Official Title:	A Randomized Trial for Patients With High-Grade Myeloid Neoplasms With Measurable Residual Disease (MRD): CPX-351 vs. Immediate Allogeneic Hematopoietic Cell Transplantation
NCT Number:	NCT04526288
Document Type:	Informed Consent Form
Date of the Document:	02/18/2021

Fred Hutchinson Cancer Research Center
University of Washington Medical Center
Seattle Cancer Care Alliance

Consent to take part in a research study:

A randomized trial for patients with high-grade myeloid neoplasms with measurable residual disease (MRD): CPX-351 vs. immediate allogeneic hematopoietic cell transplantation

Short title: BeatMRD

Principal Investigator: Filippo Milano MD PhD. Associate Professor, FHCRC, Assistant Professor, UW 206-667-5925

Emergency number (24 hours): (206) 598-8902

If you are serving as a legally authorized representative or are a parent/guardian providing permission for a child in this study, the terms "participant", "you", and "your" refer to the person for whom you are providing consent or parental permission.

Important things to know about this study.

You are invited to participate in a research study. The purpose of this research is to see if the treatment with Vyxeos (CPX-351) to eliminate measurable residual disease (MRD) prior to stem cell transplantation is preferable to direct treatment stem cell transplant in patients with acute myeloid leukemia (AML), Myelodysplastic Syndrome (MDS-EB2), or another high-risk myeloid neoplasm who have MRD.

We do not know if using CPX-351 prior to transplant would help treat your disease, and it could even make your condition worse. CPX-351 could cause side effects such as bleeding, fever with low white blood cell count, and nausea, as described below in this form.

You do not have to join this study. You can choose to receive standard methods to treat patients with AML who have MRD 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 were diagnosed with AML, MDS-EB2, or another high-risk myeloid neoplasm with MRD following intensive chemotherapy and you are eligible for a stem cell transplant. We will enroll up to 130 people in 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 see if CPX-351 treatment for MRD prior to stem cell transplant improves outcomes over immediate stem cell transplantation among patients with MRD following intensive chemotherapy. The best treatment for patients who achieve complete remission after induction chemotherapy but have persistent MRD is not clear. Such patients with MRD have a higher likelihood of relapse than those who obtain complete remission without MRD. Although stem cell transplant might be curative in some patients, the presence of MRD prior to stem cell transplant may complicate outcomes. CPX-351 is approved by the U.S. Food and Drug Administration (FDA) to treat newly diagnosed therapy-related AML and AML with myelodysplasia-related changes. However, the use of CPX-351 is considered investigational in this study- it is not approved by the FDA for treatment of AML, MDS-EB2, or another high-risk myeloid neoplasm with MRD.

Transplants using related donors or unrelated donors are performed all over the world. Doctors have been successfully treating patients with blood disorders with a transplant of blood stem cells from bone marrow and blood. The transplant takes the donor's healthy blood-forming cells and puts them into your bloodstream, where they begin to make healthy red blood cells, white blood cells and platelets.

In this study, we want to learn what effects, good or bad, CPX-351 has on people with AML, MDS-EB2, or another high-risk myeloid neoplasm with MRD who are scheduled to undergo stem cell transplant. There are two groups of participants in this study. One group will be treated with CPX-351 prior to stem cell transplant and the other group will proceed directly to stem cell transplant without CPX-351. You have a 50/50 chance of being in either group. We use a computer program to randomly decide which treatment to give, and neither you nor your doctor can choose the group you will be in. This is how we hope to find out if CPX-351 is an effective treatment for MRD in people with AML prior to stem cell transplant.

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 heart test, and a physical exam to see if you are eligible for the research study. Please tell your medical team of any past or current medical problems. These tests and physical exam are considered standard care.

Research treatment: In this research study you will be in one of two groups. Group A will proceed directly to stem cell transplant, and Group B will receive CPX-351 prior to stem cell transplant. All patients will undergo a bone marrow biopsy prior to being assigned to a group.

