The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title:	**A Phase I study to evaluate the safety and tolerability of gemtuzumab ozogamicin and midostaurin when used in combination with standard cytarabine and daunorubicin induction for newly diagnosed FLT3-mutated acute myeloid leukemia**
Principal Investigator:	**Uma Borate, MD**
Sponsor:	**The Ohio State University**
Funding Sponsor:	**Pfizer, Inc.**

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

Key Information About This Study
The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

PURPOSE:

The purpose of the study is to learn more about how safe and tolerable is the combination of gemtuzumab ozogamicin (GO) (also referred as "Mylotarg) and midostaurin with the standard induction therapy (cytarabine and daunorubicin) in patients with newly diagnosed FLT-3 mutated AML. By conducting this study, we are hoping to find out if this study approach is better or worse than the usual approach for your AML. The usual approach is defined as care most people get for FLT-3 mutated AML.

DURATION:

Your participation in the study will consist of two parts: Induction therapy and consolidation therapy. The duration of the treatment part of the study will be about 120 days. You will receive the study drugs for as long as you and the investigator feel that you are tolerating the study drugs and your disease is not getting worse. You will be hospitalized for the entire induction therapy and part of the consolidation therapy.

Your investigator will continue to follow you every 3 months for a period of 2 years to see if you are alive and well. You will be contacted, usually by phone or during a routine clinic visit.

PROCEDURES:

If you decide to take part in this study, you will be assigned 1 of 3 different dose levels of the study drugs. If you participate in this study, you will be asked to have a number of tests and procedures. Key and/or essential procedures that are to be performed in this study include: Physical exam – including vital signs (blood pressure, heart rate, and temperature), height, and weight

- Physical exams
- Pregnancy tests
- Blood tests for safety and research related exploratory studies
- Research related procedures (exploratory studies): Your blood samples will be analyzed to measure CD33 expression in the blast cells (a type of blood cell) and to test for presence of a specific protein receptor called CD33 SNP. Two tubes will be drawn for these samples, for a total of 15-20mL (which is approximately 1-1.4 tablespoons of blood)
- Bone marrow biopsy at time of enrollment, and approximately 14 days after starting treatment

We will continue to perform blood tests, pregnancy tests (if applicable), physical exam, bone marrow/aspirate and review of any changes to your health and medications throughout your participation in the study.

RISKS:

Some of the most common side effects that the investigators know about include:

- Liver damage*
- Severe or fatal bleeding
- Bleeding, infection, fever, nausea, vomiting, constipation, headache, abnormal liver tests (possible liver damage), rash, and mouth blisters/sores.
- Low number of white blood cells and platelets

***Liver problems, including severe, life threatening or fatal form of liver diseases may develop while receiving GO/Mylotarg. You may be at increased risk for developing liver disease if you may receive stem cell transplant in the future. We will monitor your liver enzyme levels and check your weight at different time points.**

It is extremely important that you, any caregivers, and other healthcare providers have the correct study team contact information for safety and management of toxicities. To address this, Trial Alert Cards have been created to record study team phone numbers, with a 24-hour option, and come in a size that can be carried in your wallet. The cards include a note to healthcare providers asking them to contact your treating physician, in case you seek care with anyone unfamiliar with the trial. You will receive this card at your first/ next visit, please keep it with you at all times.

BENEFITS: You may or may not receive direct benefit from being in this study. However, your participation in this study may help other people that have AML get better care in the future.

1. Why is this study being done?

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test the safety and tolerability of GO/Mylotarg in combination with midostaurin with the standard induction therapy (cytarabine and daunorubicin) in participants with newly diagnosed FLT-3 mutated AML. By conducting this study, we are hoping to find out if this study approach is better or worse than the usual approach for your AML. The study approach we are studying is experimental. It has not been approved by the FDA. We do not know if it is better than the usual approach for treating FLT-3 mutated AML.

GENETICS

In this study, we will look at your genetic makeup using your samples. Genes are the units of DNA—the chemical structure carrying genetic information – that determine many human characteristics such as the color of your eyes, your height, and whether you are male or female. All genetic sampling will be completed as a part of your standard of care.

2. How many people will take part in this study?

As many as 22 participants will be consented; 21 may take part in this studyat Ohio State University and Oregon Health & Science University (closed to accrual). Of these participants, about 14 will be consented and may participate in this study at OSU.

3. What will happen if I take part in this study?

WHAT ARE THE STUDY GROUPS?

There were originally 4 study groups, but as of consent version 01/23/2023 there will only be 3 groups as group 4 (dose level 4) no longer needs new participants. Each group has different dose levels for the induction/initial portion of this study. The first several study participants will receive the lowest dose (of all drugs). If the drugs do not cause serious side effects, the next group of study participants will receive higher doses and/or dosed on more days as shown in the table below. For dose levels 1-3, the dose of GO/Mylotarg remains the same, but the dosing frequency is increased for each level.

	Cytarabine (by vein)	**Daunorubicin (by vein)**	**Mylotarg/ GO (by vein)**	Midostaurin (by mouth)
Dose Level 1	100 mg/m^2; Given on Days 1 - 7	60 mg/m^2; Days 1-3	3 mg/m^2; Given on Day 1	50 mg twice daily; Given on Days 8-21
Dose Level 2	100 mg/m^2; Given on Days 1 - 7	60 mg/m^2; Days 1-3	3 mg/m^2**; Given on Days 1, 4**	50 mg twice daily; Given on Days 8-21
Dose Level 3	100 mg/m^2; Given on Days 1 - 7	60 mg/m^2; Days 1-3	3 mg/m^2**; Given on Days 1, 4, 7**	50 mg twice daily; Given on Days 8-21
Dose Level 4 (closed)	100 mg/m^2; Given on Days 1 - 7	**90 mg/m^2**; Days 1-3	3 mg/ m^2; Given on Days 1, 4, 7	50 mg twice daily; Given on Days 8-21

You and your investigator will know which dose level you will be assigned.

PROCEDURES:

Before you begin the study (Screening):
You will need to have the following *exams, tests, and procedures* to find out if you can be in the study:

- Medical history and medications (both prescribed and over the counter) - past and current
- Physical exam – including vital signs (blood pressure, heart rate, and temperature),

height, and weight

- Performance status - The investigator will evaluate your ability to perform daily activities.
- Blood tests for:
  - Routine blood tests (complete blood count, chemistry, clotting tests) – Your blood samples will be used to evaluate your health.
  - Research related procedures (exploratory studies): Your blood samples will be analyzed to measure CD33 expression in the blast cells (a type of blood cell) and to test for presence of a specific protein receptor called CD33 SNP. Two tubes will be drawn for these samples, for a total of 15-20mL (which is approximately 1-1.4 tablespoons of blood)
- Pregnancy test - If you are a woman able to become pregnant, your urine sample will be used to test for pregnancy. If the urine test is positive, your blood sample (up to 1 teaspoon/5mL) will also be used to test for pregnancy. You cannot be in this study if you are pregnant.
- Electrocardiogram (ECG) – We will place electrodes on your chest. This will measure the electrical activity in your heart.
- Echocardiogram (ECHO), performed only if the investigator determines it is appropriate. An ECHO is a test that uses ultrasound to take a picture of your heart.
- Bone marrow biopsy/aspirate – The bone marrow biopsy is done in a similar way to biopsies done for diagnosis. The biopsy samples will be used to:
  - Determine the stage of your disease
  - Test for cytogenetics - to check for abnormalities in the parts of the cell that contain genetic information of the leukemic cells, and to look for special biomarkers. These tests are routine for AML patients.

Blood (up to 15-20mL (which is approximately 1-1.4 tablespoons of blood) and bone marrow biopsy samples will be taken for the study. These samples are required in order for you to take part in this study because the research on the samples are an important part of the study. If the procedures from the Screening show that you can take part in the study, and you choose to take part, then you will continue on to the study.

During the study:
This study includes two parts of the usual approach for AML: Induction therapy (the initial, or first treatment given for a disease) and Consolidation therapy (the treatment that is given after cancer has gone into remission following the initial therapy). You will be hospitalized at OSU for both induction and consolidation therapies.

Induction/Re-induction Therapy
Induction therapy aims to kill the majority of the leukemic cells. You will receive one or two cycles of induction therapy. Each cycle of induction therapy will last approximately 28 days. You will receive the induction treatment cycle as a patient admitted in the hospital. This allows for the chemotherapy to be given safely and to closely monitor and treat you for any side effects from the study approach. If your bone marrow laboratory tests done after the

induction chemotherapy shows leukemia cells are still present, you will receive a cycle of Re-induction Therapy. It is the same or very similar to the initial induction chemotherapy. You will stay in the hospital for approximately 4 weeks for induction therapy. If you require re-induction therapy, you will then stay in the hospital for approximately 2 weeks. You will need to stay in the hospital until the bone marrow recovers to produce enough neutrophils (infection fighting white blood cells), you are in stable condition and at the discretion of the investigator.

You will continue to be followed as a patient in the outpatient clinic. You may undergo a bone marrow exam to assess disease response as described in the schedule of events table below.

In the Induction Therapy and Re-induction Therapy, the following procedures will occur:

- You will be assigned to one of the 3 open study groups. This will only occur within the Induction therapy.
- Cytarabine, daunorubicin, and midostaurin - All participants will receive these standard of care drugs. Cytarabine and daunorubicin will be given by intravenous (IV) injection. IV means the medicine is given by a small catheter (tube) inserted into the vein.
    - Cytarabine is given as a continuous IV infusion for 7 days (Days 1-7). This dose will remain fixed for all dose levels 1-3.
    - Daunorubicin is given as IV infusion for 3 days (Days 1-3). The daunorubicin dose will be consistently at 60mg/m^2 for Dose Levels 1-3.
    - Midostaurin is given by mouth 50 mg twice daily for Days 8-21. This dose will remain fixed for all dose levels 1-3.
- GO/Mylotarg- GO/Mylotarg will be given by IV infusion. The frequency of the infusions will depend on your assigned dose level.
    - For dose level 1, GO/Mylotarg will be given at Day 1 only.
    - For dose level 2, the GO/Mylotarg will be given at Days 1 and 4.
    - For dose level 3, GO/Mylotarg will be given at Days 1, 4, and 7.
- If you have persistent leukemia after the induction chemotherapy, you will receive reinduction. Re-induction therapy will be one of the standard of care treatment regimens. Your investigator can discuss this in more detail with you.
- Blood tests for:
    - Routine blood tests (complete blood count, chemistry, clotting tests)
    - Research related procedures (exploratory studies) – These are the same procedures as done at screening.
- Pregnancy test (if applicable)
- Physical exam – including vital signs (blood pressure, heart rate, and temperature), and weight
- Performance status
- Bone marrow biopsy/aspirate
- Review any changes with your health and medications

- Diary: you will be provided with a dosing diary to record information pertaining to Midostaurin intake: date, dose and time of each dosing.

At the end of this phase there are often no leukemia cells detectable in a blood or bone marrow sample. This is called being in remission.

If you are not in complete remission (CR) at the end of induction (or reinduction if needed) therapy, you will come off study and will go on to receive further treatment for leukemia, as recommended by your treating doctors. Participants who may benefit from and are eligible to undergo stem cell transplantation will go off the study when the transplant is possible.

Consolidation Therapy
It is likely that there are AML cells in you after the induction phase that cannot be detected. If you do not receive any further treatment after induction chemotherapy, your leukemia is very likely to recur. Consolidation therapy is used to kill any leukemia cells that may be left in the body after the induction phase.

If your blood count recovers, or if no count recovery is achieved (approximately Day 35 if one induction course or approximately Day 49 if reinduction therapy), you will begin the consolidation therapy phase. Consolidation will begin no sooner than 28 days from the start of your Induction therapy and will consist of one to two cycles of additional chemotherapy treatment (at the judgment of your investigator and dependent upon factors such as genetic risk and any co-existing conditions). You will be hospitalized while you receive your consolidation treatment for 5-6 days. You may be discharged from the hospital after completing consolidation treatment if your blood counts show recovery.

In the Consolidation Therapy, the following procedures will occur:

- If you are under 60 years of age:
    - High dose cytarabine (HiDAC) will be given as an IV over 3 hours. The IV will be given every 12 hours on Days 1, 3, and 5.
    - GO/Mylotarg will be given on Day 1.
    - Midostaurin will be given on Days 8-21.
- If you are 60 years of age or older:
    - Cytarabine will be given on Days 1-3
    - GO/Mylotarg will be given on Day 1.
    - Midostaurin will be given on Days 8-21.
- Blood tests for:
    - Routine blood tests (complete blood count, chemistry)
    - Research related procedures (exploratory studies) – These are the same procedures as done at screening.
- Pregnancy test (if applicable)
- Physical exam – including vital signs (blood pressure, heart rate, and temperature), and weight
- Performance status

- ECG and ECHO– to be performed only as clinically indicated
- Bone marrow biopsy/aspirate
- Review any changes with your health and medications
- Diary: you will be provided with a dosing diary to record information pertaining to Midostaurin intake: date, dose and time of each dosing.

After you are finished with the study drugs (Follow-up):
You will receive the study drugs for as long as you and the investigator feel that you are tolerating the study drugs and your disease is not getting worse. Your doctor will continue to watch you for side effects and follow your condition for 30 days after you end treatment. Beyond the 30 days after you end treatment, you will be followed every 1- 3 months for a period of 2 years to see if you are alive and well. You will be contacted, usually by phone or during a routine clinic visit.

A study schedule that shows how often these procedures will be done is attached.

Your medical records will be reviewed (from OSU or requested from another facility) to see if you qualify for the study and for any updates to your health and medications. The health information that will be reviewed may include your name and other personal information like your date of birth and gender, contact information, demographics, medical history, past and current medications, laboratory tests, ECG reports, ECHO reports, imaging scans, and disease-related content.

Please note that this study is a collaboration with Fred Hutchinson Cancer Research Center. Some of your blood samples will be shipped to Fred Hutchinson Cancer Research Center and researchers who are part of this study will run tests on your blood samples. After they run the tests on your blood samples, they will discard of the samples. Fred Hutchinson Cancer Research Center will not store any of your specimen or data.

4. How long will I be in the study?

You will receive the study drugs for as long as you and the investigator feel that you are tolerating the study approach and your disease is not getting worse. Your doctor will continue to watch you for side effects and follow your condition for 30 days after you end treatment. Beyond the 30 days after you end treatment, you will be followed every 3 months for a period of 2 years to see if you are alive and well.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study?

PHYSICAL RISKS

The study drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The investigator will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug/study approach.

Here are important points about side effects:

- The investigators do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.
- You may have some side effects we do not expect because we are still learning about study drug.
- There may be unanticipated risk to an embryo or fetus if you or your partner becomes pregnant.
- You may not have symptoms for some of these side effects, but you will be monitored by the investigator to check for any changes throughout the study.

Here are important points about how you and the investigator can make side effects less of a problem:

- Tell the investigator if you notice or feel anything different so they can see if you are having a side effect.
- The investigator may be able to treat some side effects.
- The investigator may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the investigator will discuss these with you.

Possible Side Effects of the GO/Mylotarg:

COMMON, SOME MAY BE SERIOUS
In 100 people receiving GO/Mylotarg, more than 20 and up to 100 may have:

COMMON, SOME MAY BE SERIOUS In 100 people receiving GO/Mylotarg, more than 20 and up to 100 may have:
• Infusion related reactions • Bleeding • Fever • Fatigue • Infection • Abnormal liver enzymes which may suggest liver damage • Nausea • Constipation • Sores in mouth • Headache • Rash • Vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving GO/Mylotarg, from 4 to 20 may have:
• Severe blood infection • Lung infection • Excess bilirubin in the blood (termed hyperbilirubinemia) • Liver damage (**see Veno-occlusive liver disease)

RARE, AND SERIOUS In 100 people receiving GO/Mylotarg, 3 or fewer may have:
• Fluid around lungs • Pain • Diarrhea • Abnormal heartbeat

****Veno-occlusive liver disease – GO/Mylotarg can cause veno-occlusive disease (VOD). VOD causes severe damage to the liver. Symptoms include jaundice (yellowing of the skin and eyes), weight gain, and extra build-up of fluid in the belly and other body parts. VOD can usually be managed very well, to the point where it goes away. However, complications can happen with VOD that may put your life in danger.**

Let the investigator know of any questions you have about possible side effects. You can ask the investigator questions about side effects at any time.

POSSIBLE SIDE EFFECTS OF MIDOSTAURIN

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Midostaurin, more than 20 and up to 100 may have:

The most frequent severe or life-threatening serious adverse events reported include:

- Febrile neutropenia (84%) – fever with low number of white blood cells called neutrophils

The most frequent serious adverse events reported include:

- Bleeding in the stomach or intestines (14%)
- Kidney failure (11-12%)
- Prolonged QT interval (11%) – a change in the electrical conduction of the heart, possibly causing abnormal heart rhythms
- Sepsis (9%) A serious condition that occurs in response to an infection that causes widespread inflammation, resulting in poor blood supply to vital organs (Sepsis). Symptoms may include a fast heart rate, fever, confusion and rapid breathing. Sepsis can rapidly lead to a life threatening clinical deterioration.
- Mycosis (7%) - an increased risk of infection, such as pneumonia. This infection may occur anywhere. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.
- Heart failure (6%)
- Heart attack
- Pericardial effusion (4%) – Build-up of fluid in the tissue around the heart
- Hypersensitivity reaction (4%)
- Pneumonia (2-10%)
- Interstitial lung disease - lung inflammation (possible difficulty breathing)
- Pneumonitis – Inflammation of the lungs, which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.

POSSIBLE SIDE EFFECTS OF CYTARABINE

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, more than 20 and up to 100 may have:
• Blood clot • Rash • Swelling in the rectum which may cause rectal pain • Diarrhea, loss of appetite, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Anemia which may cause tiredness, or may require blood transfusions • Fever

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, from 4 to 20 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Numbness and tingling of the arms and legs • Severe blood infection • Kidney damage which may cause swelling, may require dialysis • Headache • Dizziness • Chest pain • Hair loss • Liver damage which may cause yellowing of skin or eyes • Swelling and redness of the eye

RARE, AND SERIOUS In 100 people receiving Cytarabine, 3 or fewer may have:
• Coma

Possible Side Effects of Daunorubicin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Daunorubicin, more than 20 and up to 100 may have:
• Hair loss • Nausea, vomiting • Pink or red colored urine, sweat, or saliva

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Daunorubicin, from 4 to 20 may have:
• Damage to the heart which may cause shortness of breath, tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Daunorubicin, from 4 to 20 may have:
• Infection, especially when white blood cell count is low • Anemia which may require transfusion • Bruising, bleeding • Pain and sores in mouth and throat • Dark discoloration of the nail, skin • Loss of nails • Redness and pain at the site of previous radiation • Swelling and redness at the site of injection • Diarrhea

RARE, AND SERIOUS In 100 people receiving Daunorubicin, 3 or fewer may have:
• Cancer of the bone marrow (leukemia) cause by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Other Types Of Risks

Blood draw: We will draw blood from a vein in your arm, your peripheral venous catheter, or your port-acath. You may feel some pain when your blood is drawn. There is a small chance the needle will cause bleeding, a bruise, an infection, or fainting.

Bone marrow biopsy: Bone marrow biopsy means taking some cells from inside your bones. Before the bone marrow biopsy, we will numb an area of your skin (usually near your hip) with a shot. The shot may cause a little pain. There is a rare chance of an allergic reaction to the numbing medicine, which can be serious and life-threatening. The medical team will be watching closely for signs of an allergic reaction and will provide emergency treatment if necessary. The bone marrow biopsy involves inserting a long needle into your bone to get the cells. Some people have moderate to severe pain when the bone marrow cells are drawn out through the long needle. Your hip may hurt for about three to six days. There is a small chance you will get a bruise or an infection where the needle was inserted. You may bleed or have a scar. Your skin may temporarily itch where the needle was inserted.

Typical chemotherapy side effects: Your ability to fight infections may be reduced. This could be life threatening. Your blood may not be able to clot as well as it normally does. This may cause bleeding and you may need to receive blood transfusions. You may lose all or part of your hair. You may experience nausea or vomiting which could be severe. The investigator may give you medication to help with the nausea or vomiting. If you receive radiation, you may experience: a skin reaction like a mild to moderate sunburn, tiredness, your ability to taste may change, loss of appetite, and numbness or tingling in the fingers and toes.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby from the screening visit until 6 months following the last dose of study drug if you are female, or 4 months following the last dose of study drug if you are male. The study drug used in this study could be very damaging to a fetus. You must agree to use either a barrier method and hormonal method, or two barrier methods.
Acceptable forms of barrier birth control include:

- Diaphragm- a shallow cup that covers the cervix during sex
- Condom- a pouch that covers the penis during sex
- Copper intrauterine device (IUD)- a device implanted in the uterus that prevents sperm from reaching the egg
- Contraceptive sponge- sponge that covers the cervix to block entrance to uterus
- Spermicide- cream/gel that kills sperm.

Acceptable forms of hormonal birth control include any form of birth control that administers an estrogen and/or progestational agent via oral (birth control pill), subcutaneous (device placed under the skin or administered via injection), intrauterine (device placed in the uterus), or intramuscular (administered via injection) methods.
If you or your female partner become pregnant during the research study, please tell the investigator and your doctor immediately. Because the risk to the baby is unknown, it is recommended that you or your partner agree to medical supervision during pregnancy and after the baby is born. In the rare event that you or your partner become pregnant, we will request your consent and your partner's consent to collect confidential information about your or your partner's health and that of the baby.

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual.
- You may be asked sensitive or private questions which you normally do not discuss.
- The study drug/study approach may not be better, and could possibly be worse, than the usual approach for your cancer.
- The study drug/study approach or the dose you receive may not be effective in helping to treat your disease. This means you may spend time in the study and experience side effects taking a drug that may not provide you with any health-related benefits.

RISKS OF GENETIC TESTING

Although we have made efforts to protect your identity, there is a small risk of loss of confidentiality. If the results of these studies of the genetic testing of your cancer cells were to be accidentally released, it might be possible that the information we will gather about you as part of this study could become available to an insurer or an employer, or a relative, or someone else outside the study. This could affect your ability to get insurance or to get or keep a job. It could also affect family planning and/or your personal relationships. Even though there are certain genetic discrimination and confidentiality protections in federal law, there is still a small chance that you could be harmed if a release occurred. The researchers

believe the chance these things will happen is very small, but cannot promise that they will not occur.
There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.
If we discover new information that is important for your health care, either in this study or the future, you will be asked whether you wish to receive the results. You may be required to have the test repeated in a clinical laboratory. Because genetic information is complex and sensitive, the results should be discussed with a genetic counselor or your primary care giver who can answer your questions or discuss your concerns. You would be responsible for all costs associated with having the test repeated and visiting a doctor or genetic counselor to discuss the results.
Should you want anyone to re-test your bone marrow there may not be any bone marrow left to test. There will be the slides and reports to read. Should you decide to stop this study and ask that your bone marrow be returned, there is a chance that the bone marrow might be all gone.

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. 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. GINA also does not protect you against discrimination if you have already been diagnosed with the genetic disease being tested.

7. What benefits can I expect from being in the study?

You may or may not personally benefit from being in this study. However, by serving as a participant, you may help us learn how to benefit patients in the future.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the standard treatment
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

9. What are the costs of taking part in this study?

The drug, gemtuzumab ozogamicin, will be provided at no cost to you while you participate in this study. Tests and procedures performed solely for research purposes will be provided at

no cost to you. This includes research testing of your blood samples by a central lab Your study doctor or coordinator can tell you, specifically, which costs are covered by the study.

Midostaurin, cytarabine and daunorubicin are commercially available to treat AML and will be billed to you and your insurance provider. Most of the care you receive during this study is considered routine for your disease. Routine costs include, but are not limited to: (hospitalization during induction and consolidation, drug administration charges, doctors' fees, lab work and bone marrow biopsies). They may include the costs of care and treatment of any side effects or complications resulting from your participation in this study. The costs of routine medical care will be billed to you and your insurance provider in the usual manner. You will be responsible for any deductibles, coinsurance or copayments required by your particular plan. You may be responsible for any costs not paid by your insurance provider.

If you are a Medicare Advantage Plan participant (HMO or PPO), original Medicare is billed first for routine, study-related services while you participate in an approved trial. Your Advantage Plan is billed second for their share of your costs. You may or may not have additional out of pocket costs after Medicare or your Advantage Plan pays. Additional information can be obtained from your Advantage Plan and online at:

https://www.medicare.gov/Pubs/pdf/02226-Medicare-and-Clinical-Research-Studies.pdf

Some insurance providers will not pay for routine costs if you are participating in a research study. Others may limit what they pay or where you can receive care. Before participating in this study, we recommend that you ask your insurance provider if there are any limitations to your particular plan. Otherwise, you might experience unexpected medical costs. A financial counselor is available on request.

10. Will I be paid for taking part in this study?

You will not receive any form of compensation for participation in this study.

11. What happens if I am injured because I took part in this study?

OHIO STATE UNIVERSITY LIABILITY
If you are injured as a result of your participation in this study, you may obtain immediate care at the Ohio State University Medical Center. The cost of this treatment will be charged to you or your insurance company. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study. The Ohio State University has no funding set aside for the payment of health care expenses for this study.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of research participants.

13. Will my de-identified information and bio-specimens be used or shared for future research?

Yes, it/they may be used or shared with other researchers without your additional informed consent.

14. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

If we find information that significantly impacts your health, we will share it with you. This includes any findings that can immediately impact your health such as infections or findings affecting your organs. Your treating physician's team will call you with these results.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

15. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual;
- Information gathered for this research about:
  Physical exams
  Laboratory, x-ray, and other test results
  Diaries and questionnaires
- Records about any study drug you received;
- Records about the study device; and

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office record;
- Others: Pfizer

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;
- Governmental agencies in other countries;

- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

16. Who can answer my questions about the study?

For study questions, concerns, or complaints, to withdraw consent and HIPAA authorization, or if you feel you have been harmed as a result of study participation, you may contact:

Uma Borate, MD
1800 Cannon Drive
Lincoln Tower 1120E
Columbus, OH 43210
Phone: 614-293-3316
Email: Uma.Borate@osumc.edu

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact the HIPAA Privacy Officer in the College of Medicine at **614-292-2856** or by mail at:

HIPAA Privacy Officer
Suite E2140
600 Ackerman Rd.
Columbus, OH, 43202

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact**:**

Uma Borate, MD
1800 Cannon Drive
Lincoln Tower 1120E
Columbus, OH 43210
Phone: 614-293-3316
Email: Uma.Borate@osumc.edu

STUDY SCHEDULE

This schedule lists study procedures as well as procedures you would have even if you do not join the study (usual care).

Visit Days (± 3 Days)	Screen†	Induction Therapy* Cycle 1 (28 Days)																													Reinduction Therapy **
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28		
Cytarabine[A]		X	X	X	X	X	X	X																							
Daunorubicin[B,C]		X	X	X																											
Gemtuzumab ozogamicin		X[1]			X[2]			X[3]																							
Midostaurin[D]									X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Informed consent	X																														
Inclusion/exclusion criteria	X																														
Medical history	X																														
Medication history[E]	X																														
Physical Examination[F]	X	X													X																
Hematology[G, O]	X	X	X	X	X	X	X	X							X							X								X	
Biochemistry[H, O]	X	X	X	X	X	X	X	X							X							X								X	
Coagulation[O]	X																														
CD33 SNP	X																														
ECG[I]	X																														
ECHO[N]	X																														
Pregnancy test[J]	X																														
Bone Marrow Exam[K]	X														X[K]															X[K]	
Disease Response Assessment																														X	
LP[L]	X																														
AE assessment[M]	X	X----------																												-----X	

† To be performed within 4 weeks of baseline.
*Treatment cycle is 28 days.
[A] Cytarabine 100mg/m^2
[B] Daunorubicin Dose level #1-3, 60 mg/m^2, administered Days 1, 2 and 3, only.
[C] (Closed) Daunorubicin Dose level #4, 90 mg/m^2, administered Days 1, 2 and 3, only

Visit Days (± 3 Days)	Screen[†]	Induction Therapy* Cycle 1 (28 Days)																											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28

[D] Midostaurin Dose Level 50 mg bid PO, administered on Days 8-21. Provide diary to the participant.
[1] Dose level #1 GO, 3 mg/m^2 (up to one 4.5 mg vial), administered on Day 1 only
[2] Dose level #2 GO, 3 mg/m^2 (up to one 4.5 mg vial), administered on Days 1 and 4 only
[3] Dose level #3 GO, 3 mg/m^2 (up to one 4.5 mg vial), administered on Days 1, 4, and 7 only
[E] For concomitant medications – enter new medications started during the trial from time of consent through the end of trial visit. Record all medications taken for grade 3 and 4 SAEs as defined in protocol
[F] All physical exams will include assessing weight, vital signs, and ECOG performance status. Height will be measured at screening visit only.
[G] Hematology – CBC with differential.
[H] Biochemistry – complete metabolic panel, every day during chemotherapy as indicated. Liver function test required only once per week on Screening, and Days 1, 14, 21, and 28 of induction phase.
[I] ECG to be performed at screening and thereafter only as clinically indicated.
[J] For women of reproductive potential, a urine pregnancy test should be performed within 14 days prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated, if required, per institutional guidelines.
[K] Bone marrow biopsy at screening not required if performed within 3 months prior to starting planned study treatment. An optional bone marrow biopsy will be performed on Day 14 (+7 days) per institutional requirements. If hypoplasia is not documented or indeterminate, a biopsy may be repeated in 7 days to clarify persistence of leukemia. Additional bone marrow biopsies may be performed as clinically indicated. A bone marrow biopsy will be performed at count recovery (usually around Day 28) or at Day 42, whichever occurs first.
[L] At the discretion of the PI or treating physician, an LP may be performed as a part of a diagnostic work-up to assess for CNS leukemia.
[M] AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record grade 3 and 4 AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring up until 90 days after the last dose of trial treatment, or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs that are related to trial treatment.
[N] ECHO to be performed at screening and thereafter only as clinically indicated.
[O] Standard of care labs include: CBC, CMP (uric acid, coagulation labs and LDH as clinically indicated).
**Re-induction therapy will be administered to participants with blasts ≥5% in the bone marrow. Re-induction therapy is considered Cycle 2 and will comprise 7+3 cytarabine and daunorubicin. The addition of midostaurin to the re-induction regimen is permitted and should be discussed with the principal investigator. Participants may undergo a bone marrow examination, per standard of care, on day 21 (± 7 days) of the 28-day re-induction cycle to assess disease response. Please see section 6.2 for detailed information. Unless stated otherwise, the same schedule should be followed.

Visit Days (± 3 Days)	Consolidation Therapy – HiDAC Cycle 3 and 4 (28 Days)**[1]																												Follow-up[†]
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Cytarabine**	X		X		X																								

Visit Days (± 3 Days)	Consolidation Therapy – HiDAC Cycle 3 and 4 (28 Days)**[1]																											Follow-up[†]
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Gemtuzumab ozogamicin*	X																												
Midostaurin*								X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Medication history[A]	X																												
Physical Examination[B]	X													X															
Hematology[C]	X				X									X							X							X	X
Biochemistry[D]	X		X		X									X							X							X	
ECG[E]																													
Pregnancy test[F]	X																												
Disease Response Assessment																												X[1]	
AE assessment[G]	X----------X																												

Visit Days (± 3 Days)	Consolidation Therapy – HiDAC Cycle 3 and 4 (28 Days)**[1]																											Follow-up[†]
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	

*Participants < 60 years old will receive the HiDAC regimen, consisting of: 3 g/m^2 of cytarabine every 12 hours on Days 1, 3, 5; 3 mg/m^2 (up to one 4.5 mg vial) of GO on Day 1 (for the first cycle of consolidation only); and 50 mg PO (bid) of midostaurin on Days 8-21 (provide diary to the participant). If a participant is planned for stem cell transplantation within 60 days of beginning their first cycle of consolidation, omitting the GO dose is strongly recommended (but left to the discretion of the treating physician in consultation with the investigator)

**Treatment cycle is 28 days. Any participant that completes or discontinues treatment must be evaluated within 30 days after termination and prior to transplant or the initiation of salvage therapy, if not performed within the last 30 days.

[†]Follow-up visits to occur every 3 months for a period of 2 years following completion of on-study therapy or until death, whichever occurs first. Follow-up will include assessment of survival status.

[A]For concomitant medications – enter new medications started during the trial from time of consent through the end of trial visit. Record all medications taken for grade 3 and 4 SAEs as defined in protocol.

[B] All physical exams will include assessing weight, vital signs, and ECOG performance status. Height will be measured at screening visit only.

[C] Hematology – CBC with differential. For follow up, this should occur every 1 to 3 months for 2 years. [D] Biochemistry – complete metabolic panel, every day during chemotherapy as indicated. Liver function test required only once per week on Days 1, 14, 21, and 28 of consolidation phase.

[E] ECG to be performed only as clinically indicated.

[F] For women of reproductive potential, a urine pregnancy test should be performed prior to start of each treatment cycle. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

[G]AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record grade 3 and 4 AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring up to 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs that are related to trial treatment.

[1] Bone marrow exam/Peripheral blood draw: If a patient is discontinuing study treatment to receive a transplant, a bone marrow exam is recommended but not mandatory. If a participant is discontinuing study treatment for other reasons, a bone marrow exam may be performed at the end of consolidation (i.e., after a full count recovery, defined as ANC ≥ 1000/µL and platelet count ≥ 100,000/µL), which marks the end of protocol-directed therapy.

Visit Days (± 3 Days)	Consolidation Therapy – MiDAC*[1] Cycle 3 and 4 (28 Days)																											Follow up[†]
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Cytarabine*	X		X		X																								
Gemtuzumab ozogamicin*	X																												
Midostaurin*								X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Medication history[A]	X																												
Physical Examination[B]	X													X															

Visit Days (± 3 Days)	Consolidation Therapy – MiDAC*[1] Cycle 3 and 4 (28 Days)																											Follow up[†]
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
Hematology[C]	X				X									X							X							X	X
Biochemistry[D]	X				X									X							X							X	
ECG[E]																													
Pregnancy test[F]	X																												
Disease Response Assessment																												X[1]	
AE assessment[G]	X----------																												----------X

*Participants ≥60 years old will receive MiDAC, consisting of: 1.5 to 2 g/m^2 of cytarabine every 12 hours on Days 1, 3, 5; 3 mg/m^2 (up to one 4.5 mg vial) of GO on Day 1 (for the first cycle of consolidation only); and 50 mg PO (bid) of midostaurin on Days 8-21 (provide diary to the participant). If a participant is planned for stem cell transplantation within 60 days of beginning their first cycle of consolidation, omitting the GO dose is strongly recommended (but left to the discretion of the treating physician in consultation with the investigator)

**Treatment cycle is 28 days.

[†]Follow-up visits to occur every 3 months for a period of 2 years following completion of on-study therapy or until death, whichever occurs first. Follow-up will include assessment of survival status.

[A]For concomitant medications – enter new medications started during the trial from time of consent through the end of trial visit. Record all medications taken for grade 3 and 4 SAEs as defined in protocol.

[B] All physical exams will include assessing weight, vital signs, and ECOG performance status. Height will be measured at screening visit only.

[C] Hematology – CBC with differential as indicated. For follow up, this should occur every 1 to 3 months for 2 years.

[D] Biochemistry – complete metabolic panel, every day during chemotherapy as indicated. Liver function test required only once per week on Days 1, 14, 21, and 28 of consolidation phase.

[E] ECG to be performed only as clinically indicated.

[F] For women of reproductive potential, a urine pregnancy test should be performed prior to start of each treatment cycle. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

[G]AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record grade 3 and 4 AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring up until 90 days after the last dose of trial treatment, or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs that are related to trial treatment.

[1] Bone marrow exam/peripheral blood draw: If a patient is coming off study treatment to receive a transplant, a bone marrow exam is recommended but not mandatory. If a participant is discontinuing study treatment for other reasons, a bone marrow exam may be performed at the end of consolidation (i.e., after a full count recovery, defined as ANC ≥ 1000/µL and platelet count ≥ 100,000/µL), which marks the end of protocol-directed therapy.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of participant	**Signature of participant**
	AM/PM
	Date and time
Printed name of person authorized to consent for participant (when applicable)	**Signature of person authorized to consent for participant (when applicable)**
Relationship to the participant	**AM/PM** **Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM