A Single-Center Phase 1/2 Study of Single- or Fractioned-Dose Gemtuzumab Ozogamicin in Combination with G-CSF, Cladribine, Cytarabine and Mitoxantrone (GCLAM) for Previously Untreated Adult Acute Myeloid Leukemia or High-Grade Myeloid Neoplasm

Short title: Gemtuzumab ozogamicin plus GCLAM for AML

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Fred Hutchinson Cancer Research Center

Consent to take part in a research study:

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Short title: Gemtuzumab ozogamicin plus GCLAM for AML

Principal Investigator: Roland B. Walter, MD PhD MS. University of Washington; Fred Hutchinson Cancer Research Center. [redacted]

Emergency number (24 hours):

Call the paging operator at the University of Washington Medical Center at [redacted], and ask for the Fellow on call for Hematology/Oncology.

Important things to know about this study.

You are invited to participate in a research study. The purpose of this research is to see whether adding the drug gemtuzumab ozogamicin (here abbreviated as "GO") to a chemotherapy regimen called GCLAM is safe and effective for patients with AML or related high-grade myeloid neoplasms.

People who agree to join the study will likely be admitted to the hospital and be asked to attend frequent clinic visits over several months, as is standard for patients with AML and related diseases. The study involves the administration of multiple doses of intravenous chemotherapy.

We do not know if the combination of GO and GCLAM would help treat AML and high-grade myeloid neoplasms and could even make your condition/disease worse. Both GCLAM and GO could cause side effects during administration (e.g. chills) as well as after administration (e.g. low blood counts and complications thereof), as described below in this form.

You do not have to join this study. You can choose to receive standard methods to treat your cancer instead of participating in this study. We will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain

other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the study. If you join this study, we will give you a signed copy of this form to keep for future reference.

We invite you to join this research study.

We invite you to join this research study because you have AML or a related high-grade myeloid neoplasm. Up to 72 people will join this study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

You do not have to be in the study. You are free to say "yes" or "no", or to drop out after joining. If you say "no," you would have no penalty or loss of benefits. Whatever you decide, your regular medical care would not change.

Why are we doing this study?

We are doing this study to examine the combination of GO and GCLAM chemotherapy. We want to know if this combination is safe, whether one or three doses of GO in combination with GCLAM is safe, and ultimately whether this combination is an effective treatment for AML and high-grade myeloid neoplasms.

We are studying GO [trade-marked as Mylotarg]. GO is an antibody-drug conjugate which is FDA-approved for the treatment of AML. We are also studying GCLAM chemotherapy, which consists of granulocyte colony stimulating factor ("G"), cladribine ("Cl") [Leustatin], cytarabine ("A") [Cytosar-U] and mitoxantrone ("M") [Novantrone]. Granulocyte colony stimulating factor is a growth factor used to stimulate leukemia cells and render them more sensitive to chemotherapy drugs, and cladribine, cytarabine and mitoxantrone are all standard chemotherapy drugs used to treat AML and other cancers.

We have used GCLAM alone widely to treat people with AML and related blood cancers and found it to be safe and effective. GO has been used widely alone or in combination with other chemotherapy drugs for the treatment of the same cancer. However, GO and GCLAM together have not yet been tested in people.

In this study, we want to learn:

- How much GO can be given safely in combination with GCLAM.
- What effects, good or bad, GO plus GCLAM chemotherapy has on people with AML and high-grade myeloid neoplasms.

If you join this study, we would give you GO and GCLAM chemotherapy. People who join at the beginning of the study will receive one single dose of GO together with GCLAM. If we find this dosing safe, people who join later may receive 3 doses of GO together with GCLAM, until effects (good or bad) appear. We will watch carefully for any side effects.

What research tests, procedures, and treatments are done in this study?

If you join this study, we would do these tests and procedures:

