Official Title:	A Phase I Study Evaluating Copanlisib in Combination With R-GCD (Gemcitabine, Carboplatin, Dexamethasone, and Rituximab) With Relapsed/Refractory Diffuse Large B-Cell Lymphoma and High-Risk Follicular Lymphoma
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University of Washington
Seattle Cancer Care Alliance
Fred Hutchinson Cancer Research Center

Consent to take part in a research study:

RG1005097

A phase I study evaluating copanlisib in combination with R-GCD (gemcitabine, carboplatin, dexamethasone, and rituximab) with relapsed/refractory diffuse large B-cell lymphoma and high-risk follicular 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 find out how much of Copanlisib (Aliqopa) (also referred to as the 'study drug') with gemcitabine, carboplatin, dexamethasone, and rituximab (also referred to as 'R-GCD') for people with your disease.

People who agree to join the study will be asked to attend 9 visits over 6 weeks. The study involves screening visits to see if you are able to be part of the study, infusion of Copanlisib and R-GCD on certain days over 6 weeks, following up with your doctor after you are finished with treatment and visits with your doctor over the course of 1 year to see how you are doing.

We do not know if Copanlisib in combination with R-GCD would treat people with diffuse large B-cell lymphoma or high-risk follicular lymphoma that have not responded to other treatments or where the cancer has come back, 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 your diffuse large B-cell lymphoma or high-risk follicular 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 relapsed or refractory diffuse large B-cell lymphoma or high-risk follicular lymphoma. Up to 21 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 want to know how much Copanlisib we can give patients when we also give them R-GCD.

We are studying Copanlisib (Aliqopa). Copanlisib is an experimental drug.

Copanlisib has been tested in humans, but it has not yet been tested in people in combination with R-GCD.

In this study, we want to learn:

- the best way to give Copanlisib in combination with R-GCD
- how much Copanlisib in combination with R-GCD can be given safely.

If you join this study, we would give you Copanlisib and R-GCD. People who join at the beginning of the study will receive very low amounts of Copanlisib. People who join later will receive larger amounts, 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?

Procedure	Screening	Cycle 1-3		End of Treatment	Follow Up
	D-42 to D-1	D1	D8		
Patient informed consent	X				
Performance Status	X	X	X	X	
Clinic evaluation/physical exam	X	X	X	X	
Concomitant Medication Assessment	X	X	X	X	
Toxicity/AE assessment	X	X	X	X	
CT/tumor evaluation	X			X	
Bone marrow biopsy and aspirate	X				
Tumor FISH testing	X				
12-lead EKG	X				
Follow Up Visits					X
Lab/monitoring					
Screening labs	X				
Complete blood count with differential	X	X	X	X	
Comprehensive metabolic panel	X	X	X	X	
Optional blood sample	X			X	
Optional Archival Tissue Sample	X				
Glucose	X	X	X	X	
Blood pressure	X	X	X	X	
Drug administration					
Rituximab		X			
Copanlisib		X	X		
Gemcitabine		X	X		
Carboplatin		X			
Dexamethasone		X			

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

- **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.
- **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.

- **Urine test** – You will also provide a urine sample at screening. We may ask you to do other urine samples while you are on the study.
- **Pregnancy test** - 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.
- **Positron Emission Tomography (PET) scans**: PET scans use x-rays or radiation to allow doctors to see images of the part(s) of your body affected by cancer.
- **Combination Therapy**: You will receive the following drugs on the specified days below for each cycle of treatment:
    - **Day 1:** Copanlisib, Rituximab, Gemcitabine, Carboplatin and Dexamethasone
    - **Day 8:** Copanlisib and Gemcitabine
- **Optional Research Tests** – at the end of this form, you will be asked to participate in optional tests with your blood and archival tissue samples. You are free to say 'yes' or 'no'. You will still be able to participate in the main part of this study if you say 'no'.
    - **Optional blood sample** – we will request 1 – 2 teaspoons of blood to be taken for research tests while you are getting your other labs drawn during screening and at the end of treatment. These tests results will not be reported in your medical record.
    - **Optional Archival Tissue Sample** – we will request tissue from previous biopsies you have had in the past to run additional tests for this research. These test results will not be reported in your medical record.

After you have completed 3 cycles of Copanlisib plus R-GCD, you would enter the **follow-up** part of the study. We would do these tests and procedures:

- Visits with your doctor over the course of 1 year to see how you are doing and if your cancer has come back or not.

How long would you stay in this study?

If you join this study, you would stay in this study for about 3 cycles. Each cycle is 21 days.

You would receive Copanlisib and R-GCD for 9 weeks. After that, we will follow you during the follow-up part of this study for 1 year.

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 look into your medical record, request records from your other doctors, or contact you personally 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.

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 to see how you are doing for 1 year.

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 or R-GCD. 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 Risks More than 20% of patients	• High blood sugar • Low strength and energy • Diarrhea • Nausea • High blood pressure

	• Lower respiratory tract infections such as pneumonia • Decreased hemoglobin • White blood cell decrease, including neutrophils and lymphocytes • Platelet count decreased • Triglyceride increase • Low level of phosphates in the blood • Excess of uric acid in the blood
Less likely 10%-20% of patients	• Mouth sores • Vomiting • Rash
Rare, but serious less than 10% of patients	• Pneumonitis • Burning or tingling sensation in the mouth • Tingling or prickling feeling • Abnormal sense of touch • Fever • Loss of taste in the mouth • Inflammation in the pancreas

Risks of Gemcitibine

Likely Risks More than 20% of patients	• Flu-like symptoms of muscle pain, fever, headache, chills and fatigue • Nausea, vomiting • Rash • Hair loss • Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may require a blood transfusion • Muscle weakness • Blood in urine • Feeling of "pins and needles" in arms and legs • Numbness and tingling of the arms and legs • Tiredness • Difficulty sleeping • Swelling of arms, legs
Less likely 4%-20% of patients	• Swelling and redness of the area of radiation • Blisters on the skin • Diarrhea, constipation • Sores in mouth which may cause difficulty swallowing • Liver damage which may cause yellowing of eyes and skin, swelling • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Scarring of the lungs • Shortness of breath • Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles • Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness

Rare, but serious less than 3% of patients	• Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness • Blockage of the airway which may cause cough • Blood clot • Severe blood Infection • Anemia, kidney problems which may require dialysis

Risks of Carboplatin

Likely Risks More than 20% of patients	• Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Vomiting, nausea • Pain • Hair loss
Less likely 4%-20% of patients	• Visual loss • Diarrhea, Constipation, belly pain • Changes in taste • Numbness and tingling in fingers and toes
Rare, but serious less than 3% of patients	• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Risks of Dexamethasone

Likely Risks More than 20% of patients	• High blood pressure which may cause headaches, dizziness • Pain in belly • Infection • Diabetes • Loss of bone tissue • Damage to the bone which may cause joint pain or loss of motion • Mood swings • Swelling of the body, tiredness, bruising • Increased appetite and weight gain in belly, face, back and shoulders • Difficulty sleeping • Skin changes, rash, acne
Less likely 4%-20% of patients	• Blood clot which may cause swelling, pain, shortness of breath • Kidney stones • Glaucoma • Cloudiness of the eye, visual disturbances, blurred vision • A tear or a hole in the bowels which may cause pain or that may require surgery • Heartburn • Numbness and tingling of the arms, legs and upper body • Muscle weakness • Non-healing wound

Rare, but serious less than 3% of patients	• Bleeding from sores in stomach • Broken bones

Risks of Rituximab

Likely Risks More than 20% of patients	• Nausea • Chills, fever • Reaction during or following infusion of the drug • Infection, especially when white blood cell count is low • Anemia which may require blood transfusions • Numbness and tingling of the arms and legs • Tiredness
Less likely 4%-20% of patients	• Bruising, bleeding • Abnormal heartbeat • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Sores in eye • Diarrhea, vomiting • Pain • Swelling of the body • Hepatitis, or liver damage which may cause yellow eyes and skin • Dizziness, headache • Kidney damage which may require dialysis • Cough • Scarring of the lungs • Stuffy nose • Bowel obstruction which may cause a tear to the intestinal wall that may require surgery • Increased sweating • Itching, rash, blisters on the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Low blood pressure which may cause feeling faint
Rare, but serious less than 3% of patients	• Damage to the brain caused by a virus which may result in tiredness, weakness, changes in thinking, and disability. This is called progressive multifocal leukoencephalopathy (PML). • Heart rhythm abnormalities

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
- 18-FDG PET/CT: 19 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.

Non-physical risks

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

- You might not be able to work.

What are the benefits?

We do not know if this study would help you. The use of Copanlisib in combination with R-GCD is still investigational, and we are testing it to find the highest safe dose. We hope the information from this study will help us test Copanlisib in combination with R-GCD further 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, or 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.
- The study sponsor, Bayer, 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.
- 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. You may be eligible for travel reimbursement. Please reach out to the study team for more information.

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.

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.

Your tissue samples might help researchers develop new products. This research could be done by for-profit companies. There is no plan to share with you any revenue generated from products developed using your tissue samples.

During this study, if the researchers learn new information that could possibly be important to your general health or to your disease or condition, they will not be able to share that information with you because the tests will be investigational.
Your information and specimens will not be used for any research other than for this study.

Your tissue contains DNA. DNA makes up the genes that serve as the "instruction book" for the cells in our bodies. By studying genes, researchers can learn more about diseases such as cancer. There are many different types of genetic tests. The testing on your tissue samples might include genetic testing called whole genome sequencing. Whole genome sequencing looks at all the genetic information in your cells. This type of testing can provide useful information to researchers. It can also present risks if the test results became known to others, for example you could have problems with family members or insurance companies. There is also a risk that these test results could be combined with other information to identify you.

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.

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 need 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. Lynch at 206-606-1739. 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.

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. 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)

Optional blood and archival tissue samples:

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

Do you agree to donate your archival tissue for the optional research tests? (circle one) **YES** **NO** Do you agree to donate your blood for the optional research tests? (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:

Printed Name	Signature	Date

If you served as an 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:

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

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)