If you are in Group A, we would do these tests and procedures:

- **Stem cell transplant regimen**: Your doctor will determine the best transplant for you and the related regimen you will undergo.

If you are in Group B, we would do these tests and procedures:

- **CPX-351**:

Group B Treatment Schedule		
Day	***Treatment***	***Route***
1	*CPX-351 (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2) IV over 90 min*	*Injected into a vein through an IV*
3	*CPX-351 (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2) IV over 90 min*	*Injected into a vein through an IV*
5	*CPX-351 (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2) IV over 90 min*	*Injected into a vein through an IV*

- **Bone marrow aspirate and biopsy**
- **CPX-351 cycle 2 OR stem cell transplant**

  For patients assigned to **ARM B**, a second cycle of CPX-351 may be given at the discretion of the researcher.

Group B Treatment Schedule Cycle 2		
Day	***Treatment***	***Route***
1	*CPX-351 (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2) IV over 90 min*	*Injected into a vein through an IV*
3	*CPX-351 (daunorubicin 44 mg/m2 and cytarabine 100 mg/m2) IV over 90 min*	*Injected into a vein through an IV*

14 - 35	*Bone marrow aspirate and biopsy**
≤60	*Allogeneic HCT*

- **Stem cell transplant regimen**: Your doctor will determine the best transplant for you and the related regimen you will undergo.

After you have finished the stem cell transplant you would enter the **follow-up** part of the study. We would do these tests and procedures:

Follow-up:

If you join this study, you would stay in this study for two years.

Your follow up for your stem cell transplant will depend on the study your doctor selected for you. In order to evaluate how your new bone marrow is developing and how your immune system is recovering after your transplant, you will have bone marrow biopsies and blood draws.

You may have follow-up exams in the SCCA clinic for two years. After you have recovered from any immediate transplant related complications, we will continue to collect data from your medical chart on how your marrow is functioning at your routine follow-up visits. As part of follow up, we would like to contact you and/or your doctor around 6 months, 1 year and 2 years after transplant to see how you are doing. We may contact your doctor to request copies of blood test results and other tests and procedures done as standard post-transplant follow-up.

Your doctor or the researcher 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.

We would like to do long-term follow-up: Long-term follow-up means keeping track of someone's medical condition for a long time. You will be asked to sign another consent form to allow Fred Hutchinson Cancer Research Center to keep collecting health related information from your referring physician. This is done by the Long-Term Follow-Up Department under protocol 999.209, but some of the information will also be used for this study. This will help us learn about the long-term effects of the study.

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 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 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.

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. In some cases, side effects can last a long time or never go away. There also is a risk of death.

Risks of CPX-351:

The most common side effects associated with CPX-351 include:

• bleeding
• fever
• fever with low neutrophil blood count (febrile neutropenia)
• rash
• small red or purple spots caused by bleeding into the skin (petechiae)
• swelling (edema)
• nausea
• inflammation of mucous membranes (mucositis)
• diarrhea
• constipation
• back pain
• joint pain
• pain in extremities
• fatigue
• a loss of strength, weakness or lack of energy (asthenia)
• abdominal pain and bloating
• shortness of breath (dyspnea)
• headache
• cough
• decreased appetite
• irregular heartbeat (arrhythmia)
• increased heart rate
• pneumonia
• fluid in the lungs
• bacteria in blood (infection)
• chills
• difficulty falling asleep

• vomiting
• nose bleeds
• difficulty breathing
• low blood pressure (hypotension)
• high blood pressure (hypertension)
• dizziness
• anxiety
• confusion
• itchy skin
• low oxygen levels in the blood
• sore throat
• low potassium
• excessive sweating

Rare but serious side effects have occurred in patients treated with CPX-351. They include:

• serious or fatal bleeding with low blood platelets
• cardiotoxicity (weakening of the heart muscle)
• hypersensitivity reactions, including anaphylaxis (flushing, low blood pressure, shortness of breath, dizziness, nausea and vomiting)
• copper overload (excess amount of copper in the body)
• skin breakdown at places where there is escape of fluid into surrounding tissue (local tissue necrosis at the site of drug extravasation)
• embryo-fetal toxicity (i.e. birth defects and/or fetal death)
• vasculitis (swelling of the blood vessels)

Because CPX-351 contains copper, it should not be given to people with Wilson's Disease or any other disorder of copper metabolism (absorbing, processing or excretion). You should tell your doctor if you have any copper metabolism related disorders.

Infusion-Associated Reaction Risk

CPX-351 is given as an infusion through a vein. In large clinical trials of patients receiving chemotherapy by injection, some infusion-associated reactions were observed. These include:
• flushing
• shortness of breath
• headache
• chills
• back pain
• tightness in the chest
• low blood pressure

In most patients, these reactions went away over several hours to 1 day once the infusion was completed. In some patients, the reaction stopped when the speed of the drug being given was slowed.

Allergic Reaction Risks
Sometimes people have allergic reactions to medicines. If you have a very bad allergic reaction, you could die. Some signs that you may be having an allergic reaction are:
• Skin rash or hives
• Severe itching
• Trouble swallowing or breathing
• Swelling of the face, mouth, lips, eyes, throat or tongue

You should get medical help right away and contact the study doctor or study staff if you have any of these side effects during the study.

Unknown risks

There may be risks or side effects related to CPX-351 that are unknown at this time. You or your legally authorized representative will be informed in a timely manner if new information about CPX-351 becomes available that may impact your decision to continue with participation in this trial. Therefore, it is important that you tell your doctor or research staff right away about any changes in your health, not just the known risks and side effects listed above, even if you do not think they are because you are taking part in the study.

Reproductive risks

Chemotherapy and radiation treatments could cause sterility (unable to have children).

Taking CPX-351 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 three months after the last dose of study treatment. If you are already using a method of birth control, you would have to check with your doctor or a member of the research staff to make sure it is acceptable.

If you became pregnant after joining this study, you would have to notify your doctor or research staff 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 treatment 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 three 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.

Recurrence of disease

Although the chemotherapy regimen and stem cell transplant offered in this study may be successful, your disease may recur.

What are the benefits?

You may or may not benefit from being in this study. However, we hope that, in the future, other people might benefit from this study because it will help researchers learn whether treatment with CPX-351 improve the outcomes over immediate stem cell transplantation among patients with MRD following intensive chemotherapy.

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
- 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.
- Food and Drug Administration (FDA)

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 prevents 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. The study drug CPX-351 will be provided free of charge. Except for the blood draws and lab tests done only for research purposes, all other medical expenses of standard treatments will be paid by you and/or your insurance company. 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 standard of care chemotherapy drugs
- Paying the people who give standard of care chemotherapy drugs, and the cost of the equipment they use.
- 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.

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 doctor and research staff 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 the emergency number (206-598-8902). They will treat you or refer you for treatment. If you are injured as a result of a defect in the design or manufacturer of the study drug CPX-351, Jazz Pharmaceuticals will pay for the reasonable costs of medical treatment. You or your health insurance will have to pay for the treatment of all other injuries and any other non-medical costs, such as loss of 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.

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 the study treatment. 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 sign a separate consent form 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)	206–667-5925, Filippo Milano, MD, PhD, Principal Investigator 206-667-6264, Nancy Anderson, RN, Clinical Research Nurse
If you get sick or hurt in this study	206–667-5925, Dr. Milano
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center)
Your bills and health insurance coverage	206-606-1113

Emergency number (24 hours): 206-598-8902

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

Legally Authorized Representative: Please sign below if you:

- have read this form (or had it read to you);
- had the opportunity to ask questions;
- had the opportunity to discuss the research with the person obtaining consent; and
- agree to consent on behalf of the participant for him or her to participate in this study.

Legally authorized representative:

Printed Name	Signature	Date

Relation to the participant

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: RG1007476
Current consent version date: 1/26/2021
Previous consent version date: 11/10/2020
Copies to: