Informed Consent Form

Date: August 27, 2024

Official Title: A Phase II Study of the Efficacy and Pharmacogenomics of Cladribine-based Salvage Chemotherapy in Patients With Relapse/Refractory and Secondary Acute Myeloid Leukemia (AML) and High Risk Myelodysplastic Syndrome (MDS)

NCT03150004

EFFECTIVE

8/27/2024

MCW/FH IRB

Medical College of Wisconsin and Froedtert Hospital
INTRODUCTION TO THE INFORMED CONSENT

Name of Subject: _____

A Phase II Study of the Efficacy and Pharmacogenomics of Cladribine Based Salvage Chemotherapy in Patients with Relapse/Refractory and secondary Acute Myeloid Leukemia (AML) and high risk Myelodysplastic Syndrome (MDS)

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Milwaukee, WI 53226
414-805-6700

You are invited to take part in this research. You can decide whether to take part in this project or not. You are free to say yes or no. If there is anything that you do not understand, please ask questions.

Definitions

CLAG-M – Cladribine, Cytarabine, Mitoxantrone, and G-CSF

CLLDAC – Cladribine and Cytarabine

Purpose

This project is being done to determine how treatment with Cladribine based salvage therapy can affect the complete remission (CR) rate and achievement of no minimal residual disease.

Length

- You will be in this research project for about 48 months.

Procedures

Some of these tests and procedures are considered "standard of care" which means that they would be done even if you were not participating in this research study and some are considered "research" which means they are being done only because you have agreed to participate in this research study.

List of visits:

- Screening Visit
  - Total Number: 1-2
  - Total Time: 1-2 hours
- Treatment Visit
  - Total Number: 5
  - Total Time: 2-4 hours each
- Follow-up Visit
  - Total Number: 16
  - Total Time: about 30 minutes each

Procedures that will occur at various visits:

Invasive Procedures

Drug administration, blood sample collection, bone marrow collection, MUGA, and ECHO

Non-invasive Procedures

Full medical history exam, physical exam, urine sample collection

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

Cladribine based salvage risks:

- Lack of enough red blood cells (anemia)
- Inflammation of your GI tract
- Changes in the way your heart functions
- Decreased number of a type of blood cell that helps to clot blood (platelet)
- Decreased number of a type of white blood cell (lymphocyte)
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decrease in the total number of white blood cells (leukocytes)
- Infection
- Nausea or the urge to vomit
- Vomiting
- Loss of appetite
- Weight gain or loss
- Stomach cramps
- Diarrhea
- Constipation
- Inflammation of the covering of the eye
- Hair loss
- Bone pain
- Fever

Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:

- Joining a different project
- Routine care for this condition
- Getting no treatment for this condition

If you have more questions about this project at any time, you can call Ehab Atallah at 414-805-6700.

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are being invited to participate in this research study because you have had Relapse/Refractory and secondary Acute Myeloid Leukemia (AML) or high risk Myelodysplastic Syndrome (MDS). Because of your condition, you may be eligible for a research study drug

A total of about 90 people are expected to participate in this research the Medical College of Wisconsin/Froedtert Hospital.

The Director of the project is Ehab Atallah, MD in the Division of Hematology and Oncology. A research team works with Dr. Atallah. You can ask who these people are.

Froedtert & the Medical College of Wisconsin is funding this study.

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this project, you do not have to stay in it. You may stop at any time.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

The optimal treatment regimen for relapsed/refractory AML and high risk MDS progressing after hypomethylating agents is unknown. Although several chemotherapy options are available, there is no universally accepted regimen to date. Cladribine based salvage regimens have frequently been used at our center. In patients diagnosed with AML, the drugs Cladribine, Cytarabine, Mitoxantrone, and G-CSF are used in Cladribine based salvage. In patients diagnosed with MDS, the drugs Cladribine and Cytarabine are used Cladribine based salvage. While these therapies are frequently used, it is uncertain to predict which patients are likely to respond to Cladribine based salvage or experience treatment related toxicities. Studies have demonstrated that achievement of minimal residual disease (MRD) negative complete remission (no evidence of disease in your blood and/or bone marrow, using a sensitive test) is associated with a better overall survival. However, this has not been clearly studied in patients with relapsed-refractory AML and high risk MDS.

Through this study, we aim to demonstrate the influence of achieving minimal residual disease negative complete response on survival of patients with relapsed/refractory AML/high risk MDS treated with Cladribine based salvage. In addition to the conventionally used predictive factors, we aim to incorporate pharmacogenomics (how your genes contribute to the side effects you experience and/or how well your AML responds to treatment) to assess the efficacy and toxicity of therapy.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

Before any study tests or procedures are done, you will be asked to sign this consent form. The study doctor will discuss the study with you and answer your questions. If you decide to join the study, some screening tests will be done first to see if you are eligible.

Some of these tests and procedures are considered "standard of care" which means that they would be done even if you were not participating in this research study and some are considered "research" which means they are being done only because you have agreed to participate in this research study.

Pretreatment Period:

The screening procedures and assessments must be completed within 30 days (unless otherwise specified on the study calendar) of enrollment.

- Informed consent
- Physical examination
- Vital signs
- Medical history
- ECOG Performance status
- About 6 teaspoons (30 mL) of blood will be drawn for routine laboratory tests including tests that measure your blood counts, and the natural chemicals in your blood.
- Serum or urine pregnancy test within 14 days prior to enrollment for women of child bearing potential
- Cardiac assessment (ECHO or MUGA)
- Blood sample (10mL) (can be collected from consent to day 5)
- Bone marrow aspiration/biopsy. If peripheral blasts are present, a bone marrow aspiration/biopsy should be performed at the discretion of the treating physician
- Adverse events
- Concomitant medications (baseline medications taken within 7 days of Day 1)

If the screening information shows that you meet the requirements, then you will be able to start the study. If the screening information shows that you cannot be in the research study, the study doctors will discuss other options with you and/or refer you back to your regular doctor.

Study Procedures during Treatment

Study Procedures, Day 1:

- Physical examination
- Vital signs
- Medical History
- ECOG Performance status
- Adverse events
- Concomitant medications

- About 6 teaspoons (30 mL) of blood will be drawn for routine laboratory tests including tests that measure your blood counts, and the natural chemicals in your blood.
- CLAG-M or CLLDAC administration (dependent upon diagnosis). You will need to be admitted in order to receive treatment.

Study Procedures, Days 8, 15, and 22:

- Physical examination
- Vital signs
- Adverse events
- Concomitant medications
- About 6 teaspoons (30 mL) of blood will be drawn for routine laboratory tests including tests that measure your blood counts, and the natural chemicals in your blood.

If you are diagnosed with high risk MDS, you may receive a second cycle of CLLDAC, at the discretion of your treating physician. Should this be the case, you will begin cycle 2 no later than 49 days after cycle 1. Cycle 2 will follow the same schedule as cycle 1, as outlined above.

End of Treatment/Day 30 Procedures
To be completed at day 30(+/- 5 days). If you discontinue treatment early and/or your disease gets worse, then the end of treatment (EOT)/day 30 assessments can be completed prior to starting other therapy.

- Physical examination
- Vital signs
- ECOG Performance status
- Adverse events
- Concomitant medications
- About 6 teaspoons (30 mL) of blood will be drawn for routine laboratory tests including tests that measure your blood counts, and the natural chemicals in your blood.
- Bone marrow aspiration/biopsy will be obtained after the completion of Cladribine based salvage therapy at day 30, or when absolute neutrophil count (ANC) recovers to >1000 cells/cu.mm,or when the treating physician determines that it is clinically indicated. If peripheral blasts are present, a bone marrow aspiration/biopsy should be performed at the discretion of the treating physician.

Follow-Up Visits
You will be followed approximately every 3 months for up to 4 years from the end of Cladribine based salvage treatment to monitor your disease and check how you are doing. If you have disease progression/relapse, then you will be followed per follow-up requirements. The following procedures will be performed at the follow-up visit(s):

- About 6 teaspoons (30 mL) of blood will be drawn for routine laboratory tests including tests that measure your blood counts.

B2. HOW LONG WILL I BE IN THE PROJECT?

You will be in this research study for about 4 years (approximately 48 months).

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.

⇒ The research doctor can tell you about the effects of stopping, and you and the research doctor can talk about what follow-up care would help you the most.
⇒ You might be asked to come back for one more visit to check your health.
⇒ You might be asked to return your research drug containers.

The research doctor may take you out of this project at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that the study drugs will not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from Cladribine based salvage itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems, side effects, or changes in your health.** If you have severe side effects, call Dr. Atallah immediately at 414-805-6800. In an emergency, call 911.

C2. RISKS OF Cladribine based salvage therapy

The Cladribine based salvage itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away.

Drugs can affect individuals in different ways. Complications of some of the side effects below may lead to life-threatening events and possibly death.

Risks and side effects related to the Cladribine based salvage treatment include those which are:

Likely (≥ 10% of patients)

- Lack of enough red blood cells (anemia)
- Inflammation of your GI tract
- Changes in the way your heart functions
- Decreased number of a type of blood cell that helps to clot blood (platelet)
- Decreased number of a type of white blood cell (lymphocyte)
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decrease in the total number of white blood cells (leukocytes)
- Infection
- Nausea or the urge to vomit
- Vomiting

- Loss of appetite
- Weight gain or loss
- Stomach cramps
- Diarrhea
- Constipation
- Inflammation of the covering of the eye
- Hair loss
- Bone pain
- Fever
- Headache
- Bleeding
- Irritation or sores in the lining of the gastrointestinal tract (voice box, windpipe, mouth, the tube that goes from the mouth to the stomach, stomach, small intestine, large intestine, rectum and/or anus)
- Shortness of breath

Less Likely (1% - 10% of patients)

- High or low blood pressure
- Changes in your blood chemistries
- Back pain, muscle pain, or pain in your joints
- Blurred vision
- Decrease in heart's ability to pump blood (heart failure)
- Chest pain
- Inflammation of your heart
- Liver problems or liver failure
- Rash
- Flaking or sloughing of skin
- Changes in mood

Rare but serious (< 1% of patients)

- Nerve pain
- Keratitis (inflammation of the cornea of your eye)
- Renal failure (problems with your kidneys that may cause them to stop working)
- Steven's Johnson syndrome and toxic epidermal nercrolysis (a condition of you skin and mucous membranes that may cause rash and your skin to slough off)
- Inflammation of your lungs
- Allergic reaction that could result in death
- Serious infection that could result in death
- High dose cytarabine can cause central nervous system toxicity, which can cause symptoms such as difficulty with word finding, sleepiness, headaches, dizziness, confusion, trouble with fine motor activities, and loss of balance.

C3. OTHER RISKS OF THIS RESEARCH PROJECT

Other procedures that are part of the research also involve some risks:

Risks of Bone Marrow Aspirate/Biopsy Collection:
Bone marrow is collected using a needle under local anesthesia to aspirate (draw out) marrow tissue from the inside of your bone marrow aspirate (usually pelvic or hipbone). Biopsy refers to removal of a piece of tissue that does not cause any serious problems. The risks on bone marrow biopsy and aspirate include pain, bleeding, bruising, and/or discomfort at the biopsy site. Infection is also possible but rare.

Risks of an Echocardiograms (ECHO):
An echocardiography uses sound wavers to evaluate your heart. These high frequency sound waves have not been shown to have any harmful effects. This test does not require any specific preparation. There are no side effects or radiation exposure. There is no pain or discomfort during an echocardiogram.

Risks of a Multigated Acquisition (MUGA) Scans:
The scan may take several hours to get all the pictures. There is no pain or discomfort during a MUGA scan.

Risks of IV Injections:
For most people, needle sticks for IV injections do not cause any serious problems. Sometimes they may cause bleeding or bruising. They may also cause infections and/or pain at the needle site.

Risks of Blood Tests:
For most people, needle punctures for blood draws do not cause any bad problems. However, sometimes they may cause bleeding, bruising, discomfort, infections, and/or pain where you had the blood drawn. You may also feel dizzy.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant
The drug in this project might affect a baby, before or after the baby is born. We do not know if the drug cause(s) harm to a baby, so we do not want anyone who might be pregnant to enter the project. You should not become pregnant or nurse a baby while in this project. You must tell the research doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the project.

Risks of fathering a child
You should not father a baby while taking part in this project because it is unknown if drug could affect a baby. If your partner is able to become pregnant, one or both of you must use some form of effective birth control. You must tell the research doctor right away if you think your partner is pregnant.

Birth control methods for all subjects
Check with the research doctor about the birth control methods needed for this project and how long to use them. Some methods might not be good enough for this project. If you are having sex that could lead to pregnancy, you should use birth control while you are in this project.

Female patients must meet one of the following:

- Postmenopausal for at least one year before the screening visit, or

- Surgically sterile, or if they are of childbearing potential, agree to practice two effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, AND
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, or
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable contraception methods.)

Male patients, even if surgically sterilized (i.e., status post vasectomy), must agree to one of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last study drug dose, OR
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Birth Control Methods:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy or tubal ligation)
- Use of an intrauterine device (IUD)
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam
- Use of diaphragm with condoms (“double barrier”)
- Limiting sexual activity to a male partner who has had a vasectomy

You should continue using birth control for 90 days after stopping the study drug.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

We don’t know if this study will help you. Your condition may get better but it could stay the same or even get worse. We hope the information from this study will help us develop better treatments for relapse/refractory and secondary Acute Myeloid Leukemia (AML) and high risk Myelodysplastic Syndrome (MDS)

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

Most of the medical care that you will receive in this study is considered routine care for your condition and would be recommended whether you join the study or not. Costs for routine care will be billed to you or your insurance carrier.

Activities / costs that are part of the study will not be billed to you or your insurance company. These are the processing and shipping of research samples. Some insurers will not pay for drugs, tests or hospitalization that are part of research studies, so check with your insurer

before you join this study. If you have questions regarding study costs, please contact Dr. Atallah.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

There is no payment for being in this study.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.

Your other choices may include:

- Routine care for relapse/refractory and secondary AML
- Joining a different research study
- Receiving no treatment

The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information about the drug that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries directly related to your participation in this research project will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctors right away. Contact information: Dr. Atallah, 414-805-6700.

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

- If you have more questions about this project at any time, you can call Dr. Atallah at 414-805-6700.

- If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this project?

To be in this research project, the research team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the project. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); BloodCenter of Wisconsin (BCW); Children's Hospital of Wisconsin (CHW); any Froedtert Health Affiliate-Froedtert Memorial Lutheran Hospital (FMLH), Inc.; Community Memorial Hospital (CMH) Menomonee Falls, Inc.; St. Joseph's Community Hospital (SJH) West Bend, Inc.; Froedtert & The Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:

- Hospital/Medical Records
- Physician/Clinical Records
- Lab and/or Pathology Reports
- Radiology Reports
- Biological Samples

E2. Who will see the health information collected for this project?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

The research team may share your information with people who don't work at MCW/Froedtert Hospital because they planned, pay for, or work with us on this project. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this project, we plan to share information with those doctors, researchers or government representatives working with us on this project at the institutions or companies listed here:

- Any federal, state, or local governmental agency that regulates the study (such as the U.S. Food and Drug Administration (FDA)
- The U.S. Department of Health & Human Services (DHHS)
- The Office for Human Research Protections (OHRP)
- Other government agencies in this or other countries

- The designated Data Safety Monitoring board and Institutional Review Board which is a committee that has reviewed this research study to help ensure that your rights and welfare as a research participant are protected and that the research study is carried out in an ethical manner, and Privacy Boards and their related staff that have oversight responsibilities for this study.
- Personnel from the study site that provide study related treatment or procedures
- Those required by law

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all project records.

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information and/or biospecimens for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information and/or biospecimens, the information may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the research doctor about whether this could apply to you.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to:

Ehab Atallah, MD
Froedtert Hospital & the Medical College of Wisconsin
Division of Hematology and Oncology,
9200 W Wisconsin Avenue
Milwaukee, WI 53226

The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the project. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE PROJECT

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.

You can look up this project by referring to the ClinicalTrials.gov number (NCT03150004) or by asking the research team for a printed copy.

CONSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Witness (if applicable**)** *please print* (for short form consent process, or consent of blind or illiterate subject)	**Signature of Witness**	**Date**
*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the research team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. The Principal Investigator is responsible and accountable for the research project.*