VUMC Institutional Review Board
Informed Consent Document for Research

Study Title:	HEM 16146: PevAz: A phase II trial of Pevonedistat and Azacitidine in MDS or MDS/MPN patients who fail primary therapy with DNA methyl transferase inhibitors
Version Date:	29NOV2019
PI:	Michael R. Savona, M.D. NCT03238248

Name of participant:_____Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

What is the purpose of this study?
You are being asked to take part in this research study because you have been diagnosed with myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative neoplasm (i.e. MDS or MDS/MPN), and have previously been treated with a DNA methyltransferase inhibitor (DNMTi).

Your condition either did not respond to DNMTi treatment; or initially responded to, but then stopped responding to, DNMTi treatment.

The purpose of this study is to learn if the investigational drug pevonedistat (also known as MLN4924) can help your condition when used in combination with the drug azacitidine.

Investigational means that pevonedistat is still being tested in research studies and has not yet been approved by regulatory health authorities, such as the U.S. Food and Drug Administration (FDA). Azacitidine is approved by the FDA for treatment of myelodysplastic syndromes (MDS).

This research study was developed at Vanderbilt University Medical Center (VUMC). Michael R. Savona, M.D. at the Vanderbilt-Ingram Cancer Center (VICC) is the study chair (also known as the sponsor-investigator of this study).

This study is partially funded by Millennium Pharmaceuticals, Inc., a subsidiary of Takeda Pharmaceutical Company Limited. Millennium is the company that makes and is supplying pevonedistat for use in this study. Millennium/Takeda could benefit financially from this research study.

This study will be conducted at Vanderbilt University Medical Center and approximately 4-5 other academic medical centers in the United States. Overall, approximately 71 patients are expected to enroll in this study in about 1 year.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study

at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

There may be other treatment options that are available to you, including receiving standard therapies. You should speak to your doctor about all of your treatment options prior to deciding to participate in this study.

Side effects and risks that you can expect if you take part in this study:
During the study, you may have discomforts and risks from pevonedistat (also known as MLN4924), either identified or potential; from azacitidine; and from the study procedures. Most of these are listed here, but there may be others that we cannot predict. Discomforts and risks may vary from person to person.

Everyone taking part in the study will be carefully watched for any discomforts and risks. However, doctors do not know all the discomforts and risks that may happen. They may be mild or very serious, and in some cases may be long-lasting or may never go away. Many discomforts and risks go away after you stop receiving study treatment. Your study doctor may give you medications to help lessen some of the discomforts and risks.

There is also a risk of death. You should talk to your study doctor about any discomforts and risks that you may have while taking part in this study.

If a severe reaction to pevonedistat or azacitidine occurs, your doctor may stop the study treatment.

You may experience some, none, or all of these potential discomforts and risks. They may be mild, moderate, or severe. **If any discomforts or risks occur, you must tell your study doctor.**

You must tell your study doctor about all medications, vitamins and herbal remedies you are taking while participating in this study. Medications, vitamins, and herbal remedies may affect the way pevonedistat is metabolized.

If you take acetaminophen (i.e. Tylenol®) or other medicines containing acetaminophen, the study doctor will tell you when to stop taking it and when you may start it again.

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Biopsy Risks

When you have a bone marrow biopsy, your study doctor and the person performing the procedure will explain the procedure to you before it is performed. Bone marrow biopsies typically involve the removal of a small piece of bone and bone marrow by inserting a needle into your hip bone.

Biopsy risks can include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.
- Rarely, an infection at the biopsy site.
- You may receive an injection of lidocaine to numb the area of the biopsy site. Lidocaine, a numbing drug, may burn or cause a rash, redness, or soreness where you get the shot. There is a risk that this drug may cause problems with heart rhythm.

Blood Draw Risks

When you give blood, you may feel faint, or experience mild pain, bruising, irritation or redness at the site. In rare cases, you may get an infection**.**

Risks of Pevonedistat (also known as MLN4924)

Based upon work in animals and early human studies with pevonedistat, some of the discomforts and risks you may experience can be predicted. The potential discomforts and risks of pevonedistat identified in animals and early human studies are predicted to be manageable with regular examinations and treatment by the study doctor. However, these discomforts and risks could become serious and potentially life-threatening, or may cause death.

You may experience some, none, or all of these potential discomforts and risks. They may be mild, moderate, or severe. **If any discomforts or risks occur, you must tell your study doctor.**

In early studies where pevonedistat was administered as a single-agent to patients with blood cancers, lymphoma and other types of cancer, the following discomforts and risks were observed in at least 10% (in other words 1 or more persons out of 10) of patients treated in any single study::

Very Common Risks of Pevonedistat – Occurring in at least 20% (in other words, 2 or more persons out of 10) of patients treated in all four Phase I single-agent studies:

- Fatigue
- Nausea
- Dehydration
- Diarrhea
- Fever
- Decreased appetite
- Muscle and/or joint pain
- Vomiting
- Liver injury causing high abnormal liver function tests
- Constipation
- Dizziness
- Decreased red blood cell count (the cells which carry oxygen throughout your body) which may cause you to feel tired
- Headache
- Difficulty breathing
- Chills
- Increased heart rate

Common Risks of Pevonedistat – Occurring in greater than or equal to 10% and less than 20% (in other words, between 1 and 2 persons out of 10 of patients treated in all four Phase I single-agent studies):

- Cough
- Swelling of the hands, arms, legs and/or feet
- Abnormal electrolyte levels in your blood (potassium, magnesium, phosphate, calcium, sodium) which may require you to take supplements or receive fluids
- Muscle spasms
- Insomnia
- Decreased white blood cell count (cells that help fight infection) with fever which may increase your risk of infection
- Low blood pressure
- Pneumonia
- Low platelet count (cells that help your blood clot) which may increase your risk of bleeding
- Nose bleeds

Less Common Risks of Pevonedistat (some may be serious) – Occurring in less than 10% (in other words, fewer than 1 person in 10) of patients treated in all four Phase I single-agent studies:

- Abdominal pain and/or bloating
- Upper respiratory tract infections
- Weakness
- Low levels of creatinine in your blood which may indicate abnormal kidney function
- Elevated blood sugar levels
- Numbness or tingling in the hands and/or feet
- Excessive sweating and/or night sweats
- Build-up of fluid between the tissues that line the lungs and chest (symptoms may include cough, sharp chest pain or shortness of breath)
- Itching
- Anxiety
- Confusion
- Discoloration and/or bruising of the skin
- Abnormal lung sounds when breathing
- Wheezing
- Progress of underlying disease
- Pain, swelling and/or sores in the mouth
- Decreased urination
- Coughing up blood
- Tingling or pricking sensation
- Rash
- Inflammation of the sinuses
- Urinary tract infection
- Elevated brain natriuretic peptide levels in the blood which may indicate abnormal heart function
- Decreased oxygen levels in the blood
- Accumulation of fluid in the body (symptoms may include weight gain, swelling and/or shortness of breath)
- Nasal congestion
- Sepsis: a life-threatening infection in the blood

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Risks of Azacitidine

Most common adverse reactions (> 30%) by subcutaneous (SC) route are:

- Nausea
- Anemia (low red blood cells, which can make you feel tired)
- Thrombocytopenia (low platelets, which can increase the risk of bleeding)
- Vomiting
- Pyrexia (fever)
- Leukopenia (decreased white blood cells, which can increase the risk of infection)
- Diarrhea
- Injection site erythema (redness or rash at the injection site)
- Constipation
- Neutropenia (decreased white blood cells, which can increase the risk of infection)
- Ecchymosis (red or blue bruise under the skin at the injection site).

Most common adverse reactions by intravenous (IV) route also included:

- Petechiae (small red or blue spots under the skin at the infusion site)
- Rigors (shivering)
- Weakness
- Hypokalemia (low potassium, which can cause muscle weakness).

Risks of Pevonedistat in Combination with Azacitidine

Pevonedistat in combination with azacitidine has previously been studied in several different clinical trials (two Phase I studies, one Phase II study, and an ongoing Phase III study), which enrolled patients with Acute Myeloid Leukemia, Chronic Myelomonocytic Leukemia or MDS who had not yet been treated for their disease. Based on this information:

The most common adverse reactions (reported by at least 2 and ≥ 25% of patients treated with pevonedistat/azacitidine combinations in any study) :

- Constipation
- Fatigue
- Nausea

- Neutropenia (low white blood cells, which may increase your risk of infection) with or without fever
- Anemia (low red blood cells, which can make you feel tired)
- Fever
- Vomiting
- Diarrhea

Other adverse reactions (reported by at least 2 patients and between 10 and 25% of patients treated with the pevonedistat/azacitidine combination in any of the three studies):

- Cough
- Decreased appetite
- Thrombocytopenia or decrease in platelets (cells that help your blood clot)
- Back pain
- Insomnia
- Pneumonia (infection in the lungs)
- Swelling in your legs or arms
- Difficulty breathing
- Dizziness

Other events leading to discontinuation that were assessed by study doctors as at least possibly related to the pevonedistat/azacitidine combination were:

- Lung cancer

Myelosuppression (decreased white blood cells, platelets and red blood cells) with increased risk of infection, bleeding, and anemia and febrile neutropenia (fever with low white blood cell count) are considered potential risks of combinatorial treatment with pevonedistat and azacitidine (PevAz treatment) complicated by underlying disease or malignancy.

It is possible that pevonedistat or azacitidine may cause additional side-effects that were not seen in animal studies or early human studies.

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

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Reproductive Risks

Because pevonedistat (also known as MLN4924) has only been tested in animal and early human studies, it is unknown whether pevonedistat can affect a male patient's ability to produce sperm; or, for women, permanently stop the ovaries from producing eggs. The study medication may be a risk to an unborn child or breast-feeding baby, so it is important to read the section on "Risk to the unborn or breastfeeding child" carefully, whether you are a man or a woman. For future childbearing you should consider banking sperm or eggs, prior to administration of pevonedistat.

Although the effect of pevonedistat on a fetus or unborn child has not been studied in animals or humans, based on knowledge of how this drug works, it is reasonable to assume that it may be harmful to an embryo or fetus. Therefore, female patients should avoid becoming pregnant while participating in this study. Male patients should also avoid getting their partner pregnant while participating in this study.

PREGNANCY, CONTRACEPTION AND BREASTFEEDING (MEN AND WOMEN)

Female patients:

We do not know if the study drug pevonedistat will affect an unborn or breastfeeding child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/ infant, you should not become pregnant, breastfeed a baby, or donate an egg or eggs (ova) during this study and for 4 months afterwards.

Females who have the ability to become pregnant must have a negative pregnancy test prior to enrolling in the study. This test will be repeated just before you start taking the study medication and then regularly throughout the study. If a pregnancy test during the study shows that you may be pregnant, you will be withdraw from the study and the treatment will end.

If you have not had menstrual bleeding without an alternate medical cause for at least 1 year prior to the date of signed informed consent, you may be post-menopausal. Post-menopausal status may be confirmed with a serum FSH level before study treatment is initiated.

Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use two effective methods of birth control from the time of signing the informed consent form, for the

entire study drug treatment period, and for four months after receiving your last dose of study drug. It is strongly recommended that at least one of these two methods be highly effective (i.e. intrauterine device or hormonal contraception methods). When in line with your preferred and usual lifestyle, you may also agree to practice true abstinence (defined as complete avoidance of heterosexual intercourse).

Effective Methods of Contraception

Barrier Methods	Intrauterine Device Methods	Hormonal Methods	Surgical Methods
• Male or female latex condom plus spermicide • Cervical cap plus spermicide • Diaphragm plus spermicide	• Copper T (e.g. Paragard®) • Levonorgestrel-releasing intrauterine system (e.g. Mirena®) – also considered a hormonal method	• Implants • Hormone shot or injection • Combined pill (estrogen + progestin) • Minipill (progestin only) • Patch	• Bilateral tubal ligation • Hysterectomy • Bilateral oophorectomy

Male patients:

We do not know if using pevonedistat will affect sperm or an unborn baby fathered by someone using pevonedistat. Therefore, due to potential risk, you should not get your partner pregnant or donate sperm during the study and for 4 months afterwards. Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (e.g. latex condom with a spermicidal agent) during the entire time when you are given the study drug, and for 4 months after you have finished getting the study drug. Or, you should completely avoid having heterosexual intercourse.

If your partner should become pregnant, she should be under medical supervision during her pregnancy, and the bay should be under supervision after it is born. Your partner may be asked to give her consent to the collection of information related to both herself as well as the baby.

All patients (male or female):

If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The study doctor will advise you of the possible risks to your unborn child and discuss

options for managing the pregnancy with you. For female patients who become pregnant while on this study, the study treatment will be stopped immediately and the pregnancy will be followed until conclusion. You will be asked for the results of any tests and procedures carried out during your pregnancy and up to the birth. You may also be asked for the results from any evaluation of the baby after the birth.

