CHILDREN'S ONCOLOGY GROUP

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NCI Pediatric Early Phase Clinical Trials Network

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Dear Ms. Kruhm,

Enclosed please find Amendment #3A to **ADVL1712**, *A Feasibility Trial of MLN4924 (pevonedistat, TAK 924, IND#) given in Combination with Azacitidine, Fludarabine, and Cytarabine, in Children, Adolescents, and Young Adults with Relapsed or Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome.*

This amendment is being submitted in response to a Request for Rapid Amendment (RRA) from Dr. John J. Wright (wrightj@ctep.nci.nih.gov), dated August 7, 2020. In this amendment, the revised CAEPR for MLN4924 (Pevonedistat HCl) (Version 2.3, July 10, 2020) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised. All revisions are detailed in the summary of changes below.

Please let me know if you have any questions or need additional information.

Sincerely,
Jennifer Knothe, Protocol Coordinator (for)
Katherine Tarlock, M.D., ADVL1712 Study Chair, and
Brenda Weigel, M.D., PI, PEP-CTN

SUMMARY OF CHANGES: INFORMED CONSENT

In accordance with the above discussion, the following specific revisions have been made to the informed consent. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General	Throughout	Updated protocol version date in the footer.

2.	Risks and side effects related to MLN4924 (pevonedistat)	8-9	In response to a Request for Rapid Amendment (RRA) from Dr. John J. Wright, dated August 7, 2020, the MLN4924 (Pevonedistat HCl) risk insert has been updated as follows:
			• Decrease in Risk Attribution:
			  • Changed to Occasional from Common: Constipation; Dizziness
			  • Changed to Also Reported on MLN4924 Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Rash
			• Provided Further Clarification:
			  • Infection, especially when white blood cell count is low (under Occasional) is now reported as Infection, especially when white blood cell count is low **which may cause painful and frequent urination** (under Occasional).

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they must be justified in writing by the investigator and approved by the IRB.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ADVL1712, A Feasibility Trial of MLN4924 (Pevonedistat, TAK 924, IND#) Given in Combination with Azacitidine, Fludarabine, and Cytarabine, in Children, Adolescents, and Young Adults with Relapsed or Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

Overview

You are being asked to take part in this research study because you have been diagnosed with leukemia or myelodysplastic syndrome that has either come back ("relapsed") or does not respond to therapy ("is refractory").

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

The overall goal of this study is to find the highest dose of MLN4924 (pevonedistat) that can be given safely in combination with the commercial drugs azacitidine, fludarabine, and cytarabine.

If the exams, tests and procedures show that you can be in the study, and you choose to take part, MLN4924 (pevonedistat) will be given by vein on Days 1, 3, and 5 over a 35 day cycle. This entire 35 day period is called a cycle. You will also receive the commercial drugs azacitidine, cytarabine, and fludarabine. Cytarabine will be given into the spinal fluid prior to each cycle, azacitidine will be given by vein on Days 1-5, fludarabine will be given by vein on Days 6-10, and cytarabine will be given by vein on Days 6-10. You may continue to receive MLN4924 (pevonedistat) for up to 2 cycles unless you develop serious side effects or your cancer worsens.

Certain patients will also receive the commercial drugs cytarabine or intrathecal triples (methotrexate + hydrocortisone + cytarabine) through the spinal cord twice weekly between Days 8 and 34 of Cycle 1. This will happen to patients whose leukemia has affected their spinal fluid. Your doctor will let you know if you are one of these patients.

There will be two different amounts (doses) of MLN4924 (pevonedistat) given to children on this study – a higher dose, which is the dose given to adults, and a lower dose. Up to 6 children will be given each dose. Your dose will not increase but might be decreased depending on side effects. Dosing is done this way because we do not yet know the best dose to use in children.

All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

This study uses the investigational drug, MLN4924 (pevonedistat). Common side effects of this drug are anemia, diarrhea, nausea, vomiting, chills, tiredness, fever, loss of appetite, pain, dizziness, headache, and shortness of breath. Some less common but notable side effects are liver injury, kidney injury, lung dysfunction, and infection. The full list of risks for MLN4924 (pevonedistat) is available in the section What side effects or risks can I expect from being in the study?

You can ask your study doctor questions about side effects at any time.

We hope that this study will help you personally, but we do not know if it will. The potential benefits to you associated with participation in this study are described in the section Are there benefits to taking part in the study?