- **Baseline Assessment**. You will need tests, including a bone marrow and/or peripheral blood analysis, a heart test, and a physical exam to see if you are eligible for the trial. Please tell your medical team of any past or current medical problems. These tests and physical exam are usually considered part of regular cancer care. If you have recently had some of these tests, they may not need to be repeated. You will also need a central venous catheter inserted to receive chemotherapy and to simplify blood draws and transfusions.
- **Collection of research specimens**. You will have the option of participating in additional research by providing extra blood or bone marrow specimens to be stored in a repository for future laboratory research, e.g. to understand why some people do/do not respond to this treatment. You do not need to give specimens to participate in the trial. If you do agree to donate specimens for future research, an additional tube of blood or up to 10 ml of bone marrow per bone marrow procedure may be collected for research storage. We would only collect research bone marrow specimens at the time of bone marrow tests done for regular cancer care; extra bone marrow procedures for purposes of research specimen collection will not be required.
- **Study Treatment.** You will be assigned to received GO in combination with GCLAM chemotherapy at one of two dosing schedules.
  - **Dose level 1**: will receive a single dose of GO at a dose of 3 mg/m^2 (maximum dose 4.5 mg) through the vein (IV) on day 1 of GCLAM chemotherapy.
  - **Dose level 2**: will receive three doses of GO, each dose at 3 mg/m2 (maximum dose 4.5 mg), through the vein (IV) on days 1, 4, 7 of GCLAM chemotherapy.

  The first group of 6 patients will be enrolled at dose level 1. If these patients tolerate the treatment, the next group of 6 patients will receive dose level 2. If patients do not tolerate a certain dose level because of bad side effects, we will not give that level in the future. Once the highest tolerated dose level (also called the maximum tolerated dose) of GO plus GCLAM chemotherapy has been identified in a smaller group of patients ("Phase 1"), the remainder of the patients will receive the study treatment at that highest tolerated dose ("Phase 2")

- **The other drugs will be given as follows:**

- G-CSF will be given as a shot underneath the skin every day for 6 days, starting the day before the rest of the chemotherapy.
- Cladribine will be given in your vein over 2 hours each day for a total of 5 days.
- Cytarabine will be given in your vein over 2 hours each day for a total of 5 days.
- Mitoxantrone will give given in your vein over 1 hour every day for 3 days.

- **Monitoring during Study**. During the trial, you will need routine procedures, tests and close follow-up. This care is part of routine monitoring for patients receiving chemotherapy. Some examples of these tests, procedures, and care include the following:
  - A medical history
  - Physical examinations
  - Blood tests
  - Bone marrow examinations (i.e., aspiration and/or biopsy)
  - Radiology tests such as a chest x-ray if clinically indicated
  - Ultrasound of your heart or other heart tests if there are any concerns about your heart function
  - Red blood cell or platelet transfusions

How long would you stay in this study?

If you join this study, you would stay in it for up to 6-8 months. The exact length of treatment would depend on the side effects and your response to the treatment. If you still have your cancer after GO + GCLAM, you may be eligible to have the GCLAM component of the therapy repeated. If this were the case, your doctors would discuss this with you. If you do not achieve a good response ("remission") after 2 cycles, you would not be eligible for additional cycles as part of this trial. If you achieve a good response with GO and GCLAM, you would be able to receive up to 3 cycles of additional chemotherapy ("post-remission" chemotherapy) on this study to further decrease the amount of cancer cells that may still be left in your body. The first cycle of this post-remission chemotherapy will consist of GCSF, Cladribine, and Cytarabine (GCLA). These drugs will be dosed the same way they were during the initial treatment as long as you tolerated the treatment. The consolidation would be given after your blood counts are better and you have recovered from side effects that you may have experienced. This recovery usually takes about 1 month. Some doctors or patients may elect to use therapies other than GCLA for your consolidation (e.g. stem cell transplantation), and your doctors would discuss these options after your initial treatment. The second and third cycles of consolidation would be with cytarabine alone, given at 1000 mg/m^2 every 12 hours on days 1-6 for a total of 12 doses. Each cycle would start only after recovery from the previous cycle, which takes about 1 month.

The study doctor or your doctor may take you out of this study at any time. This would happen if:

- They think it is in your best interest not to continue in the study.

- You are not able or willing to follow study procedures.
- The whole study is stopped.

If you withdraw from the study for any reason, previously collected information would remain in the study records and would be included in the analysis of results. This information could not be removed from the study records. If you are thinking about dropping out of this study, please tell the study doctor.

Long-term follow-up means keeping track of someone's medical condition for a long time. After you have finished the study treatment, you may return to your primary oncologist or choose to receive additional care at the Seattle Cancer Care Alliance (SCCA). After you finish the study, the study doctors may want to know about your health after you leave the SCCA. The study doctors may contact you or your doctor up to every 3 months for 5 years to see how you are doing. We would also ask your doctor to send a copy of your medical records. This information will help us learn about the long-term effects of GO plus GCLAM. You do not have to be in long-term follow-up. You could say "yes" or "no". Either way, you could still join the study. If you drop out of the study, you would be asked if we could call you up to every 3 months for 5 years. If you choose not to join long-term follow-up, you would not be contacted regularly, and we would not ask your doctor to send medical records, but we might still need to contact you for some other reason.

What are the side effects (risks)?

In this part of the consent form, we describe the side effects we expect from the treatments in this study. GO plus GCLAM could cause side effects we do not know about yet. We carefully watch everyone in the study for side effects.

If you join the study, we would tell you if we discover new side effects that could affect you.

This form lists side effects of individual drugs. When we use these drugs together, there may be other side effects.

Side effects may be mild or very serious. Medicines could be given to help lessen side effects. Many side effects of chemotherapy go away soon after you stop taking the treatment. In some cases, side effects can last a long time or never go away. There also is a risk of death.

Gemtuzumab ozogamicin
Likely side effects (>20% of patients) of GO are:

- Abdominal pain
- Weakness
- Chills
- Fever
- Headache
- Infection
- Diminished appetite
- Constipation
- Diarrhea

- Nausea/Vomiting
- Mouth sores
- Low blood counts
- Low blood potassium levels
- Difficulty breathing
- Nose bleeds

Less likely side effects (3-20% of patients) of GO are:

- Back pain
- Fever associated with low white blood cell count (neutropenic fever)
- Pain
- Bleeding/Bruising
- High blood pressure
- Low blood pressure
- Fast heart rate
- Liver test abnormalities
- High blood sugars
- Low blood calcium, magnesium and phosphate levels
- Swelling in the ankles
- Muscle aches
- Anxiety and depression
- Dizziness
- Insomnia
- Cough, sore throat
- Itching
- Rash
- Herpes skin infection
- Local reaction to infusion

Rare side effects (<3% of patients)

- Abnormal uterine bleeding

G-CSF

Likely side effects (>20% of patients) of G-CSF are:

- Pain or discomfort at the injection site
- Pain and/or aching in the chest, back, arms, legs, and in the bones
- Elevated white blood cell count

Less likely side effects (3-20% of patients) of G-CSF are:

- Nausea / vomiting
- Headache
- Fever
- Lightheadedness
- Cough or shortness of breath
- Skin rash
- Low platelet count

Rare but serious side effects (<3%) of GCSF are:

- Allergic reactions (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives)
- Difficulty breathing or coughing up blood
- Bleeding in the brain
- Blood in the urine
- Blood clots
- Worsening of psoriasis if you already have psoriasis
- Kidney problems including kidney failure
- Elevated heart rate
- Low blood pressure
- Blood clot
- Rupture of the spleen (when an organ in your abdomen bursts); this may be life-threatening
- Inflammation of the liver
- Inflammation of the sac around the heart
- Hair loss

Cladribine

Likely side effects (>20% of patients) of cladribine are:

- Nausea and vomiting
- Tiredness or fatigue
- Rash
- Fever during times of low blood counts (i.e., "neutropenic fever")
- Low blood counts (low WBC, RBC, platelets)

Less likely side effects (3-20% of patients) of cladribine are:

- Decreased appetite
- Dizziness
- Diarrhea or constipation
- Cough or shortness of breath
- Abdominal pain, possibly with diarrhea or constipation
- Pain in the muscles, joints, belly, head
- Bruising
- Bleeding from the nose
- Rash
- Infections
- High heart rate
- Blood clots
- Difficulty sleeping
- Sweating

Rare but serious side effects (<3%) of cladribine are:

- Life-threatening rash (Stevens-Johnson syndrome)
- Severe anemia (aplastic anemia, hemolytic anemia)
- Blood stream infection
- Severe confusion
- Kidney problems including kidney failure
- Blood abnormalities (myelodysplastic syndrome)

- Allergic reactions (fever, chills, shortness of breath, fast heartbeat, loss of consciousness, sweating, swelling of face or tongue, tightness of throat, wheezing)

Cytarabine

Likely side effects (>20% of patients) of cytarabine are:

- Fatigue
- Low blood counts (low WBC, RBC, platelets)
- Diarrhea, nausea, vomiting, and loss of appetite
- Irritation, inflammation, or damage to the mouth, throat, esophagus (tube between the mouth and stomach), stomach, intestines or colon
- Fever during times of low blood counts (i.e., "neutropenic fever")
- Rash
- Abnormal liver tests or liver function
- Sores in or around the mouth

Less likely side effects (3-20% of patients) of cytarabine are:

- Chest pain
- Fluid collection around the heart
- Shortness of breath
- Headaches
- Dizziness
- Irritation or inflammation of nerves which causes pain in various parts of the body
- Itching
- Jaundice (yellow discoloration of the skin)
- Constriction of the lung airways causing shortness of breath or wheezing
- Inflammation of the pancreas (the organ in your abdomen that helps you digest food and controls your blood sugars)
- Difficulty in passing urine
- Inflammation or irritation of the eye or surface of the eyelids
- Kidney problems

Rare but serious side effects (<3% of patients) of cytarabine are

- Inflammation around the brain
- Heart failure
- Diffuse pain in the muscles, bones, chest, and eyes
- Severe skin rash with flat discolored areas and raised bumps
- Weakness
- Muscle damage
- Life-threatening liver damage

Mitoxantrone

Likely side effects (>20% of patients) of mitoxantrone are:

- Fatigue
- Low white blood cell counts
- Fever during times of low blood counts (i.e., "neutropenic fever")
- Nausea / vomiting

- Temporary discoloration of the urine and other body fluids (due to blue color of medication)

Less likely side effects (3-20% of patients) of mitoxantrone are:

- Skin rash
- Fast or irregular heart beat
- Fever or chills
- Decreased heart function
- Lower back or side pain
- Painful or difficult urination; decrease in urination
- Swelling of feet and lower legs
- Sore, red eyes
- Yellow eyes or skin
- Pain or inflammation at injection site
- Blue skin at place of injection

Rare but serious side effects (<3% of patients) of mitoxantrone are:

- Allergic reactions (fever, chills, shortness of breath)
- Heart failure
- Secondary acute myeloid leukemia from drug treatment
- Slow heart rate

Reproductive risks

Chemotherapy could cause sterility (unable to have children).

Taking the study medicines may involve unknown risks to an embryo or fetus (unborn baby) or nursing infant. Therefore, you could not join this study if you are pregnant, if you are planning to become pregnant, or if you are breastfeeding.

If you join this study, you would have to use an effective method of birth control from the time this form is signed until at least 3 months after the last dose of study treatment. Examples of effective methods of birth control include, but are not limited to barrier methods (condoms) for either sex and oral contraceptives for women. We would ask that you check with your doctor to make sure the method you choose is effective. If you are already using a method of birth control, you would have to check with the study doctor or a member of the study staff to make sure it is acceptable.

If you become pregnant after joining this study, you would have to notify the study doctor immediately. Participation in this study would end at that time.

The effects of fathering a child are also unknown. Men who join this study must also agree to use one or more forms of effective and acceptable birth control from the time this form is signed until at least 3 months after the last dose of study treatment

Non-physical risks

If you join this study, non-physical risks are:

- You might not be able to work.
- Breach of confidentiality

What are the benefits?

We do not know if combining GO with GCLAM will help treat AML or high-grade myeloid neoplasms. This particular combination has not been tried before, and we are testing it to find the highest safe dose and to see its effects on people with AML and related diseases. You might get better if you receive these drugs, but your condition could stay the same or even get worse. We hope the information we learn will help people with these diseases in the future.

You have other choices besides this study.

You do not have to join this study. You are free to say "yes" or "no". Your regular medical care would not change if you decide to say "no".

You have other choices for treatment. Each of these choices has risks and benefits. You should talk to your doctor or healthcare provider about these choices.

Other choices include:

- Another research treatment.
- Standard treatment.
- No treatment.
- Comfort care.

Enrollment in this study may exclude you from other research studies.

Protecting Privacy as an Individual and the Confidentiality of Personal Information

If you join this study, some people or organizations might need to look at your medical records and research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Research Center IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.

- Fred Hutchinson Cancer Research Center, University of Washington, and Seattle Cancer Care Alliance.
- Office for Human Research Protections, Food and Drug Administration and other regulatory agencies as required.

We will do our best to keep personal information confidential. But we cannot guarantee total confidentiality. Personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests. Or a court may order study information to be disclosed. Such cases are rare.

We will not use personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

If you join this study, information about your participation would be made part of your permanent medical record. This information would include a copy of this consent form. If an insurance company or employer or anyone else were authorized to see your medical record, they would see a copy of this consent form.

How is my genetic information protected?

A federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect genetic information about people who join research studies.

GINA restricts access to genetic information so that it cannot be used for health insurance coverage decisions. GINA prevent health insurance companies or group health plans from

- Asking for genetic information obtained in research studies, or
- Using genetic information when making decisions regarding your eligibility or premiums

GINA *does not* help or protect against genetic discrimination by companies that sell life, disability or long term care insurance.

Would we pay you if you join this study?

There is no payment for being in this study.

Would you have extra costs if you join this study?

If you join this study, you would have some extra costs. Your insurance company might pay these costs, but some insurance policies do not cover these costs. We could help find out whether your insurance company would cover these costs.

The extra costs are:

- Cost of tests that are given more often than usual.
- Cost of the study drugs (except GO).
- Cost of standard doctor visits and lab tests.
- Cost of any other medical care needed because of this study.

If you join this study, you or your insurance company would have to pay for the costs of standard treatment in this study.

You would **not** be billed for:

- GO.

What if you get sick or hurt after you join this study?

For a life threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is over or as soon as you can.

For all other medical problems or illness related to this research, immediately contact study physicians Dr. Roland B. Walter [redacted]. They will treat you or refer you for treatment. You or your health insurance will have to pay for the treatment. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family. State or national law may give you rights to seek payment for some of these expenses. You do not waive any right to seek payment by signing this consent form.

You or your insurer will be billed for treatment of problems or complications that result from your condition or from clinical care.

You would not lose any legal right to seek payment for treatment if you sign this form.

We invite you to donate tissue samples for other research.

After we do tests on tissue in this study, some tissue may be left over. We invite you to donate this leftover tissue for future research. This may include genetic research.

If you join this study, you would not have to donate tissue for future research. You would be free to say "yes" or "no." Regular medical care would not change if you say "no."

If you donate tissue, it would be stored in a secure location. If we want to use your tissue for other research or share it with other scientists for research, an ethics review committee (IRB) would review the request. The IRB would decide if we needed to ask you for permission to do the research.

Your donated tissue would be used only for research. This research could be done by for-profit companies. Researchers would not report their results to you or your

doctors. The research results would not be included in medical records. The results would not affect your medical care.

Research with tissue might help develop new products. If these products make money, there is no plan to share the money with the participants who donate the tissue.

If you donate tissue for research, you could withdraw the donation at any time by calling Dr. Roland Walter at [redacted] or Dr. Colin Godwin at [redacted]. You would have no penalty for withdrawing the donation, and regular medical care would not change. We could not return donated tissue, but we might be able to destroy the donated tissue. We could not destroy tissue if it is stored or shared without any label saying who donated it. In this case, it could still be used for research.

Read the question below and think about your choice. When you decide, please circle **YES** or **NO** on page 15 on this form.

Your rights

- You do not have to join this study. You are free to say "yes" or "no".
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we might learn new information that you need to know. For example, some information may affect your health or well-being. Other information might make you change your mind about being in this study. If we learn these kinds of information, we would tell you.
- If you join this study, you would not have to stay in it. You could stop at any time (even before you start). Your regular medical care would not change. You would have no penalty for stopping, but it would be better not to join the study if you think that you would change your mind later.
- If you decide to drop out, we would want you to tell the study doctor. The doctor could tell you about the effects of stopping GO and GCLAM. You and the doctor could talk about the follow-up care and testing that would help the most.
- Before you leave the study, the doctor might ask you to continue in the follow-up part of the study.

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.

Your responsibilities

If you join this study, you would have some responsibilities.

- Follow the schedule of study visits and procedures.
- Takes study medications as directed.
- Prevent pregnancy.
- Tell us about side effects.

For more information

If you have questions or concerns about this study, you could talk to your doctor anytime. Other people you could talk to are listed below.

If you have questions about:	Call:
This study (including complaints and requests for information)	[redacted] (Dr. Roland Walter) [redacted] (Dr. Colin Godwin)
If you get sick or hurt in this study	[redacted] (Dr. Roland Walter) [redacted] (Dr. Godwin)
Your rights as a research participant	[redacted] or email [redacted] (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center)
Your bills and health insurance coverage	[redacted]

Emergency number (24 hours): [redacted]

Tissue donation for future cancer research (optional)

Read the question and think about your choice. When you decide on each question, please circle **YES** or **NO**.

Do you agree to donate your tissue to study cancer? (circle one) **YES** **NO**

Signatures

Please sign below if you:

- have read this form (or had it read to you);
- had the opportunity to ask any questions you have;
- had the opportunity to discuss the research with the person obtaining consent; and
- agree to participate in this study.

Participant (age 18+):

Printed Name	Signature	Date

If you served as an interpreter or witness during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the apparent understanding of the research by the participant.

Witness or Interpreter:

Printed Name	Signature	Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

Person obtaining consent signature:

Printed Name	Signature	Date