COMIRB
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Study Title: **Concomitant Omacetaxine Mepesuccinate and Azacitidine for Patients with Previously Untreated High Grade Myelodysplastic Syndromes (MDS)**

You are being asked to participate in a research study. A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, as well as how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to participate in this study, you will be asked to sign this form.

Why is this study being done?

The purpose of this study is to learn more about a combination of two drugs and how well it might work to treat high grade myelodysplastic syndromes (MDS). The two drugs are called omacetaxine and azacitadine. You are being asked to be in this research study because you have been newly diagnosed with MDS, have relapsed, or refractory MDS.

Omacetaxine is approved by the U.S. Food and Drug Administration (FDA) to treat a type of leukemia called chronic myeloid leukemia (CML) but is not approved to treat your specific type of cancer. Azacitadine is approved by the FDA to treat MDS.

Throughout the rest of this consent form, Omacetaxine and Azacitadine will be called the “study drugs” when referenced together.

How many people will participate?

Up to 91 people from your area will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form. You will be given a copy to keep and the original form will be kept at the clinic. You can withdraw from the study at any time and without giving a reason. This will not affect the standard medical care you receive.

There are 3 parts to the study:

1. Screening (before beginning the study drugs)
2. Phase I (dose escalation)
3. Phase II (dose expansion) including relapsed and refractory MDS

During Phase I, the study doctors are trying to find the highest dose of omacetaxine that can be given safely with azacitadine. Certain serious or severe side effects may occur and these are likely to occur at higher doses. If certain serious or severe side effects are observed, the study will be stopped. Once this dose of omacetaxine has been determined, Phase II of the study will begin.

During Phase II, the study doctors will give the dose of omacetaxine determined during Phase I in combination with azacitadine.

The dose of omacetaxine that you will receive will depend on when you enroll in the study. The study doctor will tell you whether you will be participating in the Phase I or the Phase II portion. All those with relapsed or refractory MDS, will only be enrolled to Phase II.

The next section of this form lists what will be expected of you if you agree to join this study.

Study Procedures

While you are taking part in this study, some of the tests and procedures are the same type that would be performed as part of your regular cancer care even if you did not join the study. Some of the tests and procedures are required only for the study and are identified below as "**research**" procedures.

The screening tests and procedures will be done to see if you are eligible to join this study. You may have had some of these tests and procedures done recently as standard care for your cancer, and they may not need to be repeated.

- **Informed Consent (research)**
  This informed consent form will be discussed with you and you will be given a copy of this document. If you join the study, you will be asked to sign this consent form before you receive any study related tests or procedures.

- **Medical and Cancer History**
  Before you start the study we will record your date of birth, race, ethnicity, and complete medical history. This history will look at the background and progress of your cancer and any treatments you have received for your disease.

- **Physical Examination**
  A physical examination will be completed as part of your standard of care. We will also assess if the study drug is affecting your body functions including lungs, heart, abdomen, extremities, skin, head (eyes, ears, nose, hair, etc.) and neurologically.

- **Vital Signs**
  We will take your blood pressure, heart rate, respiratory rate, body temperature and weight. Height will be measured only during screening.

- **Performance Status**
  We will assess how well you are performing your daily activities.

- **Review of Current Medications**
  Your study doctor will let you know which medications you can and cannot take while taking part in this study. From the time you first receive the study drugs through 30 days after the last dose, we will record medications you may be taking.

- **Review of Side Effects (research)**
  Some risks have been identified because of the disease process or through use of the study drugs themselves and these will be followed very closely by the Principal Investigator and study staff. More information will be provided in the Risk area of this consent.

- **Electrocardiogram (ECG or EKG)**
  This is a simple, noninvasive procedure that records the electrical activity of the heart. Electrodes are placed on the skin of the chest and connected in a specific order to a machine. Output usually appears on a long scroll of paper that displays a printed graph.

- **Blood Tests**
  At various time points during the study, you will have blood collected for routine testing.

- **Bone Marrow Biopsy/Aspirate (research except at screening)**
  At various time points during the study, you will have bone marrow examined. This involves placing a hollow needle into your hip bone near the small of your back and taking a small sample of the bone (bone marrow biopsy) and 2-3 tablespoons of the liquid bone marrow inside the bone (bone marrow aspirate).