Risks that are not known:
Because this treatment is investigational, meaning non-FDA approved, there may be risks that we do not know about at this time.

Good effects that might result from this study:
a) The benefits to science and humankind that might result from this study:
This research may contribute to the understanding of cancer and its treatment, and may eventually lead to improvements in treatment.

b) The benefits you might get from being in this study:
There may or may not be a direct benefit to you as a result of your participation in the study.

Procedures to be followed:
If you qualify and agree to participate, your time in this research study will be followed in "Cycles". Each treatment Cycle lasts 28 days.

All patients enrolling in this study will receive treatment with azacitidine and pevonedistat:
- Azacitidine: On Days 1, 2, 3, 4 and 5 of each 28-day cycle.
- Pevonedistat: On Days 1, 3 and 5 of each 28-day cycle.

Depending on the local site procedure, azacitidine may be administered either by subcutaneous injection under the skin (a "shot" from a syringe and needle into, for example, the thigh, abdomen or upper arm), or by an intravenous infusion (an "i.v. bag" into a vein in the arm or similar site). If azacitidine is administered by subcutaneous injection under the skin, each azacitidine treatment may require the total azacitidine dose to be divided into 2 syringes injected into 2 separate sites (depending on the height and weight of the patient). If azacitidine is administered into a vein, the intravenous infusion occurs over about 10-40 minutes.

Pevonedistat will be infused into a vein in the arm or similar site, and each pevonedistat infusion will take about 60 minutes.

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On treatment days when patients are scheduled to receive both azacitidine and pevonedistat (i.e. on Days 1, 3 and 5 of each scheduled cycle), administration of azacitidine will be completed BEFORE initiation of pevonedistat treatment.

If you decide to participate in the study, you must first sign this consent form. Before you are treated, your study doctor will need to determine if you are eligible to take part in this study. By signing this form, you agree to follow the instructions given by the research staff during the study.

After reviewing and signing this consent form, you will be asked to undergo tests and procedures to find out if it is okay for you to take part in the research study. This is called screening. Some of these tests and procedures are likely to be part of the regular care you would receive even if you were not participating in the study. You may have had some of these tests or procedures recently. If this is the case, these tests or procedures may not need to be repeated.

After these tests are reviewed, it is possible you will not be able to be in the study. There may be other reasons why you are unable to be in this study. These reasons will be discussed with you by your study doctor or the clinic staff.

Screening

The following must be completed ≤ 28 days prior to your first dose of study treatment:

- Your study team must have documentation from an acceptable local or designated laboratory that you have been diagnosed with myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative neoplasm (i.e. MDS or MDS/MPN). Patients without documentation of eligible MDS or MDS/MPN status will not be eligible to enroll in the study.
- After informed consent, an expanded screening window of up to 28 days prior to Cycle 1, Day 1 is allowed for any necessary diagnostic testing (if acceptable results are not already available). Diagnostic testing typically involves a blood sample from your arm (about ½ tablespoon), and a bone marrow aspiration and biopsy (the removal of a small piece of bone and bone marrow by inserting a needle into your hip bone).
- Fresh bone marrow biopsy and aspirate: Even if your MDS or MDS/MPN condition is already documented on paper from an acceptable laboratory, you will still need to have fresh bone marrow biopsy and aspirate. Tissue may be collected for testing that is considered "standard of care" to evaluate your disease status (i.e. bone marrow architecture and cell counts, flow cytometry, cytogenetic and molecular testing). Additionally, bone marrow

aspirate (about 1⅓ tablespoon) may be collected for research to help understand your response or lack of response to the study treatment.

- Blood will be drawn (about 1⅓ tablespoon) prior to starting study treatment; at one time point, ideally on the same-day as your fresh bone marrow biopsy and aspirate (prior to the procedure) for the following:
  - Pharmacogenetic (PG) blood sample for research to look for possible differences in genes (also known as DNA) that may influence how different patients do or do not respond to the study treatment.
  - Pharmacodynamic (PD) blood samples to study biomarkers for research. (Biomarkers are biological indicators of how your body and illness may be reacting to the drugs that you are receiving.)

The following must be completed ≤ 21 days prior to your first dose of study treatment:

- Physical exam. You will be asked about your past and current health including any past treatments for your condition.
- Your performance status will be assessed by questions about your ability to carry out daily activities, and your height and weight will be recorded.
- You will be asked about any problems you are having and the medicines you are taking, including all prescriptions and over-the-counter medicines.
- Blood will be drawn (about ½ tablespoon) to check the following:
  - Blood Cell Counts (numbers of each type of blood cell)
  - Coagulation (how your blood clots)
  - Chemistries (proteins, elements and minerals in your blood)
  - Women Only: A blood pregnancy test will be done for women who can become pregnant (about an additional ⅓ tablespoon of blood will be drawn). Within 72 hours prior to starting study treatment, the pregnancy test must be negative for you to take part in the study. Women who are pregnant or breast feeding may not take part in the study. If you are a post-menopausal woman (a woman who can no longer become pregnant), a portion of the above blood collected for blood chemistries may be used to also measure follicle stimulating hormone (FSH) to confirm your post-menopausal status.
- Quality of Life (QOL) questionnaire: You will complete a paper form (about 2-3 pages) of questions about your well-being, symptoms and concerns about your illness. In response to

each question, you typically will circle a number (usually 0 to 4, or 0 to 10) to indicate how much or how little each question describes your condition.

- 12-Lead Electrocardiogram (ECG) to check the electrical activity of your heart, using 12 sticky pads attached to the surface of your skin.

Treatment

If, based on the results of the above screening tests and procedures, you qualify and choose to participate in the study, you will return to your study doctor's office to begin treatment.

Cycle 1, Day 1
(Unless previously completed ≤ 3 days prior to your first dose of azacitidine/pevonedistat):

- Physical exam.
- Weight.

- Blood will be drawn (about ½ tablespoon) for the following:
  - Check your Blood Cell Counts (numbers of each type of blood cell)
  - Check your Chemistries (proteins, elements and minerals in your blood).
  - Women Only: A blood pregnancy test will be done for women who can become pregnant
    (about ⅓ tablespoon of blood will be drawn).

Cycle 1, Day 1 (continued)

- Your performance status (ability to carry out your daily activities) will be assessed.
- You will be asked about any problems you are having and the medicines you are taking, including all prescriptions and over-the-counter medicines.
- Quality of Life (QOL) questionnaire.
- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).
- 12-Lead Electrocardiogram (ECG) to check the electrical activity of your heart, using 12 sticky pads attached to the surface of your skin (AFTER administration of pevonedistat)

Cycle 1, Day 2

- Azacitidine injection or infusion.

Cycle 1, Day 3

- Blood will be drawn (about ½ tablespoon) for the following:
  - Check your Blood Cell Counts (numbers of each type of blood cell)
  - Check your Chemistries (proteins, elements and minerals in your blood)
- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).

Cycle 1, Day 4

- Azacitidine injection or infusion.

Cycle 1, Day 5

- Blood will be drawn (about ½ tablespoon) for the following:
  - Check your Blood Cell Counts (numbers of each type of blood cell)
  - Check your Chemistries (proteins, elements and minerals in your blood)
- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).
- 12-Lead Electrocardiogram (ECG) to check the electrical activity of your heart, using 12 sticky pads attached to the surface of your skin (AFTER administration of pevonedistat)

Cycle 1, Day 15

- Physical exam.
- You will be asked about any problems you are having.
- Blood will be drawn (about ½ tablespoon) for the following:
  - Check your Blood Cell Counts (numbers of each type of blood cell)
  - Check your Chemistries (proteins, elements and minerals in your blood).

Cycles ≥2, Day 1

In general, you may continue to receive study treatment for up to 12 months as long as you tolerate treatment and your disease does not get worse (progress). After 1 year of study treatment you may be allowed to continue treatment, if your study doctor, Dr. Savona and Millennium/Takeda agree that your disease is still responding to the treatment and you continue to receive benefit.
If you continue beyond Cycle 1, the following will occur on Day 1 of each new 28-day cycle:

- Physical exam.
- Your performance status (ability to carry out your daily activities) will be assessed.

- Weight.
- You will be asked about any problems you are having and the medicines you are taking, including all prescriptions and over-the-counter medicines.
- Quality of Life (QOL) questionnaire
- Blood will be drawn (about ½ tablespoon) for the following:
  - To check your Blood Cell Counts (numbers of each type of blood cell)
  - To check your Chemistries (proteins, elements and minerals in your blood)
  - Women Only: A blood pregnancy test will be done for women who can become pregnant (about an additional ⅓ tablespoon of blood will be drawn). Within 72 hours prior to starting study treatment, the pregnancy test must be negative for you to take part in the study. Women who are pregnant or breast feeding may not take part in the study. If you are a post-menopausal woman (a woman who can no longer become pregnant), a portion of the above blood collected for blood chemistries may be used to also measure follicle stimulating hormone (FSH) to confirm your post-menopausal status.
- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).

<u>On Day 1 of Cycle 2 only</u>

- 12-Lead Electrocardiogram (ECG) to check the electrical activity of your heart, using 12 sticky pads attached to the surface of your skin (AFTER administration of pevonedistat)
- Blood will be drawn to check coagulation (how your blood clots)

<u>On Day 1 of Cycles 3 and 7 only</u>

- Fresh bone marrow biopsy and aspirate required prior to treatment on Cycle 3, Day 1 and
  Cycle 7, Day 1 (acceptable window up to 7 days prior to cycle 3 day 1 & cycle 7 day 1 treatments).
- Pre-Dose Pharmacogenetic and Pharmacodynamic blood samples (about 1⅓ tablespoon): on cycle 3 day 1 and cycle 7 day 1 at a single time point, prior to scheduled bone marrow procedure / scheduled azacitidine treatment.

<u>Cycles ≥2, Day 2</u>

- Azacitidine injection or infusion.

<u>Cycles ≥2, Day 3</u>

- Blood will be drawn (about ½ tablespoon) for the following:
  - Check your Blood Cell Counts (numbers of each type of blood cell)
  - Check your Chemistries (proteins, elements and minerals in your blood)
- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).

Cycles ≥2, Day 4

- Azacitidine injection or infusion.

Cycles ≥2, Day 5

- Blood will be drawn (about ½ tablespoon) for the following:
  - Check your Blood Cell Counts (numbers of each type of blood cell)
  - Check your Chemistries (proteins, elements and minerals in your blood)
- Azacitidine injection or infusion.
- Pevonedistat infusion (AFTER completion of azacitidine).

On Day 5 of Cycle 2 only

- 12-Lead Electrocardiogram (ECG) to check the electrical activity of your heart, using 12 sticky pads attached to the surface of your skin (AFTER administration of pevonedistat)

Note: If you continue study treatment beyond 12 cycles, then the frequency of blood draws to check your Blood Cell Counts and Chemistries will be at the discretion of your study doctor in cycles ≥ 13.

End-of-Treatment and Follow-up

You may stop receiving study treatment based on your disease assessments, or if you are having side effects that make you unable to tolerate study therapy. Based on discussions between you and your study doctor, you may discontinue for other reasons including your decision to stop being treated.

End-of-Treatment / Withdrawal Assessments

The following must be completed subsequent to and not later than 14 days after you permanently discontinue study treatment with azacitidine/pevonedistat (whichever treatment occurs last) and prior to any subsequent anti-cancer therapy:

- Physical Exam.
- Your performance status (ability to carry out your daily activities) will be assessed.

- Weight.
- You will be asked about any problems you are having and the medicines you are taking, including all prescriptions and over-the-counter medicines.
- Quality of Life (QOL) questionnaire.
- Blood will be drawn (about ½ tablespoon) for the following:
  - Check your Blood Cell Counts (numbers of each type of blood cell)
  - Check your Chemistries (proteins, elements and minerals in your blood)
  - Women Only: A blood pregnancy test will be done for women who can have children
    (about ⅓ tablespoon of blood will be drawn).
- Pharmacogenetic and Pharmacodynamic blood samples for research (about 1⅓ tablespoon of blood).
- Fresh bone marrow biopsy and aspirate required at End-of-Treatment, or at time of suspected Progressive Disease. If you discontinue the study treatment for reason other than progressive disease confirmed by marrow procedure (for example, because of side effects or blood tests suggesting your illness may be getting worse), then fresh bone marrow/aspirate samples and pharmacogenetic and pharmacodynamic blood samples for the study will be collected at a subsequent procedure which ultimately confirms progressive disease.
- 12-Lead Electrocardiogram (ECG) to check the electrical activity of your heart, using 12 sticky pads attached to the surface of your skin.

Also, if you discontinue study treatment for reason other than progressive disease confirmed by marrow procedure (for example, because of blood tests suggesting your illness may be getting worse), please note the study may continue to request results of laboratory tests that you have done outside of the study (but which are related to peripheral blood counts), until progression of your disease is ultimately confirmed by marrow procedure.

<u>28-Day Follow-Up Visit Assessments</u>
You will be asked to return to the study clinic 28 days after your final treatment with azacitidine or pevonedistat (whichever occurs last), in order to undergo the following:

- Physical Exam.
- Your performance status (ability to carry out your daily activities) will be assessed.
- Weight.

- You will be asked about any problems you are having and the medicines you are taking, including all prescriptions and over-the-counter medicines.
- Quality of Life (QOL) questionnaire.
- Blood will be drawn (about ½ tablespoon) for the following:
  - To check your Blood Cell Counts (numbers of each type of blood cell)
  - To check your Chemistries (proteins, elements and minerals in your blood)

Long-Term Follow-Up

After you complete all of the planned study visits, you will be contacted approximately every 3 months (± 14 days) after your final treatment with azacitidine or pevonedistat (whichever occurs last), in order to determine your health status. Contact could be by a variety of methods, including via telephone, clinic visit, medical records, or publicly available information. This will continue until end of the study, consent for communication is withdrawn, death, or for a maximum of 4 years after your final treatment with pevonedistat/azacitidine – whichever comes first.

Costs to you if you take part in this study:

If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Study Title:	HEM 16146: PevAz: A phase II trial of Pevonedistat and Azacitidine in MDS or MDS/MPN patients who fail primary therapy with DNA methyl transferase inhibitors
Version Date:	29NOV2019
PI:	Michael R. Savona, M.D.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Michael R. Savona, M.D. at (877) 936-8422. If you cannot reach the research staff, please page the study doctor at (615) 322-5000.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:
The study doctor, sponsor, or a regulatory authority (FDA, Institutional Review Board, etc) may choose to end your participation in this study without your consent. This could happen for reasons such as:

- The study doctor feels it is not in your best interest to continue in the study,
- You fail to follow the study doctor's instructions,
- You experience an adverse reaction that requires other medical treatment,
- You become pregnant, or
- The sponsor or the FDA or other regulatory authority stops the study for any reason.

If you are removed from the study, the reason will be explained to you.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Clinical Trials Reporting Program:
Vanderbilt's NCI-Designated Cancer Center or the Sponsor registers National Cancer Institute (NCI)-supported clinical trials with NCI though their Clinical Trials Reporting Program (CTRP) to provide study related information. The data provided will include the following identifiable information that may

identify you: birth month/year and five-digit zip code. NCI uses the data to manage and enhance the nation's investment in cancer research.

Confidentiality:
All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Your information and samples will be given a unique code instead of your name to help protect your identity. Dr. Savona, his staff at Vanderbilt and other authorized people will be the only people who know your personal information. Results of this study may be presented in meetings or in publications. Your identity will not be released in those presentations. Your study records will be secured in the clinical trials office. Your research data will be kept for an unknown period of time. The study results will be kept in your research record for at least six years after the study is finished. Your tissue and blood samples will be kept in locked storage and may be used or stored indefinitely from the end of the study. Any samples that are not needed will be destroyed.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Savona and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

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Study Results:

You have the right to see and copy the PHI we gather on you for as long as the study doctor or research site holds this data. To ensure the scientific quality of the research study, you will not be able to review some of your research data until after the research study is finished.

Authorization to Use/Disclose Protected Health Information

What information is being collected, used, or shared?

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?

The people who may request, receive or use your private health information include the study sponsor Vanderbilt Medical Center and its agents or contractors, study safety monitors and auditors, data managers and other agents and contractors used by the study team, researchers and study team members. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. Also, your records may be seen by people from regulatory authorities (like the US Food and Drug Administration [FDA]), auditors, and the IRB. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the funder of the study and its agents or contractors, outside providers, government agencies and other sites in the study. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?

You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?

Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

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What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. If you change your mind, we ask that you contact Dr. Savona in writing and let him know that you withdraw your consent. His mailing address is: Michael R. Savona, M.D., Vanderbilt-Ingram Cancer Center, 2200 Pierce Avenue, 777 Preston Research Building, Nashville, TN 37232. At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

Time: _____