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

Consent to take part in a research study:

RG1005103
MRD-guided abbreviation of bendamustine and rituximab chemotherapy in combination with copanlisib in chronic lymphocytic leukemia/small lymphocytic lymphoma

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Important things to know about this study.

You are invited to participate in a research study. The purpose of this research is to see how many cancer cells remain in your bone marrow after you receive Copanlisib, rituximab and bendamustine. Copanlisib is the study drug.

People who agree to join the study will be asked to attend 36 visits over (up to) 24 months. The study involves screening visits to see if you are able to be a part of the study, bone marrow biopsies, computed tomography (CT) scans, blood draws and infusion of drugs given on this study over the course of up to 12 cycles.

We do not know if Copanlisib would help treat chronic lymphocytic leukemia/small lymphocytic lymphoma and it could even make your condition/disease worse. Copanlisib could cause side effects such as high blood sugar, low white blood cell count, diarrhea, low respiratory infection and high blood pressure, as described below in this form.

You do not have to join this study. You can choose to receive standard methods to treat chronic lymphocytic leukemia/small lymphocytic lymphoma 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 chronic lymphocytic leukemia/small lymphocytic lymphoma. Up to 25 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 Copanlisib in combination with Bendamustine and Rituximab. We want to know if we give Copanlisib and Bendamustine + Rituximab to patients with chronic lymphocytic leukemia/small lymphocytic lymphoma can reduce the amount of cancer cells in their bone marrow. You will have a bone marrow biopsy to see if the amount of cancer cells in your bone marrow have decreased. The test we will run is called Minimal Residual Disease (MRD) testing. The results of this test will be used to see if you will continue treatment on this study. Making this decision based on the test results is investigational. The test itself is also investigational.

We are studying Copanlisib (Aliqopa). Copanlisib is an experimental drug. This drug is not FDA approved for your particular form of cancer.

In this study, we want to learn what effects, good or bad, Copanlisib in combination with Bendamustine and Rituximab has on people with chronic lymphocytic leukemia/small lymphocytic lymphoma. If you join this study, we would give you Copanlisib and watch carefully for any side effects.

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

You will receive up to 4 cycles of treatment in the first part of this study.

	Screening	Cycle 1				Cycle 2-Cycle 4			
		D1	D2	D8	D15	D1	D2	D8	D15
Informed consent	X								
Clinic Visit	X	X		X	X	X			
CT Scan	X								
Bone marrow biopsy (MRD testing)	X								
Electrocardiogram (EKG)	X								
Labs/monitoring									
Blood draw	X	X	X	X	X	X			
Glucose & Blood Pressure	X	X		X	X	X		X	X
Drug Administration									
Rituximab		X				X			
Bendamustine		X	X			X	X		
Copanlisib		X		X	X	X		X	X

After Cycle 4, you will have a bone marrow biopsy to see if the amount of cancer cells in your bone marrow has decreased. If the amount of cancer cells in your bone marrow has decreased, you will then receive up to 8 more cycles of treatment, for a total of up to 12 cycles.

	Cycle 5-Cycle 6				Cycle 7-12		End of Treatment	Follow up
	D1	D2	D8	D15	D1	D15		
Clinic Visit	X						X	
CT Scan	X						X	X
Bone marrow biopsy (MRD testing)	X						X	X
Labs/monitoring								
Blood draw	X				X		X	
Glucose & Blood Pressure	X		X	X	X	X	X	
Drug Administration								
Rituximab	X							
Bendamustine	X	X						
Copanlisib	X		X	X	X	X		

If the amount of cancer cells in your bone marrow has not decreased, then you will continue on the follow up portion of this study:

	End of Treatment	Follow up
Clinic Visit	X	
CT Scan	X	X
Bone marrow biopsy (MRD testing)	X	X
Blood draw	X	
Glucose & Blood Pressure	X	

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

Screening/Baseline

- **Clinic Visit –** You will have clinic visits with a health care provider. Your visits will include the following tests and questions:
    - **Medical history** - You will be asked questions about your medical history. This includes ongoing medical conditions you have and drugs you are taking.
    - **Physical exam** - Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight and height will also be recorded. You will also be asked how easily you perform daily activities.
    - **Side effects assessment (adverse events)** – Questions about symptoms and side effects will be part of each visit, to determine what side effects you are experiencing during treatment.
- **Routine laboratory tests** - Blood samples will be taken for routine tests. About 2 - 3 teaspoons of blood will be taken, and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment. A little over a teaspoon of blood will be taken to test for hepatitis and HIV. If you are a female who could become pregnant, you will have a pregnancy test. A blood sample will be taken for this test.
- **Electrocardiogram (ECG/EKG)** - Sticky patches are placed on your chest, arms and legs. These patches are connected to a machine which shows the electrical activity of your heart. Radiation is not used to obtain an ECG. If you're sensitive to the adhesive on the sticky patches, you may have a little redness where the patch was attached to your skin.
- **Computed Tomography (CT) scan**: CT scans use x-ray measurements taken from different angles to see cross-sectional images of specific areas of your body.
- **Bone Marrow Biopsy**: A bone marrow biopsy may be done to see if your cancer has spread to the bone marrow. A small piece of bone is removed. This is done under local anesthesia.

Cycle 1-4

- **Clinic Visit –** You will have clinic visits with a health care provider. We want to see how you are doing. Your visits will include the following tests and questions:
    - **Physical exam** - Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight and height will also be recorded. You will also be asked how easily you perform daily activities.
    - **Side effects assessment (adverse events)** – Questions about symptoms and side effects will be part of each visit, to determine what side effects you are experiencing during treatment.
- **Routine laboratory tests** - Blood samples will be taken for routine tests. About 2 - 3 teaspoons of blood will be taken and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment. A little over a teaspoon of blood will be taken to test for hepatitis and HIV.
- **Combination therapy**: You will receive the following drugs on the specified

days indicated below:
    - **Rituximab**: Day 1
    - **Bendamustine**: Day 1 and Day 2
    - **Copanlisib**: Day 1, Day 8 and Day 15

Cycle 5-6

- **Clinic Visit –** You will have clinic visits with a health care provider. We want to see how you are doing. Your visits will include the following tests and questions:
    - **Physical exam** - Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight and height will also be recorded. You will also be asked how easily you perform daily activities.
    - **Side effects assessment (adverse events)** – Questions about symptoms and side effects will be part of each visit, to determine what side effects you are experiencing during treatment.
- **Routine laboratory tests** - Blood samples will be taken for routine tests. About 2 - 3 teaspoons of blood will be taken and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment. A little over a teaspoon of blood will be taken to test for hepatitis and HIV.
- **Computed Tomography (CT) scan**: CT scans use x-ray measurements taken from different angles to see cross-sectional images of specific areas of your body.
- **Bone Marrow Biopsy (Only before cycle 5):** A bone marrow biopsy may be done to see if your cancer has spread to the bone marrow. A small piece of bone is removed. This is done under local anesthesia. The results of this test will be used to see if you will continue on treatment on this study. Making this decision based on the test results is investigational. This test itself is also investigational.
- **Combination therapy**: You will receive the following drugs on the specified days indicated below:
    - **Rituximab**: Day 1
    - **Bendamustine**: Day 1 and Day 2
    - **Copanlisib**: Day 1, Day 8 and Day 15

Cycle 7-12

- **Clinic Visit –** You will have clinic visits with a health care provider. Your visits will include the following tests and questions:
    - **Physical exam** - Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight and height will also be recorded. You will also be asked how easily you perform daily activities.
    - **Side effects assessment (adverse events)** – Questions about symptoms and side effects will be part of each visit, to determine what side effects you are experiencing during treatment.
- **Routine laboratory tests** - Blood samples will be taken for routine tests. About 2 - 3 teaspoons of blood will be taken, and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment. A little over a teaspoon of blood will be taken to test for hepatitis and HIV.
- **Copanlisib Infusion**: You will receive Copanlisib on Day 1 and Day 15

End of Treatment

After you have finished taking Copanlisib and Bendamustine + Rituximab you would enter the **follow-up** part of the study. We would do these tests and procedures:

- **Computed Tomography (CT) scan**: CT scans use x-ray measurements taken from different angles to see cross-sectional images of specific areas of your body.
- **Bone Marrow Biopsy:** We want to see how many cancer cells are in your bone marrow 1 year after you complete treatment. A small piece of bone is removed. This is done under local anesthesia. This test itself is also investigational.
- **Follow up appointments:** You will come in over the course of 3 years to see your physician to see how you are doing after you have completed treatment.

How long would you stay in this study?

If you join this study, you would stay in this study for up to 24 months.

You would receive Copanlisib, Rituximab and Bendamustine for up to 12 cycles. After that, you would have follow-up exams in the office or clinic every 3 months for 3 years.

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. If you join this study, we would contact you or your physician every 3 months 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 Copanlisib in combination with rituximab and bendamustine

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 every 3 months for 3 years to see how you are doing.

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

Risks of Copanlisib

Likely (more than 20% of patients) side effects of Copanlisib are:

- High blood sugar
- Low white blood cell count
- Decrease in the main part of the white blood cells
- Low platelet count
- Low strength and energy
- Diarrhea
- Nausea
- High blood pressure
- Lower respiratory tract infections such as pneumonia
- Decreased hemoglobin
- Lymphocyte count decrease
- White blood cell decreased
- Platelet count decreased
- Neutrophil count decreased
- Triglyceride increase
- Low level of phosphates in the blood
- Excess of uric acid in the blood
- Serum Lipase increased

Less likely (10%-20% of patients) side effects of Copanlisib are:

- Mouth sores
- Vomiting
- Rash

Rare but serious (less than 10%) side effects of Copanlisib are:

- Pneumonitis
- Burning or tingling sensation in the mouth
- Tingling or prickling feeling
- Abnormal sense of touch

Risks of Rituximab

Likely (more than 20% of patients), some may be serious side effects of Rituximab are:

- Anemia which may require blood transfusion
- Nausea
- Infection, especially when white blood cell count is low
- Reaction during or following infusion of the drug
- Chills, fever
- Tiredness

Less likely (4% to 20% of patients), some may be serious side effects of Rituximab are:

- Heart attack which may cause chest pain, shortness of breath
- Abnormal heartbeat which may cause fainting
- Low blood pressure which may cause feeling faint
- Swelling of arms, legs
- Damage to the lungs which may result in shortness of breath
- Blockage of the airway which may cause shortness of breath, cough, wheezing
- Swelling and redness of the throat and sinuses (might not be caused by infection) which may cause difficulty breathing and swallowing
- Bruising, bleeding
- Prior liver infection that returns which may cause yellow eyes and skin, tiredness
- Kidney damage which may require dialysis
- A tear or a hole in the bowels that may require surgery
- Diarrhea
- Headache
- Cold symptoms such as stuffy nose, sneezing, sore throat
- Itching, rash, blisters on the skin
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Rare (less than 4% of patients) but serious side effects of Rituximab are:

- Damage to the brain caused by a virus which may result in tiredness, weakness, changes in thinking, and disability
- Heart stops beating

Risks of Bendamustine

The following important adverse drug reactions have been seen in patients treated with bendamustine:

Likely (20% of patients), some may be serious side effects of Bendamustine are:

- Anemia which may cause tiredness, or may require blood transfusions
- Constipation, diarrhea, nausea, vomiting
- Fever, tiredness
- Bruising, bleeding

- Infection, especially when white blood cell count is low
- Loss of appetite
- Headache
- Cough

Less likely (4%-20% of patients), some may be serious side effects of Bendamustine are:

- Sores in mouth which may cause difficulty swallowing
- Swelling and redness at the site of the medication injection
- Scarring of the lungs
- Weight loss
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Severe blood infection
- A new cancer resulting from treatment of a prior cancer
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- Kidney damage which may cause swelling, may require dialysis
- Damage to the liver
- Blisters on the skin
- Rash
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body
- Shortness of breath

Rare (less than 4% of patients), but serious side effects of Bendamustine are:

- High blood pressure which may cause dizziness, blurred vision

Radiation risks

Some of the tests that you will have in this research study will expose you to radiation. Everyone receives a small amount of radiation every day called "background radiation". This radiation is natural and comes from space, air, water, soil, and the food you eat. Each year you are exposed to about 3 milliSieverts (mSv) of this background radiation. A milliSievert is a unit of radiation dose. For comparison, the estimated radiation dose from each of these tests is listed below. The risk to your health from this level of radiation exposure is too low to be detectable and may be nonexistent.

- CT-Neck: 3 mSv

- CT-Chest: 7 mSv
- CT-Abdomen: 8 mSv
- CT-Pelvis: 6 mSv

Reproductive risks

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

Taking Copanlisib 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 4 months after the last dose of copanlisib. 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 Copanlisib 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 4 months after the last dose of copanlisib.

Unknown Risks

In addition to the risks already descriped, copanlisib, bendamustine, rixtuximab, and the study procedures may have other unknown risks.

What are the benefits?

We do not know if this study would help you. We are testing Copanlisib in combination with rituximab and bendamustine to see its effects on people with chronic lymphocytic leukemia/small lymphocytic lymphoma. You might get better if you receive Copanlisib, rituximab and bendamustine, but your condition could stay the same or even get worse. We hope the information from this study will help other people with CLL/SLL.

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”.

If you decide not to enter this study, there are other choices available. Ask the study doctor to discuss these alternatives with you. You do not need to be in this study to receive treatment for your cancer. The other choices include:

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

The study team strongly suggests that you do not take any type of "alternative" or "naturopathic" medications because they may interfere with the study medications.

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.
- Bayer (the sponsor of the study) and their agents.
- 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.
- US National Institutes of Health, National Cancer Institute, 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 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 rituximab and bendamustine
- Cost of people and equipment to give Copanlisib, rituximab and bendatmustine. There is no charge for Copanlisib itself.
- 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:

- The cost of Copanlisib

If Copanlisib is approved as a treatment while this study is still going on, you or your insurance company might have to pay for Copanlisib in order to complete 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 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. Ryan Lynch at 206-606-1739. 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 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 and tissue samples (such as blood and tumor cells) will be used for the purposes of this study. These tests will be done as part of our routine standard of care.

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 Copanlisib. 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 long-term 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)	206-606-1739 (Dr. Ryan Lynch)
If you get sick or hurt in this study	206-606-1739 (Dr. Ryan Lynch)
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center) 206-543-0098 (Human Subjects Division, University of Washington)
Your bills and health insurance coverage	206-606-1377 (Patient Financial Services, Seattle Cancer Care Alliance)

Emergency number (24 hours): 206-598-6190
(UWMC Paging Operator)

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: RG1005103
Copies to: Researcher's File
Subject
Subject's Medical Record (if applicable)

---------- Use this section only if applicable ----------

If this consent form is read to the subject because the subject is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. The subject freely consented to be in the research study.

_____
Printed Name of the Impartial Witness

_____ _____
Signature of Impartial Witness 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.

_____
Printed Name of Interpreter

_____ _____
Signature of Interpreter Date

Copies to: Researcher's file
Subject
Subject's medical record (if applicable)