- **Study Drug Diary (research)**
  You will be provided with a drug diary to write down the date, time, and dose of study drug. A new diary will be provided at the beginning of each cycle and the completed diary will be collected at the end of each cycle.

- **Azacitadine administration**
  You will receive the standard dose of azacitadine (75mg/kg^2) intravenously as noted in the schedule of study visits section of this form.

- **Omacetaxine administration (research)**
  You will receive the dose of omacetaxine as an injection under the skin as noted in the schedule of study visits section of this form. You will receive instruction on how to self-administer this drug.

Study Visits

Screening Visit *(within 14 days before treatment)*

- Informed consent
- Review of medical history
- Complete physical exam
- Performance status
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
  - Coagulation tests (including PT and PTT/INR)
  - Pregnancy (for women who can get pregnant)
- Electrocardiogram (EKG)
- Bone marrow biopsy/aspirate (*may be performed up to 28 days prior to treatment*)

During the Study

Cycle 1 – Day 1 *(each cycle is 28 days)*

- Physical exam
- Performance status
- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Receive study drug calendar and diary
- Receive azacitadine (IV)

- Receive omacetaxine

Cycle 1 – Day 2-7

- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Receive azacitadine (IV)
- Receive omacetaxine

Cycle 1 – Day 8

- Physical exam
- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Bone marrow aspirate

Cycle 1 – Day 28

- Physical exam
- Performance status
- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Collect study drug calendar and diary
- Bone marrow biopsy/aspirate

Cycles 2+

- Physical exam
- Performance status
- Review of side effects
- Review of current medications

- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Receive study drug calendar and diary
- Receive azacitadine (IV)
- Receive omacetaxine
- Bone marrow biopsy/aspirate (Day 28 only)
- Collect study drug calendar and diary (Day 28 only)

During cycles 2+, all procedures will be done on Day 1, unless otherwise indicated. Omacetaxine and Azacitadine will be given on Days 1-7.

Bone marrow aspirate and biopsy will occur after Cycle 4, Cycle 6, and every 6 cycles thereafter.

End of Study Visit

- Physical exam
- Performance status
- Review of side effects
- Review of current medications
- Vital signs
- Blood draw for routine tests, including:
  - Hematology
  - Chemistry (including magnesium, phosphorus and LDH)
- Bone marrow biopsy/aspirate
- Collect study drug calendar and diary

Safety Follow-up Visit *(30 days after end of treatment for subjects who stop the study as a result of side effects)*

- Medical history
- Physical exam
- Performance status
- Review of side effects
- Review of current medications

The study team will continue to follow up with you at least once a year, either by phone or during a routine clinic visit. Long-term follow up will continue every year up to 5 years.

How long will I be in the study?

You may continue receiving study drugs indefinitely or until your doctor determines that you should stop receiving the study drug regimen due to side effects, progression of your disease, or until you decide to stop participating in the study.

You will be followed long term for disease status and survival information for up to 5 years.

What are the possible discomforts or risks?

You may have side effects while you are in this study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study treatment that are unknown at this time. You should tell the study doctor about anything that is bothering you or any side effects you have, even if you do not think they are related to the study treatment. Many side effects go away shortly after the medications are stopped, but in some cases side effects can be serious, long lasting, or permanent.

Risks of the Study Drugs

Potential Risks Associated with Omacetaxine

COMMON, SOME MAY BE SERIOUS (seen in more than 10% of patients):

- Decrease in your platelets (thrombocytopenia) which can cause bleeding
- Decrease in a type of white blood cells called neutrophils (neutropenia)
- Decrease in red blood cells (anemia)
- Diarrhea
- Muscle Pain
- Nausea
- Infusion/Injection Site Reactions
- Fatigue
- Fever
- Abdominal Pain
- Weakness
- Headache
- Joint Pain
- Nose bleeds
- Swelling in arms & legs
- Cough
- Hair Loss
- Constipation
- Vomiting
- Insomnia

- Rash
- Bone marrow failure
- Fever with low number of a type of white blood cell called neutrophils (febrile neutropenia)
- Decreased appetite
- Chills

Less Common, SOME MAY BE SERIOUS (seen in more than 1% but less than 10% of patients)

- Cardiac Disorders: rapid heart rate, palpitations, chest pain, irregular heart rate, slowed heart rate.
- Ear Disorders: ear pain, ear hemorrhage, tinnitus (ringing in ear).
- Eye Disorders: cataract, blurred vision, broken blood vessels in the eye, dry eye, excessive tearing, pink eye, double vision, eye pain, eyelid swelling.
- Gastrointestinal Disorders: inflammation to mouth & lips, mouth ulceration, abdominal distension, gas, GERD, bleeding gums, dry mouth, hemorrhoids, gastrointestinal hemorrhage, black, tarry bowel movements, mouth hemorrhage, oral pain, anal fissure, difficulty swallowing, pain in the gums.
- General Disorders: hot flashes, flu-like illness, swelling.
- Immune System Disorders: allergic reaction.
- Metabolism and Nutrition Disorders: diabetes mellitus, gout, dehydration.
- Musculoskeletal and Connective Tissue Disorders: bone pain, muscular weakness, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, musculoskeletal discomfort.
- Nervous System Disorders: dizziness, bleeding in the brain, numbness & tingling, convulsion, sciatica, burning sensation, changes in taste, tremor.
- Psychiatric Disorders: anxiety, depression, agitation, confusional state.
- Urinary: painful urination, damage to the kidneys.

- Respiratory: throat pain, nasal congestion, hoarseness, productive cough, lung congestion, runny nose, coughing up blood.

- Skin Disorders: redness, itching, dry skin, red spots, excessive sweating, night sweats, bruising, purpura, skin lesion, skin ulcer, skin sloughing, skin hyperpigmentation.

- Vascular Disorders: high blood pressure, low blood pressure

Potential Risks Associated with Azacitidine

The following side effects may happen with azacitidine and are common or very common (may affect more than 1 in 100 people):

- Decrease in your platelets (thrombocytopenia)
- Decrease in red blood cells (anemia)
- Decrease in white blood cells (leukopenia)
- Decrease in a type of white blood cells called neutrophils (neutropenia)
- Fever with low number of a type of white blood cell called neutrophils (febrile neutropenia)
- Bone marrow failure
- Neutropenia with infection and the presence of bacteria in your blood stream (neutropenic sepsis)
- Bacteria or viral infections including lung infection (pneumonia), upper respiratory infection, or urinary tract infection
- Fever
- Bleeding including brain and stomach/gut bleeding
- Bruising
- Injection site pain, redness, or bruising (if receiving azacitidine as an injection under the skin)
- Damage to the kidneys or kidney failure
- Abdominal pain
- Constipation
- Diarrhea
- Feeling sick to your stomach (nausea)
- Vomiting
- Chest pain
- Shortness of breath
- Feeling tired or lethargic
- Lack of appetite or interest in food
- Weight loss
- Pain including joint, muscle pain and headache

- Dizziness
- Anxiety and difficulty sleeping
- Rash
- Itching
- Decrease in blood potassium

The following events have been reported in trials with azacitidine less frequently, but can be severe in nature. These events may or may not be related to azacitidine.

- Severe or fatal infections including severe skin infections (necrotizing fasciitis)
- Severe bleeding
- Heart problems: Cardiac arrest (heart stopped), heart attack, irregular heart beat
- Liver damage in individuals with previous liver problems Severe allergic reactions (anaphylaxis)
- Tumor lysis syndrome

With both drugs given together, additional risks, warnings, and precautions, as outlined should be discussed with your study doctor. You should contact the study doctor or study staff and get medical help if you have any of the above mentioned or any other side effects during the study. Combination of azacitidine with omacetaxine may worsen the potential side effects of azacitidine or omacetaxine, or even cause other side effects that were not known before.

Risks of the Study Procedures

Blood tests

Blood sampling and needle punctures carry some risk. Possible side effects include, but are not limited to, fainting, bleeding, bruising, discomfort, dizziness, infection and/ or pain at the puncture site.

Having an IV inserted in your vein

In this study we will insert a needle, connected to a plastic tube, into a vein in your arm. We will use the tube to take blood samples or give you fluids. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein. You will have this tube inserted for about four or five hours.

