Research Study Informed Consent Document

Study Title for Participants: Testing the combination of two drugs, MLN9708 (ixazomib) and MLN4924 (pevonedistat), for relapsed and/or resistant multiple myeloma

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10249, MLN9708 (Ixazomib) and MLN4924 (Pevonedistat) in Relapsed/Refractory Multiple Myeloma Patients: A Phase 1b Trial (NCT # 03770260)

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 that has relapsed and/or is resistant to other treatment.

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:

Can we lower the chance of your multiple myeloma growing or spreading by using a new combination of drugs?

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 that has relapsed or is resistant to treatment.

What is the usual approach to my multiple myeloma?

The usual approach for patients who are not in a study is treatment with different medications that have shown to have anti-myeloma effects, including but not limited to chemotherapy. Some of these agents or combinations of agents are Food and Drug Administration (FDA)-approved while others are not. MLN9708 (ixazomib), when given in combination with lenalidomide and dexamethasone, is already FDA approved for your myeloma. Your doctor can explain which treatment may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

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 get MLN9708 (ixazomib) and MLN4924 (pevonedistat) for as long as your myeloma doesn't get worse and you don't have a side effect that requires us to stop treatment.

After you finish your study treatment with MLN9708 (ixazomib) and MLN4924 (pevonedistat), your doctor will ask you to complete a 30-day safety follow-up visit and continue to follow your condition every 2-3 months for up to 2 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 MLN9708 (ixazomib) and MLN4924 (pevonedistat) may not be as good as the usual approach at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the MLN9708 (ixazomib) and MLN4924 (pevonedistat). These side effects may be worse and may be different than you would get with the usual approach for your cancer. Tables containing the known common, occasional, and rare side effects are presented in the "What risks can I expect from taking part in this study?" section.

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

Benefits

There is some evidence in living human cells that the combination of MLN9708 (ixazomib) and MLN4924 (pevonedistat) can shrink and/or stabilize cancer, but we do not know if this will happen in people. It is unlikely that this drug combination will help you live longer than the usual approach alone. This study may help the study doctors learn things that may help other 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 Institutional Review Board (IRB), FDA, or study sponsor (National Cancer Institute [NCI]). 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 test the safety of two drugs called MLN9708 (ixazomib) and MLN4924 (pevonedistat). This drug combination has been tested in animals, but has not been tested in people. This study tests different doses of the drug to see which dose is safer for people. There will be about 66 people taking part in this study.

What are the study groups?

There are two parts in this study, a dose escalation part and a dose expansion part. You are in the dose escalation part.

In the dose escalation part of this study, different people will get different doses of the study drugs MLN9708 (ixazomib) and MLN4924 (pevonedistat).

The first 3 people taking part in this study will get the beginning dose. If the drug does not cause serious side effects, the next group of people in the study will get a higher dose. The study doctor will watch each group carefully as they increase the dose. The doses will continue to increase for every new group until people have serious side effects that require the dose to be lower. Once this dose is found, the dose escalation is stopped.

Treatment schedule: You will get MLN4924 (pevonedistat) through a vein in your arm and MLN9708 (ixazomib) as a pill you take by mouth in the clinic on the 1st, 8th, and 15th day of each cycle. Each cycle lasts 28 days. See the study calendar for more information.

MLN9708 (ixazomib) will be administered at the same time as the MLN4924 (pevonedistat) intravenous infusion. Take MLN9708 (ixazomib) capsule(s) on an empty stomach, 1 hour before or 2 hours after food. Swallow whole capsules with water. Do not open or break capsules.

You will not be able to get additional doses of the drugs. MLN9708 (ixazomib) is approved by the FDA to treat multiple myeloma. MLN4924 (pevonedistat) is not approved by the FDA for treatment of your disease.

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. Before you begin the study, you will need to have the following extra tests to find out if you can be in the study:

- Blood tests
- A test of the electrical activity of your heart (EKG)
- An ultrasound of your heart (echocardiogram)
- A pregnancy test if you are a female of childbearing potential
- Skeletal survey/CT scan

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.

These exams, tests, and procedures to monitor your safety and health include:

- Blood tests every week you receive the study drugs
- A serum pregnancy test monthly
- Skeletal survey/CT scan (repeated during treatment to confirm response or disease progression)

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

You will need to have several blood draws for the study. These blood draws will occur on the following days of the study:

- Before you begin the study
- Day 1 of the 1st cycle
- Day 9 of the 1st cycle
- Day 15 of the 1st cycle
- Day 1 of the 3rd cycle
- Day 15 of the 3rd cycle

These blood draws will be done to evaluate markers of activity of the study drugs in your system. You and your study doctor will not get the results of this testing.

A patient study calendar is attached at the end of this document. It shows how often these exams, tests, and/or procedures will be done.

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 MLN9708 (ixazomib) and MLN4924 (pevonedistat) may not be as good as the usual approach at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- You may not be able to take part in future studies
- The study drugs may not be better, and could possibly be worse, than the usual approach for your cancer.

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. You should not get pregnant, breastfeed, or father a baby while in this study and for a minimum of 4 months after the last dose of study drug. 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 4 months after you have completed the study.