You have a choice between another treatment for leukemia or myelodysplastic syndrome and this clinical trial.

The rest of this form provides detailed information about the study and what to expect should you decide to participate.

Why am I being invited to take part in this study?

You are being asked to take part in this research study because you have been diagnosed with leukemia or myelodysplastic syndrome that has either come back (“relapsed”) or that has not responded to standard therapy (is “refractory”).

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is being carried out by the Children’s Oncology Group (COG) Pediatric Early Phase Clinical Trial Network (PEP-CTN). COG is an international research group that consists of more than 200 hospitals that treat children with cancer in the United States, Canada, Australia, New Zealand, and Switzerland. The PEP-CTN is the group within COG that consists of 21 hospitals based in the United States and Canada, and participation in this study will be limited to these hospitals.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between another treatment for leukemia or myelodysplastic syndrome and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of treatment for this disease?

We are asking if you want to participate in this study because there is not a standard treatment for your cancer at this point.

Why is this study being done?

This is a Phase 1 study of a drug called MLN4924 (pevonedistat). We are testing new experimental drugs such as MLN4924 (pevonedistat) in the hopes of finding a treatment that may be effective against leukemia or myelodysplastic syndrome that has come back or that has not responded to standard therapy. This study looks at how well MLN4924 (pevonedistat) works in children and young adults with relapsed or refractory leukemia or myelodysplastic syndrome in combination with the commercial drugs azacitidine, fludarabine, and cytarabine. We are using MLN4924 (pevonedistat) because it seems to work against cancer in test tubes and animals. MLN4924 (pevonedistat) has been used in adults and there is a lot that we do not know about it yet. This is called a Phase 1 study because the goal is to find the highest dose of MLN4924 (pevonedistat) that we can give safely in combination with the commercial drugs azacitidine, fludarabine, and cytarabine.

The overall goals of this study are:

- **To find the highest dose of MLN4924 (pevonedistat) that can be given safely in combination with the commercial drugs azacitidine, fludarabine, and cytarabine;**
- **To learn what kind of side effects MLN4924 (pevonedistat) can cause when given in combination with the commercial drugs azacitidine, fludarabine, and cytarabine;**
- **To learn more about the pharmacology (how your body handles the drug) of MLN4924 (pevonedistat)*;***
- **To determine whether MLN4924 (pevonedistat) in combination with the commercial drugs azacitidine, fludarabine, and cytarabine is a beneficial treatment for your cancer.**

What will happen on this study that is research?

If the exams, tests and procedures show that you can be in the study, and you choose to take part, MLN4924 (pevonedistat) will be given by vein on Days 1, 3, and 5 of each 35 day cycle. This entire 35 day period is called a cycle. You will also receive the commercial drugs azacitidine, cytarabine, and fludarabine. Cytarabine will be given into the spinal fluid prior to each cycle, azacitidine will be given by vein on Days 1-5, fludarabine will be given by vein on Days 6-10, and cytarabine will be given by vein on Days 6-10. You may continue to receive MLN4924 (pevonedistat) for up to 2 cycles unless you develop serious side effects or your tumor worsens.

Certain patients will also receive cytarabine or intrathecal triples (methotrexate + hydrocortisone + cytarabine) through the spinal cord twice weekly between Days 8 and 34 of Cycle 1. This will happen to patients whose leukemia has affected their spinal fluid. Your doctor will let you know if you are one of these patients.

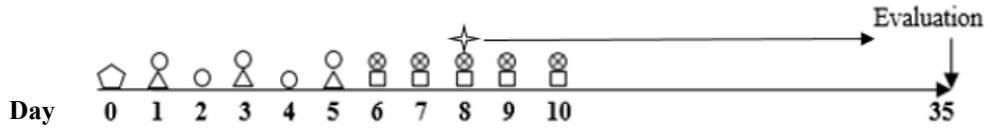
Dose Confirmation

There will be two different amounts (doses) of MLN4924 (pevonedistat) given to children on this study – a higher dose, which is the dose given to adults, and a lower dose. Up to 6 children will be given each dose. Your dose will not increase but might be decreased depending on side effects. Dosing is done this way because we do not yet know the best dose to use in children.

Diagram of Treatment

An overview of a treatment cycle is below:

⬠ Intrathecal Cytarabine
△ MLN4924 (pevonedistat)
○ Azacitidine
⊗ Cytarabine
□ Fludarabine
✦ Intrathecal Cytarabine **OR** Intrathecal Triples*



*Twice weekly during the first cycle of therapy. Only for patients whose leukemia has affected their spinal fluid. Your doctor will let you know if you are one of these patients.

The table below describes one cycle of therapy:

Drug	How the drug will be given	Days
Cytarabine	Into the spinal fluid (intrathecal)	Before each cycle
Azacitidine	By vein	1 – 5
MLN4924 (Pevonedistat)	By vein	1, 3, 5
Fludarabine	By vein	6 – 10
Cytarabine	By vein	6 – 10
Cytarabine **OR** Intrathecal Triples (Methotrexate/Hydrocortisone/ Cytarabine)*	Into the spinal fluid (intrathecal)*	Twice weekly between Days 8 and 34*

*These drugs will only be given to patients whose leukemia has affected their spinal fluid. These drugs will be given twice weekly during the first cycle of therapy. Your doctor will let you know if you are one of these patients.

For more details regarding what drugs and tests will be given on each day of therapy, please see Attachment 2.

Research Study Tests and Procedures

During the study you will have tests and procedures to check for side effects and see how your cancer is doing. These tests are part of regular cancer care, but you may have them more often because you are on the study:

- Physical exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests

- Pregnancy test
- MRI, X-rays, CT scans, or other tests that are needed to check your cancer
- Bone marrow tests
- Heart function test (EKG)

Copies of the scans used to diagnose your cancer and some of the tissue already taken may be sent to a central review center. COG does this to double check the hospitals' results and central review is performed for research purposes.

Research Study Tests

We would also like to do some extra tests called pharmacokinetic studies and biologic studies. Pharmacokinetic studies help us determine how much of the MLN4924 (pevonedistat) is in your blood. Biologic studies help us evaluate the effect of MLN4924 (pevonedistat) on your body. These tests will help us learn more about MLN4924 (pevonedistat) and may help children who receive this drug in the future. The information learned would not change the way you are treated, and the results of these tests will not be given to you. Some of these tests are required but others are optional (you can decide whether you want to do them or not). If you weigh 10 kg or less (22 pounds or less), a total of 50 mL of blood (approximately 10 teaspoons) and 6 mL of bone marrow sample (approximately 1 teaspoon) will be drawn for all the pharmacokinetic and biology study tests in this study. If you weigh over 10 kg (over 22 pounds), a total of 74 mL of blood (approximately 15 teaspoons) and 6 mL of bone marrow sample (approximately 1 teaspoon) will be drawn for all the pharmacokinetic and biology study tests in this study. *This amount of blood and bone marrow is safe to draw even from small children.* You can still be a part of the main study even if you say "No" to taking part in any of the optional research studies.

Pharmacokinetic Studies (Required)

For patients that weigh 10 kg or less (22 pounds or less):

During the study, a total of 8 blood samples will be collected (about 3 mL or about ½ teaspoon each sample) for the pharmacokinetic tests. These samples will be taken before the drug begins, at the end of MLN4924 (pevonedistat) infusion, between 4 – 6 hours after MLN4924 (pevonedistat) infusion (1 sample only between these time points) and 24 hours after MLN4924 (pevonedistat) infusion. These blood draws will occur on Day 1 and Day 5 of Cycle 1. *These samples will be required from all participants in the study.* Because we cannot draw the samples from the same IV or central line we give the drug through, we will start a separate IV to get the samples.

A total volume of 24 mL (about 5 teaspoons) will be drawn for pharmacokinetic tests in this study. *This amount of blood is safe to draw even from small children.*

You may be reimbursed up to $100 for inconveniences you experience as a result of your participation. Your doctor will explain to you what qualifies for reimbursement (e.g. costs of parking).

Please see Attachment 2 for more details on what days blood draws for pharmacokinetic studies will occur.

For patients that weigh over 10 kg (over 22 pounds):

During the study, a total of 16 blood samples will be collected (about 3 mL or about ½ teaspoon each sample) for the pharmacokinetic tests. These samples will be taken before the drug begins,

at the end of MLN4924 (pevonedistat) infusion and at 1 hour after MLN4924 (pevonedistat) infusion, 2 hours after MLN4924 (pevonedistat) infusion, 4 hours after MLN4924 (pevonedistat) infusion, between 6 – 8 hours after MLN4924 (pevonedistat) infusion (1 sample only between these time points), 24 hours after MLN4924 (pevonedistat) infusion, and 48 hours after MLN4924 (pevonedistat) infusion. These blood draws will occur on Day 1 and Day 5 of Cycle 1. A sample 72 hours after MLN4924 (pevonedistat) is given on Day 5 can be substituted for the sample taken 48 hours after MLN4924 (pevonedistat) is given on Day 5 instead. *These samples will be required from all participants in the study.* Because we cannot draw the samples from the same IV or central line we give the drug through, we will start a separate IV to get the samples.

A total volume of 48 mL (about 10 teaspoons) will be drawn for pharmacokinetic tests in this study. *This amount of blood is safe to draw even from small children.*

You may be reimbursed up to $100 for inconveniences you experience as a result of your participation. Your doctor will explain to you what qualifies for reimbursement (e.g. costs of parking).

Please see Attachment 2 for more details on what days blood draws for pharmacokinetic studies will occur.

Optional Research Study Tests

During the study we would like to collect additional blood and bone marrow samples to evaluate the effect of MLN4924 (pevonedistat) on your body. There are 2 different studies we would like your blood and/or bone marrow samples for, and you can participate in either, both, or neither.

The first study will help us evaluate the effect of MLN4924 (pevonedistat) on gene expression. The blood samples, 2 mL (½ teaspoon) each, will be obtained prior to treatment on Day 1, and 3 hours and 6 hours after treatment on Day 3 **OR** Day 5.

A total blood volume of 6 mL (about 1½ teaspoons) will be drawn for this gene expression study. *This amount of blood is safe to draw even from small children.*

The second study will help us evaluate the effect of MLN4924 (pevonedistat) on your proteins. The blood samples, 5 mL (1 teaspoon) each, will be obtained prior to treatment on Day 1, 10 hours after Day 1 treatment, 24 hours after Day 1 treatment, and at the end of Cycle 1 on the same day as bone marrow evaluation.

Bone marrow samples, 3 mL (½ teaspoon) each, will be obtained prior to treatment with MLN4924 (pevonedistat) on the same day as bone marrow evaluation and at the end of Cycle 1.

A total blood volume of 20 mL (about 4 teaspoons) and a total bone marrow volume of 6 mL (about 1 teaspoon) will be drawn for this protein study. *This amount of blood and bone marrow is safe to draw even from small children.*

Please see Attachment 2 for more details on what days blood draws for biology studies will occur.

The table below summarizes the blood volume and bone marrow volume required if you participate in all of the above studies:

Patients that weigh 10 kg or less (22 pounds or less):

Correlative Study	Blood Volume per Sample	Total Volume
Pharmacokinetics	3 mL (½ teaspoon)	24 mL (5 teaspoons)
Pharmacodynamics (mRNA Transcript Levels)	2 mL (½ teaspoon)	6 mL (1 teaspoon)
Pharmacodynamics (NEDDylated Protein Analysis) – Blood Samples	5 mL (1 teaspoon)	20 mL (4 teaspoons)
Pharmacodynamics (NEDDylated Protein Analysis) – Bone Marrow Samples	3 mL (½ teaspoon)	6 mL (1 teaspoon)
Total Volume for All Studies		**56 mL (11 teaspoons)**

Patients that weigh over 10 kg (over 22 pounds):

Correlative Study	Blood Volume per Sample	Total Volume
Pharmacokinetics	3 mL (½ teaspoon)	48 mL (10 teaspoons)
Pharmacodynamics (mRNA Transcript Levels)	2 mL (½ teaspoon)	6 mL (1 teaspoon)
Pharmacodynamics (NEDDylated Protein Analysis) – Blood Samples	5 mL (1 teaspoon)	20 mL (4 teaspoons)
Pharmacodynamics (NEDDylated Protein Analysis) – Bone Marrow Samples	3 mL (½ teaspoon)	6 mL (1 teaspoon)

Total Volume for All Studies		**80 mL (16 teaspoons)**

What side effects or risks can I expect from being in the study?

If you choose to take part in this study, there is a risk that the MLN4924 (pevonedistat) may not be as good as the usual approach for your cancer or condition 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.

The MLN4924 (pevonedistat) 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 will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- 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.

The tables below show the most common and the 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.

Risks and side effects related to 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**

Risks and side effects related to azacitidine:

COMMON, SOME MAY BE SERIOUS In 100 people receiving azacitidine, more than 20 and up to 100 may have:
• **Anemia which may require blood transfusion** • **Constipation, diarrhea, nausea, vomiting** • **Tiredness, fever** • **Swelling and redness at the site of the medication injection** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving azacitidine, from 4 to 20 may have:

- **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness**
- **Fluid around heart**
- **Abnormal heartbeat**
- **Pain**
- **Difficulty swallowing or sleeping**
- **Bleeding from multiple sites including nose**
- **Internal bleeding which may cause black tarry stool, blood in vomit or coughing up blood**
- **Sores in the mouth**
- **Chills**
- **Swelling of arms, legs**
- **Weight loss, loss of appetite**
- **Muscle weakness**
- **Dizziness, headache**
- **Worry, confusion**
- **Cough, shortness of breath, postnasal drip**
- **Hair loss, itching, rash**
- **Low blood pressure which may cause feeling faint**

RARE, AND SERIOUS
In 100 people receiving azacitidine, 3 or fewer may have:

- **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**
- **Kidney damage which may cause swelling, may require dialysis**

Risks and side effects related to cytarabine when given into the spinal fluid (intrathecal):

COMMON, SOME MAY BE SERIOUS
In 100 people receiving cytarabine (ara-c) when given into the spinal fluid, more than 20 and up to 100 may have:

- **Nausea, vomiting**
- **Fever**
- **Headache**

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving cytarabine (ara-c) when given into the spinal fluid, from 4 to 20 may have:

- **Anemia which may cause tiredness, or may require blood transfusions**
- **Infection, especially when white blood cell count is low**
- **Bruising, bleeding**
- **Tiredness, dizziness, loss of coordination**
- **Numbness and tingling of the arms and legs**
- **Inflammation of the lining of the brain that can lead to headache, numbness and tingling**

RARE, AND SERIOUS In 100 people receiving cytarabine (ara-c) when given into the spinal fluid, 3 or fewer may have:
• **Seizure** • **Paralysis** • **Blurred vision with a chance of blindness** • **Damage to the brain that may result in a decrease in the ability to learn**

Risks and side effects related to cytarabine when given by vein:

COMMON, SOME MAY BE SERIOUS In 100 people receiving cytarabine, more than 20 and up to 100 may have:
• **Blood clot** • **Rash** • **Swelling in the rectum which may cause rectal pain** • **Diarrhea, loss of appetite, nausea, vomiting** • **Sores in mouth and GI tract which may cause difficulty swallowing or pain** • **Fever**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cytarabine, from 4 to 20 may have:
• **Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Damage to the lungs which may cause shortness of breath** • **Anemia which may cause tiredness, or may require blood transfusions** • **Numbness and tingling of the arms and legs** • **Severe blood infection** • **Kidney damage which may cause swelling, may require dialysis** • **Muscle pain** • **Headache** • **Dizziness** • **Flu-like syndrome with fever, bone pain, rash, redness of eyes, or chest pain** • **Chest pain** • **Hair loss** • **Liver damage which may cause yellowing of skin or eyes** • **Swelling and redness of the eye**

RARE, AND SERIOUS In 100 people receiving cytarabine, 3 or fewer may have:
• **Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness** • **Difficulty speaking, trouble standing or walking**

Risks and side effects related to fludarabine:

COMMON, SOME MAY BE SERIOUS In 100 people receiving fludarabine, more than 20 and up to 100 may have:
• **Infection, especially when white blood cell count is low** • **Vomiting, loss of appetite** • **Tiredness, fever** • **Pain** • **Bruising, bleeding** • **Cough** • **Increased risk of unusual infections lasting more than 6 months**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving fludarabine, from 4 to 20 may have:
• **Anemia, kidney problems which may cause tiredness, bruising, or swelling** • **Nausea, chills** • **Feeling of "pins and needles" in arms and legs** • **Damage to organs (brain, lungs, others) which may cause tiredness, changes in thinking or shortness of breath** • **Confusion**

RARE, AND SERIOUS In 100 people receiving fludarabine, 3 or fewer may have:
• **Kidney damage which may require dialysis**

Rarely, fludarabine has also been associated with damage to or inflammation of the optic nerve (the nerve from the brain to the eye) which can cause blurred vision with a chance of blindness, decreased vision, other visual disturbances, or pain with eye movements.

Risk and Side Effects of Intrathecal Triples (cytarabine, methotrexate, and hydrocortisone) when given into the spinal fluid:

COMMON, SOME MAY BE SERIOUS In 100 people receiving intrathecal triples, more than 20 and up to 100 may have:
• **Nausea, vomiting** • **Fever** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving intrathecal triples, from 4 to 20 may have:
• **Inflammation of the lining of the brain that can lead to headache, stiff neck, numbness and tingling** • **Bruising, bleeding** • **Pain** • **Numbness and tingling of the arms and legs** • **Tiredness, sleepiness, dizziness, loss of coordination, confusion** • **Rash**

RARE, AND SERIOUS In 100 people receiving intrathecal triples, 3 or fewer may have:
• **Seizure** • **Damage to the brain which could lead to coma** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Bleeding into the space of the spine at the site of the injection** • **Paralysis, weakness** • **Blurred vision with a chance of blindness**

You will be provided a patient drug handout and wallet card for the study drug MLN4924 (pevonedistat). MLN4924 (pevonedistat) may interact with other drugs. Talk to your doctor, pharmacist, or study team before starting any new prescription or over-the-counter drugs, herbals, or supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

If you have a drop in the red blood cell count, the cells that carry oxygen around the body, you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.

If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the blood stream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell count is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Transfusions may be accompanied by or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S (acquired immune deficiency syndrome) and other infections.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

Reproductive risks

Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study and for 4 months after the completion of MLN4924 (pevonedistat) administration. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

Risks of blood drawing or placing an intravenous catheter for blood drawing:
Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

Bone Marrow Examination Risks:
You will be required to take a bone marrow test for diagnostic purposes. You will be informed of the risks associated with the procedure and your study doctor will obtain a separate consent form.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

We hope that this study will help you personally, but we do not know if it will.

Potential benefits to you could include:
- your cancer may stop growing or shrink for a period of time
- you may have lessened symptoms, such as pain, that are caused by the cancer

It is extremely unlikely that this treatment will cure your cancer. With any cancer treatment, sometimes treatment does not make the cancer go away. Or, sometimes treatment makes the cancer go away for a while but the cancer comes back later.

We expect that the information learned from this study will benefit other patients in the future.

What other options are there?

Instead of being in this study, you have these options:

- **Getting treatment for your cancer without being in a study**
- **Taking part in another study**
- **Getting comfort care, also called palliative care.** This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

How many people will take part in the study?

The total number of people enrolled on this study is expected to be between 4 and 38.

How long is the study?

People in this clinical trial are expected to receive treatment on this study for about 4 months (2 cycles of therapy). After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health for about 30 days after you finish study treatment. By keeping in touch with you for a while after you complete treatment, we can better understand the long-term effects of the study treatments.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study if any of the following occur:

- Your cancer gets worse
- The side effects of MLN4924 (pevonedistat) are too harmful for you
- You need a treatment that is not allowed on this study
- You are not able to follow study-related treatment instructions
- New information becomes available
- The study is not in your best interest
- The study is stopped
- You get pregnant

What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Children's Oncology Group has 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 Children's Oncology Group will do their best to make sure that any information that goes out to others will not identify who you are. Information about this Certificate of Confidentiality is included in **Attachment 1**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include groups such as:

- **Children's Oncology Group and research partners**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board (IRB) of this hospital**
- **Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **The study sponsor and any drug company supporting the study or their designated reviewers**

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.

What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will not be charged for the costs of the special blood studies and bone marrow studies that are being done for research purposes only, such as the pharmacokinetic and biology studies. The NCI will be covering the costs of the EKGs that are being performed for research purposes before the study treatment begins.

The NCI will supply the MLN4924 (pevonedistat) at no charge while you take part in this study. The NCI does not cover the cost of getting the MLN4924 (pevonedistat) ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the MLN4924 (pevonedistat) to the NCI for some reason. If this does happen, other possible options are:

- You might be able to get the MLN4924 (pevonedistat) from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no MLN4924 (pevonedistat) available at all, no one will be able to get more and the study would close.

If a problem with getting MLN4924 (pevonedistat) occurs, your study doctor will talk to you about these options.

Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

The drug company that makes MLN4924 (pevonedistat) is providing money to the Children's Oncology Group to do the research.

This study includes providing specimens to the researcher, there are no plans for you to profit from any new product developed from research done on your specimens.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* Institutional Review Board (IRB) Administrator at *XXXX.*

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at https://www.childrensoncologygroup.org/index.php/cog-family-handbook.