Bone marrow biopsy

In this study we will take four samples of bone marrow from your pelvic bone. Before we take each sample, we will give you some numbing medication on the skin outside your

pelvic bone (on your hip). After your skin is numb, we will push a special needle into the center of your pelvic bone. Then, we will draw the bone marrow up into the syringe. When we do this, you will have a pulling feeling as the marrow leaves the bone and goes into the syringe. The area around the bone will be sore for a few days.

There is a very small chance that you will be allergic to the numbing medicine. There is also a very small chance that you could bleed or develop an infection.

Electrocardiogram (EKG)
An electrocardiogram (EKG) is a test that records the electrical activity of the heart. Skin irritation is rare but could occur during an EKG from the electrodes or the gel that is used.

Risks Associated with Pregnancy

While participating in this research study, you should not become pregnant, nurse a baby, or father a baby. Women who are able to have children must use a highly effective means of birth control approved by your study doctor. You must continue the use of birth control during the entire time of your study participation at least 3 months after the last dose of azacitidine.

If you are a female who has stopped having menstrual periods for at least 1 year (menopause), please discuss with your study doctor the need for birth control. If you become pregnant, you must stop taking the study drugs at once and notify your doctor immediately. You will not be allowed to continue in the study. You may be asked questions about the outcome of your pregnancy and the baby.

Risk of Loss of Confidentiality

There is a risk that people outside the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence your willingness to continue, this new information will be discussed with you.

What are the possible benefits of the study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other individuals with MDS in the future.

Are there alternative treatments?

There may be other ways of treating your cancer. Instead of taking part in this study:

- You may choose to receive treatment with an approved therapy or drug combination.
- You may choose to participate in a different study with another experimental drug.
- You may choose to receive comfort/ palliative care.
- You may choose to get no treatment at all.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

Teva Pharmaceuticals, Inc. is providing a grant of funding support for this study. Teva manufactures the study drug, omacetaxine, and will provide this drug for the study. This research is being conducted by Dr. Daniel Pollyea. The research study will only pay for procedures not considered standard of care.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

The drug manufacturer, Teva, will pay for the cost of the study drug, omacetaxine. The funding for this study will also pay for any tests or procedures that are related to the research study.

The study drug, azacitadine, is considered standard treatment for your disease. This drug will be obtained through your insurance, and you will be responsible for any applicable copays required by your insurance policy.

There are some medical procedures that you would get for your condition whether you were in this study or not, such as blood draws. These are considered standard of care. You and/or your health insurance may be billed for the costs of medical care during this study, if these expenses are related to standard of care procedures. If you have health

insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs, or you do not have insurance, these costs will be your responsibility.

Ask your study doctor to discuss the costs that will or will not be covered by this research study. This discussion should include the costs of treating possible side effect. Otherwise, you might have unexpected expenses from being in this study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Pollyea immediately. His phone number is 720-848-8084.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Daniel A. Pollyea, MD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Pollyea at 720-848-8084. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Pollyea with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov. This Web site will not include information that can identify you. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Daniel A. Pollyea, MD
Anschutz Medical Campus
1665 N. Aurora Court
Mail Stop F754
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB).
- The study doctor and the rest of the study team.
- Teva Pharmaceuticals, Inc., manufacturer of omacetaxine who is also providing a grant of funding support.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current medical records that are relevant to this study, including but not limited to diagnosis(es), history and physical, laboratory or tissue studies, radiology studies, procedure results.
- Research visit and research test records.
- Blood or biopsy samples and the data with the samples.
- Billing or financial information.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.

- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

Agreement to be in this study and use my data

The research project and the procedures associated with it have been explained to me. The experimental procedures have been identified and no guarantee has been given about the possible results. I will receive a signed copy of this consent form for my records.

I agree to participate in this study. My participation is voluntary and I do not have to sign this form if I do not want to be part of this research study.

Subject Signature: _____ Date: _____

Subject Print Name:_____

Consent form explained by: _____ Date: _____

Print Name: _____

---------- Use Only if Applicable ----------

Signature Line for witness; required for consent of non-reading subjects and consent using a short form, if you requested such consent procedures

Witness of Signature ☐
Witness of consent process ☐

Witness Signature:_____ Date:_____

Witness Print Name: _____