SUMMARY OF CHANGES -- Consent

NCI Protocol #: 10246
Local Protocol #:
Protocol Version Date: 02/16/2022

Protocol Title: A Phase 1 Study of MLN4924 (pevonedistat) and Belinostat in Relapsed/Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome

Informed Consent Version Date: 02/16/2022

#	*Section*	*Page(s)*	*Change*
1.	General	1-15	The date has been changed to match the most recent version of the protocol.
2.	Risks	2-5	Language was included to discuss the resulst of the P2001 PANTHER trial as required by Takeda
3.	Drug Risks	7	Included updated safety information from Pevonedistat IB Edition 13, febrile neutropenia (development of a fever when white blood cell count is low) (Pevonedistat +azacitidine combination)
4.	Reproductive Risks	9	Reproductive risk language updated. Changed from 4 months post-treatment to 6 months post-treatment

Study Title for Participants: Testing MLN4924 (pevonedistat) with belinostat for acute myeloid leukemia or myelodysplastic syndrome not responsive to usual treatments

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol NCI-10246, A Phase 1 Study of MLN4924 (pevonedistat) and Belinostat in Relapsed/Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome (NCT03772925)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. 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 relapsed/refractory Acute Myeloid Leukmia (AML) or Myelodysplastic Syndrome (MDS). Either your cancer is not responding to treatment or the type of cancer you have is not expected to respond to standard 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 cancer growing or spreading by giving MLN4924 (pevonedistat) with belinostat?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your cancer. The usual approach is defined as care most people get for leukemia or a blood or bone marrow cancer that is not responsive to the usual treatments.

What is the usual approach to my cancer?

The usual approach for patients who are not in a study is treatment with chemotherapy or other drugs, if any are available for their type of cancer. While the chemotherapeutic drugs are approved by the Food and Drug Administration (FDA), they do not necessarily have indications for AML. Belinostat and MLN4929 (pevonedistat) are not FDA approved for use in AML or MDS patients and are not standard therapies.

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 continue to get MLN4924 (pevonedistat) and belinostat as long as they are keeping your cancer from getting worse or until you decide you no longer want to be treated on the study or your study doctors decides it is no longer in your best interest to continue treatment. If your cancer has responded to treatment, you can discuss with your doctor about staying on treatment or stopping treatment.

When you stop taking MLN4924 (pevonedistat) and belinostat, your doctor will continue to watch you for side effects for about 1 month. If your cancer responds to the treatment or doesn't get worse and you stop treatment, your study team will continue to follow your cancer by reviewing your medical records or contacting you about every 2 months for about 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.

Recently, Takeda announced its Phase 3 PANTHER (P3001) study did not meet its primary goal of improving time patients lived or the amount of time before a patient's cancer gets worse. The study looked at whether pevonedistat and azacytidine given together as first-line treatment for patients with higher-risk myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and low-blast acute myeloid leukemia (AML) improved the outcome compared azacitidine alone. The risk of this treatment matched with previously known information for the pevonedistat plus azacitidine combination and was in line with azacytidine treatment alone.

The NCI10246 study evaluates a different combination treatment pevonedistat and belinostat in patients with relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome. The decision to continue to participate in this study should be made in consultation with your doctor. You should discuss any questions you have with your doctor.

If you choose to take part in this study, there is a risk that MLN4924 (pevonedistat) and belinostat may not be as good as at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the MLN4924 (pevonedistat) and belinostat. These side effects may be worse and may be different than you would get with other approaches for your cancer.

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

- Tiredness.
- Fever.
- Diarrhea.
- Nausea.
- Vomiting.

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

This drug combination has not been tested in humans before. All the possible side effects and risks are based on limited information. This study will produce the first data in humans.

Benefits

There is some evidence in living human cells that this treatment can shrink cancer. However, we do not know if this will happen in people. It is unlikely that MLN4924 (pevonedistat) and belinostat will help you live longer. 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), Food and Drug Administration (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 giving belinostat with MLN4924 (pevonedistat). Belinostat has been approved by the FDA for the treatment of relapsed peripheral T-cell lymphoma. MLN4924 (pevonedistat) has not yet been approved by the FDA and is currently being studied in patients with cancer, including leukemia. Up to 45 people will take part in this study.

What are the study groups?

Different people taking part in this study will get different doses of the study drugs (MLN4924 [pevonedistat] and belinostat). You will get belinostat on Days 1-5 of each cycle and MLN4924 (pevonedistat) on Days 1, 3 and 5 of each cycle. MLN4924 (pevonedistat) and belinostat will be given into your vein through intravenous (IV) tubing. On the days that you get both study drugs, you will be given belinostat before MLN4924 (pevonedistat). MLN4924 (pevonedistat) is given over 60 minutes. Belinostat is given over 30 minutes. In some instances, the infusion time for belinostat may be extended to as long as 3 hours. The one-week treatment period is followed by 2 weeks of no treatment. This 21-day period is called a treatment cycle.

There are two parts to this study, dose escalation (Part 1) and dose expansion (Part 2).

In the dose escalation part of this study, the first several people taking part will get the lowest doses of study drugs. If the study drugs do not cause serious side effects, the next group of people in the study will get higher doses. 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 doses to be lower. Once these doses are found, the next part of the study will begin.

If you are in Part 1, you will still be able to get additional doses of the drugs when Part 2 begins. These drugs are not approved by the FDA for treatment of your disease.

In the dose expansion part of this study, the highest doses (from Part 1) with manageable side effects will be given to up to 12 more people. This will help study doctors better understand the side effects that may happen with these study drugs.

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.

These exams, tests, and procedures to monitor your safety and health include (please refer to the Study Calendar for more detail):

- An assessment of how well the heart is pumping blood from the left ventricle before you start the study.
- An ECG before you begin treatment and ECGs on Day 4 of the first cycle.
- Some blood tests to measure blood clotting and liver function before and during treatment.
- Pregnancy tests before you begin treatment and on the first day of each cycle.

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 extra blood tests for research studies of drug levels and biological markers of cancer. They are not part of the usual approach for your type of cancer.

Blood samples will be collected at the following times over the first 2 days of treatment:

- Before you start taking the study drugs (about 5 teaspoons).
- About 5 minutes before the belinostat infusion is finished (about 1 teaspoon).
- About 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours (about 1 teaspoon each time).
- About 30 minutes, 1 hour, 2 hours, 2.5 hours, 5 hours, 8 hours after starting the MLN4924 (pevonedistat) infusion (about 1 teaspoon each time).
- About 24 hours after you get the study drugs (about 5 teaspoons).

These samples are required in order for you to take part in this study because the research on these samples is an important part of the study. The results will not be added to your medical records and you or your study doctor will not know the results.

Two research bone marrow procedures may be requested if your bone marrow is expected to contain enough cancer cells. Collection of the research bone marrow samples are optional. The bone marrow procedures required to obtain the samples are not part of the usual approach for your type of cancer. It may be possible to collect the first sample at the same time you have bone marrow collected to check for cancer cells before beginning study treatment. For these research samples, bone marrow will be collected before you begin treatment and about 24 hours after your first dose of treatment. The purpose of the optional research is to learn more about how the study treatment affects the bone marrow cancer cells. The researchers will study the genes and proteins found in the cancer cells.

If you are interested, please read the section on "Optional studies you can choose to take part in".

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

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.

Common side effects of the blood collection are brief pain, a small amount of bleeding, and bruising at the puncture site used to collect the blood sample. There is also a small risk of infection, light-headedness, and fainting.

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 4 months after you have completed the study.

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 study drugs. This different combination of drugs may increase your side effects or may cause new 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 MLN4924 (pevonedistat HCl)
(Table Version Date: **Version 2.3, July 10, 2020**)

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 • Febrile neutropenia (development of a fever when white blood cell count is low) (Pevonedistat +azacitidine combination)
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

Possible Side Effects of Belinostat
(Table Version Date: **Version 2.7, October 29, 2018**)

COMMON, SOME MAY BE SERIOUS In 100 people receiving belinostat (PXD-101), more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Loss of appetite
OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving belinostat (PXD-101), from 4 to 20 may have:

• Anemia which may require blood transfusion • Belly pain • Constipation • Dry mouth • Swelling of arms, legs • Fever • Swelling and redness at the site of the medication injection • Infection, especially when white blood cell count is low • Change in the heart rhythm • Bruising, bleeding • Weight loss • Dehydration • Dizziness, headache • Changes in taste • Shortness of breath • Rash • Flushing
RARE, AND SERIOUS In 100 people receiving belinostat (PXD-101), 3 or fewer may have:
• Kidney damage which 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.

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:** Continue contraceptive precautions for 6 months after the last dose of the study drug. Tell your study doctor right away if you think that

you or your partner have become pregnant during the study or within 6 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 getting the MLN4924 (pevonedistat) and belinostat ready and giving it 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 extra blood tests for research, including some tests of blood clotting and liver function.
- Testing to evaluate how well the heart pumps blood from the left ventricle.
- ECG testing before you begin treatment and on Day 4 of the first cycle.
- The bone marrow procedures done to collect research bone marrow samples (if you choose to have those samples collected).

You or your insurance provider will not have to pay for the belinostat 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 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 drugs now or in the future.
- The 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.
- Virginia Commonwealth University

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, 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*).

^Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here. ^

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.

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample collections for known laboratory studies and/or 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.

Known future studies

If you choose to take part in this optional study, researchers will collect bone marrow for research on how MLN4924 (pevonedistat) and belinostat affect markers in your cancer cells.

What is involved in this optional sample collection?

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

The study doctor for the main study would like to collect 2 bone marrow samples for the optional laboratory study.

The bone marrow samples will be collected before your study treatment begins and the day following your first treatment. It may be possible to collect the first sample at the same time you have bone marrow collected to check for cancer cells before beginning study treatment. For a bone marrow procedure, an area in the back of your hip will be numbed with a local anesthetic and a bone marrow needle will be inserted. After removing the aspirate, the needle is removed.

The collected samples will be sent to the laboratory for the research described above. When the research tests have been completed, any remaining samples will be destroyed. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.

What are the risks in this optional sample collection?

- The risks of the bone marrow procedure include pain, bleeding, infection of the skin or tissues, and allergy to the local anesthetic. You may have some soreness at the site for a day or so after the procedure.
- 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. 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 sample 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 sample 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, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the research laboratory for this study know. Then, any sample that remains in the research laboratory for this study 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, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*).

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

Samples for known future studies:

I agree that my bone marrow samples and related health information may be used for the laboratory study described above.

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

Attachment A: Study Calendar for Protocol 10246 Consent Form

	Pre-Study	Cycle 1							Subsequent Cycles							End of Treatment Visit	30-Day Safety Follow-up	Extended Follow-up
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15			
Blood draws[A]	X	X	X	X		X	X	X	X		X		X			X		
MLN4924 (pevonedistat)[B]		X		X		X			X		X		X					
Belinostat[C]		X	X	X	X	X			X	X	X	X	X					
Pre-study procedures including informed consent, demographics, height, baseline symptoms, general health conditions, HIV and hepatitis testing	X																	
History, physical exam, weight, and general well-being	X	X							X							X		
Assessment for how well your heart pumps blood from the left ventricle—within 4 weeks before the study begins	X																	
Urine collection	X																	
Vital signs	X	X		X		X			X		X		X			X		
Other current medications	X	X							X							X		
Side effect assessment		X----------													----------X	X	X	
Electrocardiogram (ECG)—pre-study and before and after treatment on Day 4 of Cycle 1.	X				X													
Pregnancy test (blood or urine)	X	X							X									
Bone marrow biopsy for disease assessment	X	After every two cycles																
Bone marrow procedure for research aspirate	X		X															

	Pre-Study	Cycle 1							Subsequent Cycles							End of Treatment Visit	30-Day Safety Follow-up	Extended Follow-up
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15			
sample (optional)																		
Clinical status assessment																		X

A: Blood will be drawn at various timepoints throughout the study for a number of reasons. Blood will be drawn to monitor your blood counts as well as side effects on your liver and kidney. Your blood clotting system will be evaluated regularly. In addition, some of the blood samples will look at how your body gets rid of the drugs as well as how the drugs affects some proteins in your blood. On most days you have blood taken, about one tablespoon (15 mL) will be removed. Over the first 24 hours of treatment, you will have about 1/4 pint (120 mL) of blood drawn. A blood drive donation is 1 pint (473 mL).
B: MLN4924 (pevonedistat) will be given at the assigned dose intravenously (IV) once a day on Days 1, 3, and 5 of each 21-day cycle.
C: Belinostat will be given at the assigned dose IV once a day on Days 1-5 of each 21-day cycle.

Attachment B: Study Timeline for Protocol 10246 Consent Form