THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

A phase II Study of Azacitidine, Venetoclax and Trametinib for Patients with Acute Myeloid Leukemia or Higher-Risk Myelodysplastic Syndrome

2020-0506

Subtitle: Astellas Pharma-MDACC Alliance

Study Chair: Nicholas Short

_____ _____
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.

STUDY SUMMARY

The goal of this clinical research study is learn if the combination of azacitidine, venetoclax, and trametinib can help to control acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The safety the study drug combination will also be studied.

This is an investigational study. Azacitidine is FDA approved and commercially available for the treatment of MDS. Venetoclax is FDA approved and commercially available for the treatment of chronic lymphocytic leukemia (CLL) and AML. Trametinib is FDA approved and commercially available for the treatment of certain types of lung cancer, melanoma, and thyroid cancer. It is considered investigational to give azacytidine, venetoclax, and trametinib together to patients with AML or MDS.

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. If you take part in this study, you may experience challenges related to the cost of staying in Houston, traveling to the clinic for study visits, and not being eligible for other studies or therapies.

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

You may receive up to 24 cycles of azacitidine, venetoclax, and trametinib.

You and/or your insurance provider will be responsible for the cost of azacitidine, venetoclax, and trametinib.

You may choose not to take part in this study. You may choose to receive standard treatment for AML that includes cytarabine in combination with idarubicin or daunorubicin, or a combination of commercially available drugs that may include venetoclax. You may choose to receive azacitidine and venetoclax alone. You may choose to receive other drugs or supportive care alone (including transfusions). There are approved treatments that have been shown to be effective in treating the disease. 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 be done within 2-4 weeks before your first dose of the study drugs to help the doctor decide if you are eligible:

- You will have a physical exam.
- You will have either an echocardiogram (ECHO) or a MUGA scan to check your heart function.
- Blood (about 5-6 teaspoons) will be drawn for routine tests and biomarker testing. Biomarkers are found in the blood and may be related to your reaction to the study drugs.
- You will have a bone marrow aspirate to check the status of the disease and for genetic testing and biomarker testing. Genetic testing in this study tests for genetic mutations (changes) in DNA found in the bone marrow. To collect a bone marrow aspirate, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow is withdrawn through a large needle.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for a pregnancy test

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.

Up to 40 participants will be enrolled in this study. All will take part at MD Anderson.

Study Drug Administration

Each study cycle is 28 days. If you are found to be eligible to take part in this study, you may receive the study drugs for up to 24 cycles.

You will receive azacitidine by vein (IV) over about 30-60 minutes on Days 1-7 of each cycle. If you prefer, you may instead receive azacitidine as an injection under the skin, which is generally quicker to give compared to an IV. If you are receiving azacitidine at a clinic that closes over the weekend, alternate dosing schedules (such as receiving azacitidine on Days 1-5 and 8-9 of each cycle) are possible.

You will take trametinib by mouth 1 time each day on Days 1-28 of each cycle. You should fast (not eat or drink anything except water) for at least 1 hour before the dose and then at last 2 hours after the dose.

You will take venetoclax by mouth 1 time each day on Days 1-28 of Cycle 1 and then on Days 1-21 of following cycles. Venetoclax should be taken with food.

During Cycle 1, your dose of venetoclax will be slowly increased over Days 1-3. After that, you will receive the same dose for the rest of the study cycles. For all 24 cycles, you will receive the same dose of azacytidine and trametinib.

You may be hospitalized for Days 1-3 of Cycle 1 while the venetoclax dose is increased or for all of Cycle 1 to monitor your health. This will be discussed with you.

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.

If you experience side effects from azacytidine, trametinib, and/or venetoclax, dosing for the drug(s) that caused the side effects may be paused, and the dose level may be lowered. You may also continue to receive the remaining study drug(s) that are not causing side effects. The study doctor will discuss this with you.

You will no longer be able to receive 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 **Day 1 of each cycle:**

- You will have a physical exam.
- Blood (about 2-3 teaspoons) will be drawn for routine tests.

At least 1-2 times each week during Cycle 1, blood (about 2-3 teaspoons) will be drawn for routine tests.

On **Day 21 of Cycle 1, Day 28 of Cycle 4, every 2-4 cycles after that,** and **if the doctor thinks it is needed**, you will have a bone marrow aspiration to check the status of the disease and for genetic testing (only during Cycles 1-4 and if the

disease comes back). If the disease does not get better by around Day 21 of Cycle 1, you may also have a bone marrow aspiration on Day 28 of Cycle 1 and/or Cycle 2.

Every 2-3 cycles, if you are continuing to take trametinib, you will have either an ECHO or a MUGA scan.

End-of-Dosing Visit
As soon as possible after your last dose of the study drugs, you will be called by the study staff and asked how you are doing. The call should last about 5-10 minutes.

Long-Term Follow-up
About 30 days after your last dose of the study drugs and then about every 6 months after that, you will be called by the study staff and asked how you are doing. This call should last about 5-10 minutes.

Other Information

- Within 3 days before your first dose of the study drugs and while taking venetoclax, avoid grapefruit, Seville (sour) oranges, star fruit, and pomegranate, including juices and products containing these fruits.
- Tell the study doctor/staff about all medications you are taking or may take during this study. Some medications are not allowed during this study or may change how your body processes the study drugs. The dose level of venetrolax you receive may need to be lowered because of the medications you are taking. This will be explained to you in more detail.
- If you take part in this study, you will not be able to receive any other investigational, anticancer drugs or treatments outside of this study.

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.

Venetoclax, azacitidine, and trametinib may each cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.

- 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.
- 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 difficulty breathing.

Venetoclax Side Effects

Common (occurring in more than 20% of patients)

• fatigue • diarrhea	• nausea • low blood counts (red, platelets, white)	• upper respiratory tract infection

Occasional (occurring in 3-20% of patients)

• swelling (arm/leg) • fever • headache • 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)	• vomiting • constipation • back pain • high blood levels of uric acid (possible painful joints and/or kidney failure)	• pneumonia • cough • 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) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

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.

You should wear ear plugs or other hearing protection when involved in a loud activity.

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**.

Azacitidine Side Effects

The following side effects have been reported when azacitidine is given either by vein or as an injection under the skin:

Common (occurring in more than 20% of patients)

• fever • fatigue/lack of energy • headache • nausea • vomiting	• diarrhea • constipation • loss of appetite • low blood cell counts (red, white, platelets) • weakness	• pain • shivering • cough • difficulty breathing • injection site redness and/or pain

Occasional (occurring in 5-20% of patients)

• chest pain • pale skin • swelling (arm/leg) • abnormal heart sound • fast heartbeat • low blood pressure (possible dizziness/ fainting) • high blood pressure • fainting • dizziness • anxiety • depression • difficulty sleeping • numbness	• low blood levels of potassium (possible weakness /or muscle cramps) • weight loss • abdominal pain, tenderness, and/or swelling • bleeding gums • tongue sores • bleeding in the mouth • mouth blisters and/or sores (possible difficulty swallowing) • upset stomach • hemorrhoids	• muscle cramps • nosebleed • stuffy and/or runny nose • abnormal breath sounds • wheezing • build-up of fluid around the lungs • lymph node swelling • infection • hardened tissue/inflammation/skin discoloration at the injection site

• hives and/or skin redness • skin bump/sores/rash • dry skin and/or itching • sweating	• difficulty swallowing • difficult and/or painful urination • blood in the urine • sore throat	• injection site swelling, itching, and/or rash • increased risk of bleeding after a procedure/surgery • reaction to a blood transfusion

Rare but serious (occurring in fewer than 5% of patients)

• irregular heartbeat • heart failure • bleeding in and/or around the brain • seizures • skin condition with fever and skin lesions • decay of body tissue • lesions due to skin infection • abnormal blood acid/base balance (possible organ damage) • dehydration • gallbladder inflammation (possible abdominal pain) • digestive system bleeding	• tarry stool • enlarged spleen • bone marrow failure • liver failure • kidney failure • build-up of bodily waste products in the blood (possible kidney problems) • coughing up blood • lung inflammation (possible difficulty breathing) • tissue death at the injection site caused by drug leakage • bleeding in the eye • catheter site bleeding • infection at the injection site	• allergic reaction, which may be life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure) • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

Azacitidine may cause you to develop another type of cancer (such as leukemia, a type of blood cancer).

<u>Trametinib Side Effects</u>

Common (occurring in more than 20% of patients)

• skin rash/redness • acne-like skin rash • hand-foot syndrome (palms of hands/soles of feet having pain,	• low blood levels of albumin (possible swelling, weakness, and/or fatigue) • diarrhea • low red blood cell counts	• lymphedema (swelling of arms/legs/torso) • abnormal liver test (possible liver damage)

swelling, and blistering)		

Occasional (occurring in 3-20% of patients)

• high blood pressure • enlarged heart • heart failure • severe heart problems • itching	• dry skin • mouth blisters/sores (possible difficulty swallowing) • abdominal pain	• bright red, tarry or coffee ground-like blood in the stool • bleeding (gums, uterus, vagina, hemorrhoids, nose, and/or eye) • blood in the urine

The drug may cause an increased risk of infection, such as pneumonia. This infection may occur anywhere, such as the skin (including the nails and/or hair follicles) or lungs. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Frequency Unknown but occurring between 1 and 10% of patients:

• slow heartbeat • dizziness	• blistering skin rash • abnormal taste • dry mouth	• breakdown of muscle tissue (possible kidney failure) • blurry vision • dry eyes

Rare but serious (occurring in fewer than 3% of patients)

• detachment of part of the retina (possible blurry vision, vision changes, and/or vision loss)	• blood clot in the eye (possible vision loss)	• lung inflammation (possible difficulty breathing)

Trametinib may cause eye problems, such as bleeding or blood clots in the eye. This may lead to blindness or other visual damage. If you have any vision changes, you should not drive a car or work with machinery.

Tell your doctor about glaucoma, diabetes, any pre-existing lung problems, if you have high blood pressure, or are on drugs to treat high blood pressure.

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 aspirations** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the aspiration. An allergic reaction to the anesthetic may occur. A scar may form at the aspiration 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 effective birth control methods during the study and for at least 4 months (for males) or 6 months (for females) after your last dose of study drugs, if you are sexually active.

Birth Control Specifications: The study doctor or staff will discuss effective birth control methods with you.

Males: Do not donate sperm while on study and for 4 months after your last dose of study drug. Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

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.

Getting pregnant will result in your removal from this 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 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. Nicholas Short, at 713-563-4485) 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.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, 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.

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

study.

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/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.

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

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.

Outside Care

Part of your care may be provided outside of MD Anderson by your home doctor(s). Your home doctor(s) will be given a copy of the informed consent as well as information about the study drug dosing and study tests. If your home doctor thinks the dose of the study drug(s) you are receiving or the dosing schedule you are following during a study cycle should be changed, the study doctor will make the final decision. If any study tests are performed by your home doctor, the results will be sent to the study doctor for review.

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
   - 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.

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

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)
The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

_____ _____
SIGNATURE OF LAR DATE

_____
PRINTED NAME and RELATIONSHIP TO PARTICIPANT

WITNESS TO CONSENT
I was present during the explanation of the research to be performed under Protocol **2020-0506**.

_____ _____
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