Women of childbearing potential should practice 1 highly effective method and 1 additional (barrier) method of contraception, at the same time during the study and for 4 months after you have completed the study. Or agree to abstain from heterosexual intercourse.

Men should practice effective barrier contraception during the study and for 4 months after you have completed the study. Or agree to abstain from heterosexual intercourse.

Blood Draw Risks

You may feel discomfort during some of the tests or procedures during this study or may experience some inconveniences. Some of the risks from drawing blood from your arm may include pain, bruising, lightheadedness, and rarely, infection. Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

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 that could be severe or life threatening.

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:

- Tell your study doctor if you notice or feel anything different so they can see if you are having a side effect.
- Your study doctor may be able to treat some side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

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.

Possible Side Effects of MLN9708 (Ixazomib citrate)

(version 2.1, 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 • 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

Possible Side Effects of MLN4924 (Pevonedistat)

COMMON, SOME MAY BE SERIOUS In 100 people receiving MLN4924 (Pevonedistat HCl), more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness, fever • Loss of appetite • Pain

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MLN4924 (Pevonedistat HCl), from 4 to 20 may have:
• Anemia which may require blood transfusion • Infection, especially when white blood cell count is low which may cause painful and frequent urination • Bloating, constipation • Sores in the mouth which may cause difficulty swallowing • Chills • Swelling of arms, legs • Cold symptoms such as stuffy nose, sneezing, sore throat • Bruising, bleeding • Dehydration • Dizziness, headache • Muscle weakness • Numbness, tingling or pain of the arms and legs • Feeling of “pins and needles” in arms and legs • Worry, confusion • Difficulty sleeping • Cough, shortness of breath, wheezing • Nose bleed • Fluid around lungs • Increased sweating • Itching • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving MLN4924 (Pevonedistat HCl), 3 or fewer may have:
• Abnormal heartbeat • Kidney damage which may cause swelling, may require dialysis

Additional Drug Risks

The study drug could interact with other drugs. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. 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

The skeletal survey/CT scan that you get in this study will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

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.

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 4 months after your last dose of study drug.

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 cancer. 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.
- the costs of CT scans.
- the costs of the pregnancy tests
- the costs of getting the study drugs ready and giving them to you.
- 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:

- The blood draws collected for research purposes.
- the costs of tests of the electrical activity of your heart (EKG).
- The cost of an echocardiogram.

You or your insurance provider will not have to pay for the study drugs (MLN9708 [ixazomib] and MLN4924 [pevonedistat]) while you take part in this study.

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.

There are organizations that may look at or receive copies of some of the information in 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 company supporting the study now or in the future. This would include any organization helping the company with the study.
- 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.

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 and shared 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 (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

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

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.

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Attachment A: Study Calendar for Protocol 10249 Consent Form

	Pre-Study	Cycle 1				Cycle 2				Cycle 3				Cycle 4+				Off Study
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	
MLN9708 (Ixazomib)[A]		X	X	X		X	X	X		X	X	X		X	X	X		
MLN4924 (Pevonedistat)[B]		X	X	X		X	X	X		X	X	X		X	X	X		
Pre-study procedures including informed consent, demographics, medical history, height	X																	
Concurrent meds	X	X----------															X	
Physical exam, weight, and general well-being	X	X				X				X				X				X
Vital signs[G]	X	X	X			X	X			X	X			X	X			X
Blood draws for health status	X	X	X	X		X	X	X		X	X	X		X	X	X		X
Urine collection	X																	
EKG	X																	X
Echocardiogram	X																	
Adverse event evaluation		X----------															X	X
Pregnancy test[C]	X	X				X				X				X				
Plasma collection to study what your body does to the drugs[D]		X		X						X		X						
Blood draws for scientific study	X		X[E]															X
Disease assessment[F]	X					X				X				X				X
Medical imaging scans (Computed Tomography)	X	Repeated during treatment if clinically indicated to confirm response or disease progression																

A: MLN9708 (ixazomib) will be given as assigned on Days 1, 8, and 15 of each 28-day cycle.
B: MLN4924 (pevonedistat) will be given as assigned on Days 1, 8, and 15 of each 28-day cycle.
C: Serum pregnancy test is for women of childbearing potential.
D: Plasma will be collected before treatment beings and approximately 1 hr after treatment begins during the first week of Cycle 1. Additional collections may occur at 0.5 hrs, 2 hrs, 2.5 hrs, 5 hrs, 8 hrs, and 21 hrs after treatment during Week 3 of Cycle 1 and Weeks 1 and 3 of Cycle 3.
E: Collected on Day 9 of Cycle 1 approximately 4 hours after treatment.
F: 24-hour urine and blood will be collected within 7 days before the study begins, before each cycle (starting with Cycle 2), and at time of study discontinuation. When clinically indicated, assessments may also include a physical exam with measurements, CT scan of the chest, abdomen/pelvis, and an ultrasound of the liver/spleen or abdomen.
G: Vital signs will be collected at screening, pre-dose on Days 1, 3, and 8 of each cycle, at off study, and as clinical indicated.