THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Phase Ib/II study of omacetaxine and venetoclax for patients with relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome harboring mutant RUNX1

2020-0890

Study Chair: Courtney DiNardo, MD

_____ _____
Participant's Name Medical Record Number

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

This research has been reviewed and approved by an Institutional Review Board (IRB - a committee that reviews research studies).

STUDY SUMMARY

The goal of this clinical research study is to learn about the safety and tolerability of different doses of omacetaxine and venetoclax when given to patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is relapsed (has come back)/refractory (has not responded to treatment) and has a genetic change (mutation) called RUNX1.

This is an investigational study. Omacetaxine is FDA approved and commercially available for the treatment of certain phases of chronic myeloid leukemia but not for the treatment of AML or MDS. Venetoclax is FDA approved and commercially available for the treatment of relapsed/refractory (has not responded to treatment) AML and newly diagnosed AML in older patients that cannot receive intensive chemotherapy. It is considered investigational to give omacetaxine in combination with venetoclax. The study doctor can explain how the study drugs are designed to work.

The study drugs may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment.

You can read a full list of potential side effects below in the Possible Risks section of this consent.

You may receive omacetaxine and venetoclax for up to 12 study cycles.

Omacetaxine will be provided at no cost to you while you are on study. You and/or your insurance provider will be responsible for the cost of venetoclax.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard chemotherapy. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. The following screening tests will help the doctor decide if you are eligible:

- You will have a physical exam.
- Blood (about 4 tablespoons) will be drawn for routine tests and biomarker testing, including testing to check for the RUNX1 mutation. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drugs. Please note that the test used to look for the RUNX1 mutation is investigational, meaning that it has not yet been approved for use.
- You will have a bone marrow aspirate or biopsy for biomarker testing, which may include genetic biomarkers. To collect a bone marrow aspirate/biopsy, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow and bone is withdrawn through a large needle.
- If you can become pregnant, blood from the routine sample above or urine will be collected for a pregnancy test. To take part in this study, you must not be pregnant.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Study Groups

If you are found to be eligible to take part in this study, you will be assigned to a study group based on when you join this study. Up to 2 groups (one group of MDS participants and one group of AML participants) of 12 participants each will be enrolled in Phase 1b of the study, and up to 60 participants will be enrolled in Phase 2.

All participants will receive the same dose of omacetaxine and venetoclax. However, your dosing schedule may change depending on your study group (described in more detail below). The study doctor will tell you which group you are in.

Up to 84 participants will be enrolled in this study. All will take part at MD Anderson.

Study Drug Administration
Each study cycle is 28 days.

You will injection yourself or, if preferred, a caregiver may inject you with **omacetaxine** at home on Days 2-4 or Days 2 and 3 of each cycle, depending on when you enroll in the study. The study staff will show you or your caregiver how to give the injection and answer any questions you may have.

You will be given a diary to write down when you take each dose of omacetaxine. Bring the diary and any unused intact medication syringes with them to all study visits.

You will also take venetoclax tablets by mouth on Days 1-7, 1-10, or 1-14 of each study cycle, depending on when you join the study.

Venetoclax may cause a side effect called tumor lysis syndrome (TLS--when breakdown products of cancer cells enter the blood stream, described in more detail below under “Possible Risks”). To help prevent TLS, you may be given standard drugs to help decrease the risk of side effects. You may ask the study staff for information about how the drugs are given and their risks. On Day 1 of Cycle 1, blood (about 2 tablespoons each time) will also be drawn to check for signs of TLS before the dose and then 6-8 hours and 24 hours after the first dose.

Venetoclax should be taken in the morning with a cup (about 8 ounces) of water within 30 minutes after eating a meal, preferably a low- or moderate-fat breakfast.

While taking venetoclax you should not have grapefruit or grapefruit products, Seville oranges, or Star fruit within the 3-day period before your first dose of venetoclax and until your last dose of venetoclax.

If you miss a dose of venetoclax and you remember within 6 hours of your scheduled dosing time, you can take it when you remember. If it has been more than 6 hours or if you vomit a dose, wait and take your next dose as scheduled. Do not take a “make-up” dose. If you miss or vomit a dose, write this down in your study drug diary.

You will no longer be able to take the study drugs if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Study Visits

On **Days 1, 8, 15, and 22 of Cycles 1 and 2:**

- You will have a physical exam (Day 1 of Cycles 1 and 2 and Day 15 of Cycle 1 only).
- Blood (about 3 tablespoons) will be drawn for routine and biomarker testing.

On **Days 2, 5, and between Days 21-28 of Cycle 1,** blood (about 3 tablespoons) will be drawn for biomarker testing. In addition, between Days 21-28, you will also have a bone marrow biopsy/aspirate to check the status of the disease and for biomarker testing.

On **Day 1 of Cycles 3 and beyond:**

- You will have a physical exam.
- Blood (about 3 tablespoons) will be drawn for routine tests.
- At Cycles 3, 5, and every 3 cycles after that (Cycles 8, 11, 14, and so on), you will have a bone marrow biopsy/aspirate to check the status of the disease. You may have this done more often, if the doctor thinks it is needed.

If the disease appears to get worse, blood will be drawn for biomarker testing and you will have a bone marrow biopsy/aspirate to check the status of the disease.

End-of-Study Visit

Within 30 days after your last dose of study drug(s):

- You will have a physical exam.
- Blood (about 3 tablespoons) will be drawn for routine and biomarker tests.
- You will have a bone marrow aspirate/biopsy to check the status of the disease and for biomarker testing.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. You should discuss these with the study doctor. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Side effects will vary from person to person, and some may occur after you have stopped receiving treatment. Tell the study staff about any side effects you may have, even if you do not think they are related to the study drugs/procedures.

Omacetaxine and venetoclax may commonly cause low blood cell counts (red, white, and/or platelets):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.

- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.

Omacetaxine Side Effects

Common (more than 20% of patients)

• fatigue • fever • nausea • abdominal pain	• high blood levels of uric acid (possible painful joints and/or kidney failure) • low blood cell count (red, white, platelets)	• injection site reaction (swelling, skin rash/redness/itching, bruising, bleeding, hardened skin, and/or pain) • weakness

Occasional (occurring in 3-20% of patients)

• swelling (arm/leg) • headache • chills • difficulty sleeping • skin rash	• hair loss (partial or total) • high blood sugar (possible diabetes) • vomiting • loss of appetite • constipation	• abnormal kidney test (possible kidney damage) • pain (muscle, joint, arm/leg, back) • difficulty breathing

Frequency unknown but occurring in 1-10% of patients:

• heart attack • chest pain (possibly due to heart trouble) • slow/irregular/fast heartbeat • high blood pressure • low blood pressure (possible dizziness/fainting) • agitation • anxiety • bleeding in the brain • confusion • depression • dizziness • numbness • mental status change	• skin sore • skin peeling • skin redness/itching • darkening of the skin • night sweats • dry skin • low blood sugar • dehydration • diabetes • painful joint inflammation • muscle spasms • hot flashes • abdominal swelling • mouth/anal sores • abnormal taste • dry mouth • difficulty swallowing	• hemorrhoids • tarry stool • painful urination • abnormal liver tests (possible liver damage and/or yellowing of the skin and/or eyes) • blurry vision • cataracts (clouding of the lens of the eye) • bleeding in the tissue lining the eye • painful red eyes • double vision • swelling (eyelid) • eye pain • dry/teary eyes • ear pain • ringing in the ear

• abnormal sensation (such as pins and needles) • pain shooting from the lower back to the thighs • seizure • tremors • voice disorder • burning sensation on the skin	• upset stomach • inflammation of the stomach and/or intestines • heartburn/indigestion • digestive system bleeding • gum pain/disease/bleeding	• coughing up blood • flu-like symptoms • stuffy nose • runny nose • allergic reaction • reaction to a blood transfusion

Venetoclax Side Effects

Common (occurring in more than 20% of patients)

• swelling • fatigue • high blood sugar (possible diabetes)	• abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure)	• diarrhea • nausea • low blood counts (red, platelets, white) • abnormal liver test (possible liver damage) • muscle and/or bone pain • cough

Occasional (occurring in 3-20% of patients)

• fever • headache • dizziness • skin rash • mouth blisters/sores (possible difficulty swallowing)	• vomiting • constipation • abdominal pain • joint pain • high blood levels of uric acid (possible painful joints and/or kidney failure)	• pneumonia • difficulty breathing • tumor lysis syndrome (TLS)--breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

TLS is a problem that can occur when cancer cells break down rapidly and the body has to get rid of the broken up cell parts. Sometimes your body, especially the kidneys, cannot remove the cell parts quickly enough, so the level of some of these cell products in your blood, such as salts and acids, can rise. This can happen especially in participants with large tumors or a high number of cancerous white cells in the blood. TLS can lead to serious problems, such as effects on your kidneys and heart (including abnormal heart rhythms), seizures, or even death.

If you develop TLS, your urine may look dark, thick, or cloudy. You may have fever, chills, nausea/vomiting, diarrhea, confusion, shortness of breath, irregular heartbeat, fatigue, muscle pain, joint discomfort, and/or seizure. If you notice any of these, tell your doctor or nurse right away. Your study doctor will closely watch and treat you as needed to lower the risk of any serious changes in your blood or other complications of TLS. You may need to have extra blood tests or EKGs to check for signs of TLS.

If you notice any rash, hives, itching, or other signs of an allergic reaction such as swelling, wheezing, or you are having a hard time breathing, tell your doctor right away.

At this time, there are no known serious side effects that **occur in fewer than 3% of patients**.

Using the study drugs together may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Having **bone marrow biopsies/aspirates** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control during the study if you are sexually active

Birth Control Specifications: You must use highly effective birth control methods while on this study and for at least 90 days after the last dose of study drug(s). Highly effective methods include:

- Hormonal birth control (oral or injections)
- Intrauterine device (IUD)
- Double barrier methods (such as a condom in combination with spermicide)

If you can father a child, you must use a condom while on this study and for at least 90 days after your last dose of study drug(s).

Males: You must not donate sperm during the study and for at least 90 days after the last dose of study drug(s). Tell the doctor right away if your partner becomes pregnant or suspects pregnancy. If your partner/spouse becomes pregnant while you are on this study, the sponsor would like to collect information about the pregnancy. The study sponsor's contact information will be made available so that, if you and your partner wish to, you can share information about the outcome of the pregnancy with the sponsor. If you and/or your partner choose not to share this information, it will not result in any penalty or loss of benefits to which you are otherwise entitled.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away. The sponsor will ask for information about the pregnancy.

Getting pregnant may result in your removal from this study.

Loss of Confidentiality
Although every effort will be made to keep study data safe, there is a chance that your personal health information could be lost or stolen, which may result in a **loss of confidentiality**. All study data will be stored in password-protected computers and/or locked file cabinets and will continue to be stored securely after the study.

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or TEVA for this injury. You may also contact the Chair of MD Anderson’s IRB at 713-792-6477 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

Samples that are collected from you in this study may be used for the development of treatments, devices, new drugs, or patentable procedures that may result in commercial profit.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. Courtney DiNardo, at 713-794-1141) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson. The study staff may ask if they can continue collecting the results of routine care from your medical record.

   Otherwise, you may continue to be on the study, unless the investigational chemotherapy is no longer available.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, TEVA, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

7. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

   Any clinically relevant research results, including individual research results, will not be disclosed to you.

8. MD Anderson may benefit from your participation and/or what is learned in this study.

9. This study is supported by: Teva Pharmaceuticals.

10. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s)/supporter. If you have any questions about this, you may call the IRB at 713-792-6477.

Future Research

Data
Your personal information is being collected as part of this study. These data may be used by researchers at MD Anderson and Teva and/or shared with other researchers and/or institutions for use in future research.

Samples
Samples (such as blood and/or tissue) are being collected from you as part of this study. Researchers at MD Anderson may use any leftover samples that are stored at MD Anderson in future research. Leftover samples stored by Teva will be used in future research.

Before being used or shared for future research, every effort will be made to remove your identifying information from any data and/or research samples. If all identifying information is removed, you will not be asked for additional permission before future research is performed.

In some cases, all of your identifying information may not be removed before your data or research samples are used for future research. If future research is performed at MD Anderson, the researchers must get approval from the
Institutional Review Board (IRB) of MD Anderson before your data and/or research samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data and/or samples

Genetic Research
Samples collected from you as part of this study will be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you.

This research study involves genetic testing. The Genetic Information Nondiscrimination Act (GINA) prohibits health insurers or health plan administrators from requesting or requiring genetic information of you or your family members, or using such information for decisions regarding your eligibility for insurance or your premiums. However, this law does not provide the same protection for disability, life insurance, or long-term care insurance. GINA also prohibits most employers (with 15 employees or more) from using genetic information when making decisions on your employment, including decisions related to hiring, firing, promotion, pay, and job assignments. Please contact the study doctor if you would like more information about GINA and how it protects you from genetic discrimination.

Outside Care

Part of your care may be provided outside of MD Anderson by your home doctor(s). The study doctor can discuss with you the tests and procedures that can be completed by your home doctor in more detail.

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:
   - Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
   - The IRB and officials of MD Anderson
   - Teva Pharmaceuticals, who is a supporter of this study, and/or any future supporters of the study
   - Study monitors and auditors who verify the accuracy of the information
   - Individuals who put all the study information together in report form

   Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it.

   The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

   Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

E. 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.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol 2020-0890.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into_____and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

_____ _____ _____
NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION DATE
(OTHER THAN TRANSLATOR, PARENT/GUARDIAN,
OR STUDY CHAIR)

_____
PRINTED NAME OF WITNESS TO THE VERBAL TRANSLATION