Official Title	Randomized Phase 2 Trial of CPX-351 (Vyxeos) vs. CLAG-M (Cladribine, Cytarabine, G-CSF, and Mitoxantrone) in Medically Less-Fit Adults with Acute Myeloid Leukemia (AML) or Other High-Grade Myeloid Neoplasm
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Fred Hutchinson Cancer Center
University of Washington

Consent to take part in a research study:

Randomized Phase 2 Trial of CPX-351 (Vyxeos™) vs. CLAG-M (Cladribine, Cytarabine, G-CSF, and Mitoxantrone) in Medically Less-Fit Adults with Acute Myeloid Leukemia (AML) or Other High-Grade Myeloid Neoplasm

Short title: CPX-351 vs. CLAG-M for Less-Fit Adults with Aggressive Myeloid Neoplasms

Principal Investigator: Roland B. Walter, MD PhD MS. University of Washington; Fred Hutchinson Cancer Center. Pager: 206-560-0657

Emergency number (24 hours)

Call the paging operator at the University of Washington Medical Center at 206-598-6190 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 examine 2 different types of chemotherapy as first-line treatment for medically less-than-fit people with acute myeloid leukemia (AML) or a similar aggressive blood cancer.

People who agree to join the study will assigned randomly (i.e. via computer program [“roll of the dice”]) to receive either CPX-351 (commercial name: Vyxeos; a lipid formulation of two drugs, cytarabine and daunorubicin, that have been used to treat patients with AML for many decades) or CLAG-M (a combination of cladribine, cytarabine, a growth factor [G-CSF], and mitoxantrone). The study involves assessments of how effectively your blood cancer is treated, what side effects occur, and how your quality of life is during the study treatment.

We do not know if CPX-351 or CLAG-M would help treat your blood cancer, and it could even make your condition/disease worse. CPX-351 and CLAG-M could cause side effects such as nausea/vomiting, low blood counts (leading to fever/infection and/or bleeding) and gastrointestinal tract upset, as described below in this form.

You do not have to join this study. You can choose to receive standard methods to treat your blood 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 another high-grade myeloid neoplasm. Up to 60 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?

Because of older age and/or existing medical problems, many people diagnosed with AML or a similar aggressive blood cancer are, medically-speaking, less-than-fit. It is unknown how best to treat such people. In previous research studies conducted at our institution, we have explored the use of two different types of chemotherapy in these people and found that these treatments are tolerated and can be effective in treating blood cancers. However, we have so far not compared these treatments to each other. Therefore, we are doing this study to examine the effects of these 2 treatments directly in a head-to-head comparison. We want to learn what effects, good or bad, CPX-351 and CLAG-M have on medically less-than-fit people with AML or a similar aggressive blood cancer. Jazz Pharmaceuticals, Inc. the company that makes CPX-351, is providing funding to Fred Hutchinson Cancer Center to conduct this study.

If you join this study, we would give you either CPX-351 or CLAG-M and watch carefully for any side effects. That is, there are 2 groups of participants in this study. We will give different treatments to different groups and compare the results. This is how we hope to find out if CPX-351 or CLAG-M leads to better treatment outcomes.

In this study, we use a computer program to decide which treatment to give. If you join this study, you and your doctor would not be allowed to choose the treatment. You would have a 1-in-2 chance of receiving CPX-351 and a 1 in 2 change of receiving CLAG-M.

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 (both arms).** 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. You will also fill out a questionnaire about your current symptoms. 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 catheter inserted to receive chemotherapy and to simplify blood draws and transfusions.
- **Study treatment.** A computer program will be used to assign you to receive either CPX-351 or CLAG-M (see below).
- **Monitoring during study (both arms).** 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 (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
  - Questionnaires asking about your symptoms

If you are assigned to the CPX-351 group, you would receive the following treatment:

- **Induction treatment.** In the first induction cycle, you will receive treatment with CPX-351 (daunorubicin 44 mg/m^2, cytarabine 100 mg/m^2) on days 1, 3, and 5. The treatment is a 90-minute infusion into your veins. It can be given either in the hospital or the outpatient clinic, depending on the presence/absence of other medical problems.
- **Re-induction treatment.** If a complete remission not achieved after one cycle, re-induction with CPX-351 at the same dosing (daunorubicin 44 mg/m^2, cytarabine 100 mg/m^2) on days 1 and 3 will be given.
- **Post-remission (consolidation treatment).** If a complete remission is achieved with induction (with/without re-induction) treatment, you will be able to receive up to 4 cycles of treatment with a lower dose of CPX-351 (daunorubicin 29 mg/m^2, cytarabine 65 mg/m^2) given on days 1 and 3 of each treatment cycle.

If you are in CLAG-M group, you would receive the following treatment:

- **Induction treatment.** In the first induction cycle, you will receive treatment with CLAG-M, which consists of: cladribine 5 mg/m^2/day (days 1-5), cytarabine 2 g/m^2/day (days 1-5) G-CSF (filgrastim) 300 or 480 µg/day (for weight </≥76 kg; days 0-5), and mitoxantrone 18 mg/m^2/day (days 1-3). All these drugs are infused into your veins, except the G-CSF which is given as an injection under the skin
- **Re-induction treatment.** If a complete remission is not achieved after one cycle, re-induction with CLAG-M at the same dosing will be given.
- **Post-remission (consolidation treatment).** If a complete remission is achieved with induction (with/without re-induction) treatment, you will be able to receive up to 4 cycles of treatment with cytarabine (500 mg/m^2 daily for 6 days) alone.

How long would you stay in this study?

If you join this study, you would stay in it for up to 6-10 months. The exact length of treatment would depend on the side effects and your response to the treatment.

If you are assigned to treatment with CPX-351, you would receive CPX-351 for up to 6 cycles. If you are assigned to treatment with CLAG-M, you would receive CLAG-M for up to 2 cycles and, subsequently, cytarabine alone for up to 4 cycles, for a total of up to 6 treatment cycles. After study treatment is completed, you would have follow-up exams in the office or clinic at a frequency decided by your treating physician.

Doctors could 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.

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 the study treatment.

You do not have to be in long-term follow-up. You could say "yes" or "no". Either way, you could still join this 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 tests and treatments in this study. CPX-351 and CLAG-M could cause side effects we do not know about yet. We carefully watch everyone in the study for side effects.

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

This form lists side effects of *individual* drugs. Other side effects could occur when we use these drugs *together*.

Side effects may be mild or very serious. Medicines could be given to help lessen side effects. Many side effects go away soon after you stop taking CPX-351 or CLAG-M. In some cases, side effects can last a long time or never go away. There also is a risk of death.

Side effects (risk) with CPX-351

Likely side effects (>20% of patients) of CPX-351 are:

- Rash
- Fever and/or chills
- Nausea and/or vomiting
- Diarrhea or constipation
- Pain
- Fatigue
- Blood infection with bacteria
- Localized swelling caused by excess fluid in body tissues
- Decreased appetite
- Cough
- Headache
- Shortness of breath
- Nose bleed
- Inflammation or irritation of the stomach
- Decrease in salts in the blood (potassium)
- Bleeding in the skin
- Anxiety
- Belly pain
- Difficulty sleeping or falling asleep
- Decreased number of blood cells (e.g. neutrophils, granulocytes, platelets, red blood cells) which could lead to infection, bleeding, and/or fatigue

Less likely side effects (3-20% of patients) of CPX-351 are:

- Itching
- Rapid heart beat
- Fatigue, tiredness
- Swelling caused by excess fluid in arms and legs
- High blood pressure
- Belly distention or belly pain
- Depression
- Throat pain
- Abnormal collection of fluid between the lining of the lung and the chest wall
- Excessive swelling
- Severe infection
- Low oxygen in the brain
- Bleeding in the mouth
- Catheter site pain
- Redness around the catheter site
- Decrease in salts in the blood (magnesium, phosphate)
- Redness of the skin
- Upset stomach
- Confusion
- Inflammation or irritation of the mucous membranes (inner lining of body cavities such as the mouth)
- Skin infection
- Abnormal lung sounds (rales)
- Small bruises of the skin or mucous membranes
- Night sweats
- Irregular heart beat originating in an area located above the ventricle (atrium)
- Dry mouth
- Joint pain
- Increased blood level of a liver pigment (bilirubin) often as a sign of liver problems
- Weight loss
- Chest pain
- Infection with particular organism ("Clostridium difficile") that mostly occurs in people that are very sick and/or are receiving antibiotics
- Muscle pain

Rare but serious side effects (<3%) of CPX-351 are:

- Kidney failure
- Respiratory failure

- Fluid overload
- Buildup of fluid in the air spaces of the lungs
- Fungal infection/pneumonia
- Heart failure
- Multi-organ failure due to severe infection
- Pain resulting from not enough blood flowing to the heart
- Blood clot
- Irregular heart beat
- Heart attack
- Abnormally low thyroid function
- Abnormal function of the nerves that are responsible for muscle function
- Life-threatening bleed
- Blindness

Side effects (risks) with CLAG-M

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")
- Decreased number of blood cells (e.g. neutrophils, granulocytes, platelets, red blood cells) which could lead to infection, bleeding, and/or fatigue

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
- Decreased number of blood cells (e.g. neutrophils, granulocytes, platelets, red blood cells) which could lead to infection, bleeding, and/or fatigue
- 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

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 G-CSF 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

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

- Fatigue
- Decreased number of blood cells (e.g. neutrophils, granulocytes, platelets, red blood cells) which could lead to infection, bleeding, and/or fatigue
- Fever during times of low blood counts (i.e., "neutropenic fever")
- Nausea and/or 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, 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 breast-feeding.

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 became pregnant after joining this study, you would have to notify the study doctor immediately. Participation in this study would end, and you would receive counseling and follow-up throughout the pregnancy and for about 6 months after the child is born.

The effects of the study medicines on 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 this study would help you. We are testing CPX-351 and CLAG-M to see their effects on medically less-fit people with AML or another high-grade myeloid neoplasm. You might get better if you receive CPX-351 or CLAG-M, but your condition could stay the same or even get worse. We hope the information from this study will help other 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:

- Standard treatment
- Another research study
- 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.
- Jazz Pharmaceuticals, Inc. (the company that is providing funding for the study) and their agents.
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Center IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Fred Hutchinson Cancer 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.

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

You would **not** be billed for:

- CPX-351.

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 Dr. Roland B. Walter; pager: 206-560-0657, phone: 206-667-3599. He 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 standard clinical care.

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

What will my information and/or tissue samples be used for?

Your information will be used for the purposes of this study.

During this study, if the researchers learn new information that may be important to your general health or to your disease or condition, they will share that information with you.

In addition, be aware that by agreeing to participate in this study, your information could be used for future research studies or sent to other investigators for future research studies without additional consent from you. These future research studies will be reviewed by an oversight group known as an institutional review board if required by law. The information that identifies you will first be removed from your information. If you do not want your information to be used for future research studies without your consent, you should not participate in this study.

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 CPX-351 or CLAG-M. 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.
- Take study medications as directed.
- Prevent pregnancy.
- Tell us about side effects.

For more information

If you have questions or concerns about this study, you can 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)	206-667-3599 (Dr. Roland B. Walter) 206-667-5226 (Nicole Stinnett, Clinical Research Coordinator)
If you get sick or hurt in this study	206-667-3599 (Dr. Walter)
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Center) 206-543-0098 (Human Subjects Division, University of Washington)
Your bills and health insurance coverage	206-606-6226

Emergency number (24 hours): 206-598-6190

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:

Printed Name	Signature	Date

If you served as an interpreter or impartial witness during the consent process, sign below to indicate you attest to the accuracy of the presentation and the participant's apparent understanding of and willingness to participate in the research.

Impartial 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

Protocol: #RG1005577
Current consent version date: 09/16/2022
Previous consent version date: 10/16/2019
Copies to: patient, medical records