THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Phase I/II Study of Azacitidine in Combination with Quizartinib for patients with Myelodysplastic syndromes and Myelodysplastic/Myeloproliferative Neoplasms with *FLT3* or *CBL* mutations

2019-1178

Study Chair: Guillermo Montalban Bravo

_____ _____
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 find the recommended dose of quizartinib that can be given in combination with azacitidine to patients with myelodysplastic syndromes or myelodysplastic/myeloproliferative neoplasms. Researchers also want to learn more about the safety, effects, and overall response of the drug combination.

This is an investigational study. Quizartinib is FDA approved and commercially available for the treatment of AML. It is being used for research purposes only. Azacitidine is FDA approved and commercially available for the treatment of MDS. The use of this combination in this study is investigational. The study doctor can explain how quizartinib and azacitidine 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. If you take part in this study, you may experience side effects that may be severe or fatal.

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

You may continue taking the study drugs for as long as the doctor thinks it is in your best interest.

Quizartinib will be provided at no cost to you while you are on study. Azacitidine will be billed to you and your insurance.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard of care treatments for MDS outside of this study. Your study doctor will talk to you about other treatments or therapies that are available and their benefits/risks. You may choose to receive other investigational therapy, if available. You may choose not to have treatment 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 2 teaspoons) will be drawn for routine tests and biomarker testing. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug.
- You will have 3 EKGs in a row and either an echocardiogram (ECHO) or MUGA to check your heart function.
- You will have a bone marrow aspirate and/or biopsy to check the status of the disease and for biomarker testing. 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, urine or blood (about 1 teaspoon) 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 3 groups of up to 6 participants

will be enrolled in Phase 1 of the study, and up to 40 participants will be enrolled in Phase 2.

If you are enrolled in Phase 1, the dose of quizartinib you receive will depend on when you join this study. The first group of participants will receive the lowest dose level of quizartinib. Each new group will receive a higher dose of quizartinib than the group before it, if no intolerable side effects were seen. This will continue until the highest tolerable dose of quizartinib is found.

If you are enrolled in Phase 2, you will receive quizartinib at the recommended dose that was found in Phase 1.

All participants will receive the same dose level of azacitidine.

Up to 58 participants will be enrolled in this study. All will take part at MD Anderson.

Study Drug Administration
Each study cycle will be 28 days long.

You will receive azacitidine by vein over about 30 minutes or as an injection under the skin on Days 1-5 of each cycle.

You will take quizartinib by mouth 1 time each day while you are on study. You should take it at about the same time each day, with about a cup (8 ounces) of water. You will need to swallow tablets whole and not to chew them.

A dose missed earlier in the day can be made up later that day as long as it is taken within 6 hours after the missed dose. If more than 6 hours have passed, then that dose should be skipped, and you should resume treatment with the next scheduled dose.

You will be given a drug diary in which you will document when you take the drug each time. Any missed doses should be documented in this diary and should be returned at your next study visit.

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 **Day 1 of each cycle**:
- You will have a physical exam.
- Blood (about 2 teaspoons) will be drawn for routine tests.
- Blood (about 2 teaspoons) will be drawn for biomarker testing.

On **Day 2 of Cycle 1**, you will have 3 EKGs in a row.

On **Days 8 and 15 of Cycle 1**:

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

On **Day 22 of Cycle 1**:

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

On **Day 28 of Cycle 1,** you will have a bone marrow aspiration and/or biopsy to check the status of the disease and for biomarker testing.

Every 3 cycles for the first 6 months, then every 6-12 months after that, you will have a bone marrow aspiration and/or biopsy to check the status of the disease and for biomarker testing. If the disease is getting better, you will then have this done If the disease is not getting better, you will continue to have this test at the end of every cycle until it appears to be getting better.

These samples will also be collected if at any time the disease appears to be responding or getting worse.

End of Treatment

After your last dose of study drug:

- You will have a physical exam.
- Blood (about 1 teaspoon) will be drawn for routine tests.
- You will have a bone marrow biopsy/aspirate to check the status of the disease and for biomarker testing.

Follow-Up

About 30 days after your last dose of study drug, and then about every 6 months after that, you will be called by a member of the study team and asked how you are feeling. Each call should last about 10 minutes.

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.

Quizartinib and azacitidine may each cause low blood cell counts (red blood cells, platelets, and 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. You may have an infection of the sinuses, lungs, and/or digestive system. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Quizartinib Side Effects

It is not well known how often the side effects of quizartinib may occur.

• abnormal EKG • irregular heartbeat • changes in heart rhythm and cardiac arrest (sudden stopping of the heart) • low blood pressure (possible dizziness/fainting) • fast heartbeat • swelling (arms/feet/ lower legs) • inflammation of the membrane covering the heart • blood clots in a vein (possible pain, swelling, and/or redness) • fatigue • weakness • fever • headache • dizziness • chills	• loss of hair color (white hair) • hair loss (partial or total) • 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) • dehydration • nausea • sour or metallic taste • bleeding in the mouth • abdominal pain and/or swelling • diarrhea • vomiting (including vomiting blood) • loss of appetite • chronic heartburn and indigestion • constipation	• abnormal taste • weight loss • low blood counts (red, white, platelet) • abnormal kidney tests (possible kidney damage or injury) • abnormal liver tests (possible liver damage) • pain (muscle/bone/ ligament/ tendon/nerve) • joint inflammation and swelling • nosebleed • cough • throat inflammation • difficulty breathing • build-up of fluid around the lungs • lung infection • kidney stones • eye infection • severe life-threatening infection (possible low

• difficulty sleeping • confusion • bleeding around the brain • skin rash and/or sores • skin redness, swelling, pain to hands and feet • bleeding under the skin (petechiae) • skin sensitivity to sunlight or lamps (which may cause you to easily sunburn)	• decreased urination • mouth, throat, and digestive system pain • bleeding in the digestive system • anal fissure (sores) and/or hemorrhoids	blood pressure, kidney failure, and/or heart failure) • multiorgan failure

Quizartinib may cause a change in EKG pattern called QT prolongation, which may occur more frequently in women than in men, and may cause an irregular heartbeat. In extreme cases, this may cause death.

Drugs similar to quizartinib have caused tumor lysis syndrome (TLS). TLS happens when breakdown products of the cancer cells enter the blood stream, causing possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage. TLS can be serious or life-threatening, so you should tell your doctor right away if you have any of these side effects. TLS has not been seen so far in patients receiving quizartinib, but it is still a possibility.

Sepsis and neutropenic sepsis have been reported by patients who received multiple doses of quizartinib as a part of a clinical research study. Sepsis is a condition in which your body is fighting a severe infection that has spread via the bloodstream. One or more of your body organs may stop working properly or fail. Organs affected can include your heart, lungs, kidneys, liver, and/or your blood clotting system.

Neutropenic sepsis is a condition in which your body is fighting a severe infection that has spread via the bloodstream and is associated with a decreased level of neutrophils (a type of white blood cell that helps fight infection) in your blood.

Laboratory and animal studies showed that the drug may cause genetic damage.

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	• diarrhea	• pain

• fatigue/lack of energy • headache • nausea • vomiting	• constipation • loss of appetite • low blood cell counts (red, white, platelets) • weakness	• 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 • hives and/or skin redness • skin bump/sores/rash • dry skin and/or itching • sweating	• 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 • difficulty swallowing • difficult and/or painful urination • blood in the urine • sore throat	• 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 • 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	• 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	• 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)

• abnormal blood acid/base balance (possible organ damage) • dehydration • gallbladder inflammation (possible abdominal pain) • digestive system bleeding	• 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	• 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).

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 **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.

EKGs/ECHOs may cause discomfort while lying on the exam table, and the tape on the EKG pads may cause skin irritation.

MUGA scans may cause allergic reactions to the radioactive tracer, injection site soreness, and/or swelling. They may cause damage to cells or tissue from being exposed to the radiation used in the scan. These side effects may occur in less than 10% of patients.

The current data suggests that you may only benefit from quizartinib if the leukemia cells have a genetic change called the FLT3-ITD mutation. The test being used to check for the FLT3-ITD mutation is investigational, so there is a chance of either a **false positive or false negative** result:

- A “false positive” result means the test found the FLT3-ITD mutation, but it is actually not present in the tumor. As a result, you would be considered eligible to move forward with screening for the main study and could be exposed to potential risks of the study drug without receiving any potential benefit.

- A “false negative” result means the test did not find the FLT3-ITD mutation, but it is actually present in the tumor. As a result, you would not be considered eligible to move forward with screening for the main study that may benefit you.

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.

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.

Males: You must use condoms while you are on study. Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: Acceptable methods of birth control include birth control pills, injections, or patches; intrauterine device (IUD); a double barrier method (spermicidal jelly or foam with condom or diaphragm); or surgical sterilization. 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 may 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 or Daichii Pharmaceuticals 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. Guillermo Montalban Bravo, at 713-794-3604) 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.

   If you stop being in the research, already collected data may not be removed from the study database. You may be asked whether the study doctor can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

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

9. This study is sponsored and/or supported by: Daichii 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 Daichii Pharmaceuticals 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.

If you do not want your samples or data to be used for future research, tell the study doctor. You may withdraw your samples at any time by telling your study team. If you decide to withdraw your samples, they will be returned to the lab they came from or destroyed. However, the data and test results already collected from your samples will be kept and may be used.

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. The results of this research may also be able to

be linked to you. The same level of data protection that covers your individual data does not apply to summary results (when data from the whole study is combined).

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Nor does this federal law prohibit discrimination based on an already known genetic disease or disorder.

Conflict of Interest

Outside relationships are disclosed to and approved by the Conflict of Interest Committee, which reviews these relationships for compliance with institutional policy. This review helps the IRB to assure that financial relationships do not have an impact on the conduct of this study. The following members of the study staff have disclosed compensation from the funding source(s) of this study:

- Guillermo Garcia-Manero (Co-Principal Investigator)
- Elias Jabbour (Collaborator)
- Naval Daver (Collaborator)

Outside Care

Part of your care may be provided outside of MD Anderson by your home doctor(s).

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
   - Daichii Pharmaceuticals, who is a sponsor or supporter of this study, and/or any future sponsors/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 this protocol.

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

A witness signature is only required for non-English speakers utilizing the short form consent process (VTPS) and patients who are illiterate.

_____
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