7, 13, 19, 25, 31, 37, 43, and 49). This will take about 3-4 minutes to complete.

The fourth questionnaire will ask you questions about your employment, financial position, care support status, health insurance, and where you live. This questionnaire will help the study doctors learn more about factors in your life that may impact your health. This will take about 3-5 minutes to complete, and you will be asked to complete it at the following times:

- Prior to starting study treatment
- At the end of every 6 cycles for the first 2 years of starting treatment (before starting cycles 7, 13, 19, and 25)
- At time of early discontinuation of treatment prior to 2 years of starting treatment

If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach at shrinking your cancer/preventing your cancer from coming back.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The study drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 90 days after you have completed the study. Ask your doctor about the risks involved with different types of contraception methods.

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection can occur. You may sign a separate consent form for the study biopsy

that describes the risks in more detail.

Side Effect Risks

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drugs.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

There are also risks associated with blood draws that include pain, bleeding, bruising, getting a blood clot, and feeling faint or fainting. You may develop an infection with redness and irritation of the vein at the site where blood is drawn. However, these usually go away on their own.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 and Group 2 – Possible side effects of lenalidomide are listed in the tables below. This drug is part of the usual approach for treating this type of cancer:

Possible Side Effects of Lenalidomide

(Table 2.8 Version Date: June 27, 2019)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving lenalidomide (CC-5013), more than 20 and up to 100 may have:

- Anemia which may require blood transfusion
- Constipation, diarrhea
- Tiredness
- Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving lenalidomide (CC-5013), from 4 to 20 may have:

- Infection, especially when white blood cell count is low
- Dizziness, fainting
- Blurred vision
- Cloudiness of the eye, visual disturbances
- Pain
- Dry mouth, skin
- Heartburn, nausea, vomiting
- Chills, fever
- Swelling of the body
- Fall
- Weight loss, loss of appetite
- Dehydration
- Muscle weakness
- Abnormal unpleasant sensation, body movement
- Changes in taste
- Headache
- Feeling of "pins and needles" in arms and legs
- Numbness, tingling or pain of the arms and legs
- Depression
- Difficulty sleeping
- Change in mood
- Cough, shortness of breath
- Nose bleed
- Increased sweating
- Itching, rash
- Sores on the skin
- High blood pressure which may cause headaches, dizziness, blurred vision
- Low blood pressure which may cause feeling faint
- Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving lenalidomide (CC-5013), 3 or fewer may have:
• Abnormal heartbeat • Heart attack, heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Liver damage which may cause yellowing of eyes and skin, swelling • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Damage to organs in the body when donor cells attack host organs • Kidney damage which may require dialysis • Damage to muscle which may cause muscle pain, dark red urine • Cancer of bone marrow caused by chemotherapy • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Increased tumor size • A new cancer unrelated to an earlier cancer • A new cancer resulting from treatment of earlier cancer • Stroke which may cause paralysis, weakness • Damage to the lungs which may cause shortness of breath • Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Difficulty stimulating enough stem cells in the bloodstream for future transplant

Occasional adverse events such as atrial fibrillation (irregular heartbeat), myocardial infarction (heart attack), and congestive heart failure (condition where the heart becomes weak and cannot pump enough blood to the rest of the body) have been reported with the use of lenalidomide from clinical studies and post-marketing.

Deep vein thrombosis and pulmonary embolism

Lenalidomide has demonstrated an increased risk of deep vein thrombosis (DVT, blood clot in a larger blood vessel) and pulmonary embolism (PE, a blood clot in or around the lungs) in some people with certain medical conditions. The study staff will ask you about any risk factors you may have. If you have a history of blood clots your doctor will prescribe treatment with a blood thinner for the first four months of the study treatment. The doctor may continue to prescribe the medication or aspirin for the remainder of your course of study treatment. All other patients will receive (at the discretion of the treating physician) either oral low–dose aspirin or another treatment to prevent blood clotting during study participation. Patients unable or unwilling to undergo treatment for prevention of blood clots

will not be eligible to participate in this study. You will be instructed on the signs and symptoms of DVT and PE and if symptoms occur you should contact your study doctor promptly.

Second new cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer although this risk is very small. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant, followed by lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant, and then placebo (a capsule containing no medication). In clinical studies of patients whose multiple myeloma either did not respond to treatment or returned after treatment, a higher number of second cancers were reported in patients previously treated with multiple chemotherapy regimens and radiation than the drug carfilzomib. Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

Other risks of Lenalidomide

If any physician other than the study doctor prescribes medication for you for another condition or you are taking any over-the-counter medications or vitamins, you must inform the study staff. **This is important because the interaction of some medications may cause serious side effects.**

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

Pregnancy:

Lenalidomide is related to the drug thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Patients who are able to become pregnant must not become pregnant while taking lenalidomide. You have been informed that the risk of birth defects is unknown. If you are a patient who is able to become pregnant, you agree not to become pregnant while taking lenalidomide.

In order to participate in this study you must also register into and follow the requirements of the REMS program of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. You will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate for you and take telephone surveys regarding your compliance with the program.

You understand and agree to receive counseling and to comply with the pregnancy precaution requirements of the REVLIMID REMS® program. You will be registered in the REVLIMID REMS® program.

FOR PATIENTS WHO *ARE ABLE* TO BECOME PREGNANT*

*Anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche (the first occurrence of menstruation) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Please read thoroughly and initial each space provided if you understand each statement:

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that my unborn baby may have birth defects and can even die, if I am pregnant or become pregnant while I am taking lenalidomide.

_____: I understand that I must NOT take lenalidomide if I am pregnant, breast-feeding a baby or able to get pregnant and not using 2 reliable methods of birth control.

_____: If I am having sexual relations with a man, my uterus and/or both ovaries have not been removed, I have had at least one menstrual period in the past 24 months and/or my menses stopped due to treatment of my disease, I understand that I am able to become pregnant. I must use one highly effective method of birth control plus one additional effective method of birth control (contraception) at the SAME TIME.

Highly Effective Methods	**Additional Effective Methods**
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	

_____: These birth control methods must be used during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide therapy; 2) while participating in the study; during interruptions in therapy and 3) for at least 28 days after lenalidomide has been stopped. I must use these methods unless I completely abstain from heterosexual sexual contact. If a hormone (birth control pill, injection, patch or implant) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.

_____: I know I must have a pregnancy test done by my doctor within 10 – 14 days and again within 24 hours prior to starting lenalidomide therapy, even if I have not had my menses due to treatment of my disease or had as little as one menstrual period in the past 24 months. If I have regular or no menstrual cycles, I will then have pregnancy tests every week for the first 28 days, then every 28 days while I am taking lenalidomide, again when I have been taken off of lenalidomide therapy and then 28 days after I have stopped taking lenalidomide. If I have irregular menstrual cycles, I will have pregnancy tests every week for the first 28 days, then every 14 days while I am taking lenalidomide, again when I have been taken off of lenalidomide therapy, and then 14 days and 28 days after I have stopped taking

lenalidomide.

_____: I know I must immediately stop taking lenalidomide and inform my doctor, if I become pregnant while taking the drug, if I miss my menstrual period or have unusual menstrual bleeding, if I stop using 2 reliable forms of birth control, or if I think for any reason that I may be pregnant. I must talk to my doctor before changing any birth control methods.

_____: I am not now pregnant, nor will I try to become pregnant for at least 28 days after I have completely finished taking lenalidomide.

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to anyone who is pregnant or able to have children.

_____: I agree any unused drug supply will be returned per the instructions provided by REMS.

_____: I know that I cannot donate blood while taking lenalidomide and for 28 days after stopping lenalidomide. Study patients who become pregnant will be monitored throughout the pregnancy and will continue to be monitored for 30 days after delivery (premature delivery, aborted fetus, full-term pregnancy, or no longer pregnant).

FOR ALL MALES

Please read thoroughly and initial each space provided if you understand each statement:

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that an unborn baby may have birth defects and can even die, if anyone is pregnant or becomes pregnant while taking lenalidomide.

_____: I have been told by my doctor that I must NEVER have unprotected sexual contact with a partner who can become pregnant. Because lenalidomide is present in small quantities in semen, my doctor has explained that I must completely abstain from sexual contact with partners who are pregnant or able to become pregnant, or I must use a latex condom every time I engage in any sexual contact with partners who are pregnant or may become pregnant. I must do this while I am taking lenalidomide and for 28 days after I stop taking lenalidomide, even if I have had a successful vasectomy.

_____: I know I must inform my doctor if I have unprotected sexual contact with a partner who is pregnant or can become pregnant or if I think, for ANY REASON, that my sexual partner may be pregnant. Partners of male patients taking lenalidomide should be advised to call their own physician immediately if they get pregnant.

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to anyone who is able to have children.

_____: I agree any unused drug supply will be returned per the instructions provided by REMS.

_____: I know that I cannot donate blood, sperm or semen while taking lenalidomide and for

28 days after stopping lenalidomide.

FOR PATIENTS THAT ARE *NOT* ABLE TO BECOME PREGNANT

Please read thoroughly and initial each space provided if you understand each statement:

_____: I understand that birth defects may occur with the use of lenalidomide. I have been warned by my doctor that an unborn baby may have birth defects and can even die, if anyone is pregnant or becomes pregnant while taking lenalidomide.

_____: I certify that I am not now pregnant, nor am I of child bearing potential as I have been in a natural menopause for at least 24 months (been through the change in life without even 1 menstrual period for the past 24 months); or I had my uterus removed (hysterectomy) or had both my ovaries removed (bilateral oophorectomy).

_____: I understand that lenalidomide will be prescribed only for me. I must not share it with ANYONE, even someone that has similar symptoms to mine. It must be kept out of reach of children and should never be given to anyone who is pregnant or able to have children.

_____: I agree any unused drug supply will be returned per the instructions provided by REMS.

_____: I know that I cannot donate blood while taking lenalidomide and for 28 days after stopping lenalidomide.

FOR ALL PATIENTS

You will be counseled at least every 28 days during lenalidomide treatment and again one last time when you stop taking lenalidomide about not sharing lenalidomide (and other study drugs), the potential risks of fetal exposure, abstaining from blood and other donations, the risk of changes in blood counts and blood clots, and you will be reminded not to break, chew or open lenalidomide capsules.

Study Group 1 – In addition to side effects listed above, people who are in Group 1 may also have some side effects of ixazomib. These side effects are listed below:

Possible Side Effects of Ixazomib

(Table Version Date: March 26, 2022)

COMMON, SOME MAY BE SERIOUS In 100 people receiving MLN9708 (Ixazomib citrate), more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MLN9708 (Ixazomib citrate), from 4 to 20 may have:
• Anemia which may require blood transfusion

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MLN9708 (Ixazomib citrate), from 4 to 20 may have:
• Pain • Constipation • Fever • Cold symptoms such as stuffy nose, sneezing, sore throat • Bruising, bleeding • Loss of appetite • Headache • Muscle Weakness • Numbness, tingling or pain of the arms and legs • Cough, shortness of breath • Rash

RARE, AND SERIOUS In 100 people receiving MLN9708 (Ixazomib citrate), 3 or fewer may have:
• Blood clot which may cause confusion, paralysis, seizures and blindness • Swelling of arms, legs • Liver damage which may cause yellowing of the eyes and skin

Some discomforts and risks that occur with lesser frequency (<1%) than those mentioned above, 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) 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, 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. Transverse myelitis, also a rare condition (<1%), 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 (<0.1 %) in patients taking ixazomib. It is not known whether ixazomib may contribute to the development of PML.

Ixazomib should not be taken if you have ever had an allergic reaction to boron or boron containing products.

The following side effects may also be a risk with ixazomib because they have been reported with another proteasome inhibitor, bortezomib, in patients with diseases requiring this type of treatment, or in patients who receive ixazomib in combination with other drugs for cancer treatment:

- Reactivation of the herpes virus infection such as herpes zoster (shingles) that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time;
- 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);
- Worsening of your heart function (congestive heart failure) that may require additional drugs for treatment or hospitalization;
- Disorders of your lung that could be serious enough to result in death

Other Risks of MLN9708 (ixazomib citrate)

There are some additional risks associated with MLN9708 (ixazomib citrate).

Common risks (which occur greater than 20% of the time) include infection, a low number of a particular white blood cell which is important to the immune system (lymphopenia), and joint pain (arthralgia).

Less likely risks (which occur 20% of the time or less) include back pain, upper respiratory tract infection, sensation of lightheadedness or vertigo (spinning sensation or dizziness), blood chemical imbalance (electrolyte imbalance), and pneumonia.

Rare risks (which occur less than 2-3% of the time) include low or high blood pressure, a painful blistery red rash that is confined to one side of the body similar to chicken pox (Herpes zoster), esophageal ulcer, chest pain, abnormal liver tests, weight loss, fainting episodes, decreased level of consciousness, tremors, blood clots, inflammation of the lungs, increased blood pressure in the lungs, nosebleeds, changes in mood, swelling around the eyes, muscle aches, and an inflammatory response associated with an increase in your white blood cell count, fever, and a change in certain protein levels and chemistries in the body,

Rare and serious risks also include abnormal heart rhythms, congestive heart failure, disorders that could affect the function of your lung that could be serious enough to result in death, blockage of your bowel function, and a condition that can be associated with abnormal neurological function and seizures (posterior reversible encephalopathy syndrome; PRES).

Tumor lysis is another rare but serious complication that may occur if the cancer cells die too

quickly and includes inappropriate increase or decrease of various natural chemicals in the blood stream, called uric acid, phosphorus, potassium, creatinine, and calcium. Severe tumor lysis can result in kidney failure and may harm muscle or nerve function (tumor lysis syndrome). Another rare and serious risk is high creatinine which may indicate renal failure. The amount of creatinine (a waste product made by your body) in your blood helps your doctor understand how your kidneys are working. High creatinine means your kidneys are having trouble working well. Patients who had lost body water 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).

Furthermore, there are some risks when MLN9708 (ixazomib citrate) is used for maintenance treatment after a stem cell transplant. Out of 100 people taking ixazomib, 20 to 100 people may experience the following risks, some of which maybe serious: viral upper respiratory infections and fevers, nausea, vomiting and diarrhea, cough, and joint pains. Out of 100 people taking ixazomib, 4 to 20 people may experience the following risks, some of which may be serious: flu (influenza), low platelet counts, muscle pain, infections, headache, fatigue, and numbness and tingling. Out of 100 people taking ixazomib, 3 or fewer people may experience the following rare and serious risks: neutropenia (low levels of white blood cells that make it hard for your body to fight infections) and thrombocytopenia (low levels of platelets which cause an increased risk of bleeding and bruising). The use of ixazomib as maintenance treatment with or without prior transplant, has resulted in longer time for myeloma recurrence in two randomized trials. At the current time, the final results on overall survival have not been reached from those trials. When those results are complete, we will inform you as soon as we know what they are, whether there is a detriment to survival, no effect on survival, or an improvement. Based on the results thus far from those trials, there is no evidence that ixazomib given as maintenance after transplant will improve overall survival.

Additional Drug Risks

The study drug could interact with other drugs. Share this information with your family members, caregivers, other health care providers, and pharmacists.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Imaging Risks

Procedures such as CT scans, X-rays, and/or radioactive drugs will be used during this research study to see how you are doing. Some of the scans are what you would normally undergo with your disease. The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect you or your disease. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to your risk of injury or disease. When deciding to enter this study, think about your past and future contact with radiation. Examples of contact with radiation include x-rays taken for any reason or radiation therapy for cancer treatment.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.
- Write down in your medication diary when you take the study drug at home.

For women: Do not get pregnant or breastfeed while taking part in this study.

For men: Do not father a baby while taking part in this study.

For all: Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 28 days after your last dose of study treatment.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your MM. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- bone marrow biopsies and aspirates.
- imaging scans.
- lenalidomide.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- scheduled MRD testing on the bone marrow biopsy/aspirate samples. This does not include the costs of the biopsy/aspirate itself.
- patient reported outcomes questionnaires

You or your insurance provider will not have to pay for ixazomib/placebo while you take part in this study.

Celgene Patient Support: Celgene has a Celgene Patient Support (CPS) team that is focused on providing assistance accessing lenalidomide to patients who are insured, uninsured and/or

underinsured. CPS can work with patients, caregivers, and/or physicians' offices who opt in for support. Please discuss with your doctor if you would like to use this support team.

Taking part in this study 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 cancer. You may:

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

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

The ECOG-ACRIN Cancer Research Group is conducting this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any drug company supporting the study now or in the future.

- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research including the Imaging and Radiation Oncology Core (IROC).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ [*name(s)*] at _____ [*telephone number and email address if appropriate*].

For questions about your rights while in this study, call the _____ [*name of organization or center*] Institutional Review Board at _____ [*telephone number*].

Optional studies that you can choose to take part in.

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records

and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Optional sample collections for storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, leftover bone marrow from the laboratory research studies will be stored. Storing samples for future studies is called "bio-banking." The biobank is being run by ECOG-ACRIN and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use.

Right now, we don't know what research may be done in the future using your bone marrow samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. Your leftover bone marrow from the laboratory research studies will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
2. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
3. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.

In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your samples and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your samples and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, _____ [*name(s)*], at _____ [*telephone number*], who will let the biobank know. Then, any samples that remain in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, _____ [*name(s)*], at _____ [*telephone number*].

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:

May we keep any bone marrow samples leftover after the laboratory research studies for future research?

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature _____

Date of signature _____

Signature of person(s) conducting the informed consent discussion _____

Date of signature _____