Visit the NCI's Web site at http://cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at:

1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

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 will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Specimens for optional research tests

The choice to let us use specimens for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies.

If you decide that your specimens can be used for research, some of your health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

If you decide now that your specimens can be used for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any specimens that we have will be destroyed.

If you want to learn more about tissue research with specimens, the NCI website has an information sheet called "Providing Your Tissue For Research: What You Need To Know." This sheet can be found at: https://www.cancer.gov/publications/patient-education/providing-tissue.pdf.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

1.) *Please indicate by initialing below whether you choose to participate in the gene expression study.*

Yes_____ No_____ _____ / _____
Initials Date

2.) *Please indicate by initialing below whether you choose to participate in the protein study.*

Yes_____ No_____ _____ / _____
Initials Date

Signature

I have been given a copy of all ____ pages of this form. The form includes 2 attachments.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

Attachment 1

Certificate of Confidentiality

This trial is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.
The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Attachment 2

STUDY CHART

You will receive MLN4924 (pevonedistat) by vein once a day on days 1, 3, and 5 every 35 days. This entire 35-day period is called a cycle. The chart below shows what will happen to you during Cycle 1 and Cycle 2.

Cycle 1		Cycle 2	
DAY	**WHAT YOU DO**	**DAY**	**WHAT YOU DO**
Before Starting Study	Come into the hospital and do the following: • Get routine blood tests • Get urine tests • Get a physical exam by your doctor • Get a pregnancy test (if you are a woman) • EKG • Get a bone marrow test • Get a disease evaluation that will be done by your doctor. Depending on the results of this evaluation, your doctor will tell you whether or not you may begin treatment on this study. • Get the commercial drug cytarabine into the spinal fluid	Before Cycle 2	Come into the hospital and do the following: • Get routine blood tests • Get urine tests • Get a physical exam by your doctor • EKG • Get the commercial drug cytarabine into the spinal fluid
Day 1	Come into the hospital and do the following: • Get the study drug MLN4924 (pevonedistat) as well as the commercial drug azacitidine • Get optional blood tests for biology studies • Get routine blood tests and blood tests for Pharmacokinetic (PK) studies	Day 1	Come into the hospital and do the following: • Get routine blood tests • Get the study drug MLN4924 (pevonedistat) as well as the commercial drug azacitidine
Day 2	Come into the hospital and do the following: • Get the commercial drug azacitidine	Day 2	Come into the hospital and do the following: • Get the commercial drug azacitidine
Day 3	Come into the hospital and do the following: • Get routine blood tests and blood tests for Pharmacokinetic (PK) studies • Get the study drug MLN4924 (pevonedistat) as well as the commercial drug azacitidine • Get optional blood tests for biology studies	Day 3	Come into the hospital and do the following: • Get routine blood tests • Get the study drug MLN4924 (pevonedistat) as well as the commercial drug azacitidine
Day 4	Come into the hospital and do the following: • Get the commercial drug azacitidine	Day 4	Come into the hospital and do the following: • Get the commercial drug azacitidine
Day 5	Come into the hospital and do the following: • Get the study drug MLN4924 (pevonedistat) as well as the commercial drug azacitidine • Get routine blood tests and blood tests for Pharmacokinetic (PK) studies • Get optional blood tests for biology	Day 5	Come into the hospital and do the following: • Get routine blood tests • Get the study drug MLN4924 (pevonedistat) as well as the commercial drug azacitidine

	studies		
Days 6 to 10	**Come into the hospital and do the following:** • **Get the commercial drugs fludarabine and cytarabine**	**Days 6 to 10**	**Come into the hospital and do the following:** • **Get the commercial drugs fludarabine and cytarabine**
Days 2 to 34	**Come into the hospital and do the following:** • **Get a physical exam weekly** • **Get routine blood tests twice weekly** • **Get urine tests weekly**	**Days 2 to 34**	**Come into the hospital and do the following:** • **Get routine blood tests weekly**
Day 35	**Come into the clinic and do the following:** • **Get a bone marrow test** • **Get optional blood tests for biology studies** • **Your doctor will tell you whether or not you may continue to the next cycle and continue to receive MLN4924 (pevonedistat). If you continue, please follow the schedule listed under "Cycle 2".**	**Day 35**	**Come into the clinic and do the following:** • **Get a bone marrow test** • **ECHO or MUGA** • **EKG**