PRINCIPAL INVESTIGATOR:	Mark Roschewski, M.D.
STUDY TITLE:	A Phase 2 Study of Response-Adapted Therapy with Copanlisib and Rituximab in Untreated Follicular Lymphoma
STUDY SITE:	NIH Clinical Center
Cohort:	*Affected patient* - Standard
Consent Version:	07/17/2023

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Mark Roschewski, M.D.
Phone: 240-760-6183
Email: mark.roschewski@nih.gov

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The main purpose of this study is to see if the study drug, copanlisib, in combination with rituximab is effective in slowing the growth of follicular lymphoma.

Copanlisib (Aliqopa®) has been shown to slow the growth of cancer cells and cause tumor cell death. It does this by inhibiting, or interfering, with several cell-signaling pathways that lymphoma cells use to grow. Rituximab (Rituxan®) is a type of drug called a "monoclonal antibody". It is believed that rituximab works by using the body's immune system to attack the cancer. Rituximab may work by attaching to the cancer cells (lymphocytes) and causing the cells to die or by signaling your immune system to destroy the cancer cells.

Copanlisib is approved by the Food and Drug Administration (FDA) for treatment of follicular

lymphoma that has relapsed (or progressed) after prior treatment. Rituximab is approved by the FDA for several types of Non-Hodgkin's lymphoma, including types of follicular lymphoma, both as a single agent or in combination with other chemotherapy. The use of these two drugs together for initial treatment in follicular lymphoma is considered experimental. The FDA is allowing us to use these drugs together in this study.

Other purposes of this study include to draw blood and collect tissue to measure certain "biomarkers." "Biomarkers" refer to different types of markers found in the blood and tissue that are associated with the cancer and/or your response to the treatment. For this, samples of your blood and tumors or lymph nodes will be collected. The purpose of this research is to find out if there are any disease-related markers that may help predict how patients respond to copanlisib and rituximab. We also hope to learn more about why patients respond differently to treatment.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You are being asked to take part in this study because you have follicular lymphoma for which you have not received any prior treatment.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 65 patients will be enrolled on this trial.

DESCRIPTION OF RESEARCH STUDY

WHAT WILL HAPPEN IF YOU TAKE PART IN THIS RESEARCH STUDY?

During the study

If the screening process shows that you are eligible for the study, and you choose to be in it, you may need to have a few additional standard tests completed or tests and procedures performed at screening repeated, if not done recently prior to receiving study therapy. You will also have additional samples collected for research tests. Tests and procedures that will need to be completed and/or repeated if not performed recently are outlined before:

- Physical examination: This will include weight, vital signs (temperature, blood pressure, heart rate, breathing rate), how you function in your daily activities, any current symptoms of your cancer and a review of all medications that you take.
- Blood tests/urine tests:
    - To check your blood counts, blood chemistries, organ function and immune system characteristics.
    - For females of child-bearing potential, a pregnancy test will be done (urine or blood sample). You will not be able to participate if you are pregnant.
    - A routine urine sample will be taken to check kidney function.
- Imaging: Imaging will include an FDG PET/CT scan and CT scan of chest, abdomen and pelvis to assess the sites of your cancer. If you are not able to have CT scans, MRI may be used.
- Electrocardiogram (ECG)

- Research samples:
    - Blood samples: These will be collected to look at biomarkers and other research studies.
    - Tumor biopsy: Required only if we do not have enough tissue available from previous procedures. A sample may be collected even if there is enough tissue, but this is not required, and we will ask your permission before proceeding. You may need to be sedated for the biopsy.
    - Cheek swab or saliva samples: A cheek swab and/or saliva sample to collect normal tissue will be done, likely at the beginning of the study only. To obtain a cheek swab, a small brush is rubbed against the inside of the cheek to wipe off some cells. To obtain saliva, a special collection tube will be used and it may take a few minutes to collect the saliva.

You will come to the NIH Clinical Center for treatment and procedures. The treatment will be given in the outpatient setting at the Clinical Center. If there is a reason to give any part of the treatment and/or testing as an inpatient, your doctor will discuss this with you. You will receive medications to help decrease the risk of certain infections. The study team will tell you about these.

Treatment with Copanlisib and Rituximab

If the tests and procedures show that you are able to take part, you will receive treatment with copanlisib (alone), followed by copanlisib with rituximab. Each treatment cycle is a 28-day cycle.

Copanlisib is given weekly (Day 1, 8, and 15) for 3 weeks, by intravenous (IV) infusion over about 60 minutes, followed by a 1-week break (no infusion on Day 22). For the first 4 weeks (or cycle) of treatment you will receive copanlisib alone. This is called a "window" study. After the window study, we will collect research samples and repeat imaging studies to assess your disease. Then, you will receive copanlisib with rituximab. Since copanlisib may elevate your blood sugar or may raise your blood pressure after the infusion, special precautions will be taken prior to each infusion. You must fast for at least 8 hours prior to your first dose of copanlisib. After your first dose of copanlisib, you may be asked to eat no more than a small, light meal that is low in carbohydrates (also called a "low glycemic index meal") within 4 hours before the start of the copanlisib infusion. The timing of these meals, including what and how much you will eat, will be discussed with you by the study team. If you have type 1 or type 2 diabetes, you will be asked to consult with an endocrinologist prior to starting the infusions. If your blood sugar remains elevated at times other than the first 5-8 hours after the infusion of copanlisib, you may be asked to monitor your blood sugar at home before and after meals.

The first six (6) cycles of combined treatment of copanlisib and rituximab is called "induction therapy." Rituximab is given also by IV infusion over several hours weekly (Days 1, 8, 15 and 22) for four (4) weeks (first induction cycle), followed by once (on Day1 of induction cycle 2-6) every 4 weeks.

If you have a significant response to treatment (such as your tumor going away, also known as a complete response), your doctor may choose to stop treatment. If your tumor does not have a significant response to induction therapy, your doctor may choose to continue treatment for up to

another 6 cycles. The additional 6 cycles are called "maintenance therapy" and refers to similar therapy given for extended periods of time, but at a lower intensity level.

During maintenance therapy, if you receive it, you will receive copanlisib every two (2) weeks (every other week, Day 1 and Day 15). The rituximab will continue at the same schedule (that is, once every 4 weeks). Maintenance therapy is given for 6 cycles.

If at any time during or after treatment with copanlisib and rituximab your cancer worsens or if your tumor does not have any response to the first 6 cycles of therapy, your doctor will stop therapy and monitor your disease very closely. If it is not determined safe to monitor your disease without therapy, then you may be recommended to switch to another chemotherapy regimen on this protocol or you may be recommended to get therapy on another clinical trial at the NIH. This treatment may also be able to be given at the NIH. Your doctor will discuss the treatment options with you and what it will involve if needed.

Tests and Procedures During Treatment

Similar to the tests done at the beginning of the study, the following will be repeated during the study to see how you are doing and how the cancer may be responding to treatment: The following is a list of most of the tests and procedures you will have during the study. Your study team will tell you about additional test and procedures to be done, if indicated for your care.

- At least every 4 weeks while receiving study treatment:
    - Review of medical history and physical exam, including vital signs and weight, obtaining information about how you function in your daily activities, side effects that you have experienced and medications that you are taking
    - Routine blood and urine tests to check your blood counts, blood chemistries and other tests to monitor your health (some of these will be done prior to each dose of copanlisib and/or rituximab)
- Additional tests to be performed at certain time points after start of treatment:
    - Bone marrow biopsy: If you had disease in your bone marrow before starting treatment you will be asked to have a bone marrow biopsy and aspiration about every 6 cycles. Bone marrow is the soft material in the center of bones that produces new blood cells. The area will be numbed with lidocaine and, once numb, a large needle will be inserted through a small cut to draw about 4 tablespoons of marrow out of the bone and to possibly remove a small piece of bone. Your level of pain will be monitored throughout the procedure and you'll be encouraged to voice any concerns. Additional numbing medicine may be utilized if necessary. The entire procedure will take about 1 hour to complete. We will call you about 2 days after the procedure to see how you are doing.
    - ECGs – if your first ECG showed abnormalities or if you take certain medications, ECGs will be repeated every 3 cycles.
    - Research blood samples for biomarkers and other research studies (after the first 4 weeks of treatment in the window study, with each tumor imaging/response assessment, and at time of disease progression)

- Optional research tumor biopsy: biopsy of available lymph nodes or other site of disease (after the first 4 weeks of treatment in the window study and at time of disease progression). You may need to be sedated for the biopsy.
- Imaging: CT, PET, and MRI scans will be used to monitor your disease while you are on this study. The procedures for each type of imaging you may receive on study are outlined below:
  - **CT scans**: You will have a CT (Computed Tomography) scan at screening (repeated at baseline if screening scans occurred more than 14 days prior to start of treatment), after treatment window with only copanlisib, after Cycle 3, after Cycle 6, and at the end of your study treatment.

    The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures showing the inside of your body. During the procedure, you will need to lie still on a table inside the CT machine. The table will move you in and out of the machine during the scan and you will be instructed to hold your breath. The scan itself will only take a few minutes to complete, the entire visit will take about 30-90 minutes.
  - **[^{18}F] FDG PET/CT scans**: You will have PET/CT (Positron Emission Tomography/Computed Tomography) scan at screening (repeated at baseline if screening scans occurred more than 14 days prior to start of treatment), after treatment window with only copanlisib, after Cycle 6, after Cycle 12 or at the end of your study treatment. The scan performed at the end of window treatment will be specifically for research purposes.

    The PET scanner is a doughnut-shaped machine that uses x-rays combined with a dose of a radioactive substance (tracer) to create computer pictures showing the inside of your body.

    Before the scan, you will have a radioactive substance injected into your arm after which, you will need to wait for approximately 30 minutes for the substance to be absorbed. We will place an intravenous catheter which is a small plastic tube inserted into a vein in your arm using a needle. After 30 minutes, you'll lie on a narrow, padded table and be positioned for the scan. The scan itself is painless and won't make much noise. During this time, you will need to lie very still. It will take about another 30 minutes to complete.
  - **MRI:** You may have an MRI (Magnetic Resonance Imaging) scan of your brain, if your study doctor thinks this is needed. An MRI creates pictures of the inside of your body using strong magnets instead of x-ray energy. At the time of each scan you will be asked to fill out a screening form to verify that it is safe for you to have the scan. You will also be asked to remove any metallic objects you may be wearing (for example, watches, earrings or piercings) and possibly to change into a hospital gown. Then you'll be asked to lie on a narrow bed that will move into the MRI scanner. Before moving you into the scanner, special padding will be placed around your head to help keep your head still. Once you are comfortable, the table will

be moved into the scanner (the scanner is a long, narrow tube that is open at each end). You will need to lie still on the table during the scan which will take about 30 minutes to complete. You will hear normal "hammering" or clicking and squealing noises during the scan. While in the scanner you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the technician running the scan the entire time and will be provided an emergency button to squeeze at any time if you decide you want the scan to stop.

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for medical purposes.

It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

- Blood tests for Hepatitis B viral load: A risk of rituximab is reactivation of hepatitis. If you were exposed to HBV at some point prior to coming onto this study, your blood will be tested for HBV before every cycle and for six months after stopping treatment.
- Blood tests for CMV viral load: A risk of copanlisib is reactivation of CMV. Your blood will be tested for CMV before every cycle and for six months after stopping treatment.

The following sections describe studies to be done on your samples for research:

What tests will be done on my samples?

Your tissue (tumor and normal tissue) and samples that are collected will be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) are the molecules inside cells that carry genetic information and pass it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow. To determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA that are common to a particular type of tumor. To examine the tumor and normal tissue we may use several different techniques depending on the type of tissue we collect. These could include growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells), xenograft studies (placing or growing cells in another animal, such as mice), and looking in detail at the parts of the genes that produce specific proteins. When we are examining these pieces of your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to provide another sample to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and provided a referral to a genetic healthcare provider to discuss the results.

Who else besides the investigators on this study will know the results of my sample testing?

Once we obtain any of the samples listed above, the investigators take all your personal information off those samples and label them with a study code number. Only the investigators on this study know who the sample came from. The key linking your personal information with the code number is kept in a secure computer database, with access only to the limited research staff who will be discussing this study with you. Once the sample has been labeled with a code, it is sent to a variety of NIH laboratories for storage and testing. No one testing your samples will be able to link the results to you personally. Specimens obtained during your participation in this study may be sent for testing to investigators outside of NCI or the NIH. All samples will be coded to protect your privacy and no personal information will be included. Other investigators on this study will have access to limited clinical and biologic data such as age, gender and disease status.

How long will your samples be stored?

The samples collected during this study will be stored for as long as the study is open. When this study is closed, we will keep the samples for future research.

When you are finished taking the drugs (treatment)

When you finish the study treatment, we will ask you to come to the clinic about 30 days after the last dose of study drug to see how you are doing. If you stop the study drug and your cancer has improved or is stable at the time you stop, you will be followed every 3 months for the first 2 year after completion of treatment; every 6 months for years 2-5, and then once a year indefinitely. The tests and procedures to be completed at each visit include:

- Physical exam, including vital signs and weight

- Blood tests to check your blood counts, blood chemistries, immune system and other tests to monitor your health
- CT scan of your chest, abdomen and pelvis
- Bone marrow aspiration/biopsy
- Research blood samples for biomarkers and other research studies
- HBV viral load (for 6 months) if you had a positive HBV serology test at screening
- CMV viral load (for 6 months)

If you stop the study drug and your cancer has worsened or you have started another anti-cancer therapy, you will be contacted about every 3 months by phone (or we will review with you if you come to clinic) to get information on any new medications, treatments, or procedures you are currently taking or have recently received for the cancer. You will be followed on this study until the end of the study or your voluntary withdrawal from the study or your death.

BIRTH CONTROL

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine combination would affect your baby or your unborn child. If you are a woman who can become pregnant or are the partner of a woman who can become pregnant, you must agree to use one highly effective method or two combination methods of contraception beginning when you sign this consent. You must continue contraception for at least 1 month after the last dose of copanlisib or 12 months after the last dose of rituximab, whichever is later. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Highly Effective Methods (use of one method required):

- Intrauterine device (IUD)
- Partner's vasectomy
- Contraceptive rod implanted into the skin

Other Effective Methods (requires the use of TWO of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (option for women who have never been pregnant only)
- Contraceptive sponge (option for women who have never been pregnant only)
- Male condom or female condom (cannot be used together)
- Hormonal (birth control pills, skin patch, vaginal ring, injections)

RISKS OR DISCOMFORTS OF PARTICIPATION

You should talk to your study doctor about any symptoms that you experience while taking part in the study.

What side effects or risks can I expect from being in this study?

If you choose to take part in this study, there is a risk that

- you may lose time at work or home and spend more time in the hospital or doctor's office than usual
- you may also be asked sensitive or private questions which you normally do not discuss

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.
- The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drug.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

You should report and discuss with the study doctor any other medication(s) you are taking while you are treated with the study drug, so that he/she can take action to prevent any potential drug interactions

Possible Risks of Copanlisib

The copanlisib used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. These risks are described in more detail below.

There is also a risk that you could have other side effects from the study drug, including those below, or those that are not yet known.

COMMON, SOME MAY BE SERIOUS In 100 people receiving copanlisib, more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness • Infection, especially when white blood cell count is low • High blood pressure which may cause headaches, dizziness, blurred vision • High blood sugar (see additional information below) • Low white blood cells count (see additional information below)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving copanlisib, from 4 to 20 may have:
• Anemia which may require blood transfusion • Dry mouth • Sores in the mouth which may cause difficulty swallowing • Vomiting • Bruising, bleeding • Loss of appetite • Muscle spasms • Changes in taste • Feeling of "pins and needles" in arms and legs • Damage to the lungs which may cause shortness of breath • Rash • Low blood platelet counts (Thrombocytopenia) • Inflammation of the pancreas (Pancreatitis) • Low blood sodium levels (Hyponatraemia) which can lead to symptoms of headache, muscle cramps, low energy, confusion and nausea • Skin condition which causes shedding of the top layers of your skin (exfoliative dermatitis) • Inflammation of the colon (colitis) • Abdominal Pain

Other risks and additional information about copanlisib:

The most common toxicities that required the dose of copanlisib to be changed or stopped in prior studies were high blood sugar (hyperglycemia), low neutrophil count (a type of white blood cell; neutropenia), and high blood pressure (hypertension). It is common for high blood sugar and high blood pressure to happen without any noticeable symptoms. However, if you notice symptoms including dizziness, lightheadedness, headaches, frequent urination, excessive thirstiness, or excessive hunger, you should notify your doctor. Another serious risk is lung infection (pneumonia) and inflammation of the lungs that may happen without an associated infection (pneumonitis). Other changes in blood levels and infections have also been seen.

Call your study doctor if you have any diarrhea, even if it is mild. Close monitoring and early management of diarrhea is essential for successful treatment of patients with copanlisib. Early and appropriate intervention by your study team can prevent the development of more severe diarrhea.

There is also the possibility of an allergic reaction to copanlisib and it might be severe. We will monitor for symptoms and treat as appropriate.

There is also the possibility you may experience abnormal electrical conduction within the heart which may lead to an irregular heartbeat. You should notify your doctor if you experience abnormal heart sensations.

Cytomegalovirus (CMV) Reactivation: CMV is a common virus that infects most people worldwide. It is a member of the herpesvirus family. Other members of the herpesvirus family cause chickenpox, infectious mononucleosis ("mono"), fever blisters, and genital herpes. These viruses all share the ability to remain alive, but dormant, in the body for life. Dormant means the virus lives in the body silently without causing obvious damage or illness, but may reactivate such as when the immune system weakens during sickness or stress. Even upon reactivation, there are usually no symptoms produced and is detected only on a blood test. You will be monitored closely with a blood test each time you return to clinic for signs of this infection.

Possible Risks of Rituximab

COMMON, SOME MAY BE SERIOUS In 100 people receiving rituximab, more than 20 and up to 100 may have:
• 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

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving rituximab, from 4 to 20 may have:
• Bruising, bleeding • Abnormal heartbeat • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Sores in eye • A tear or a hole in the bowels that may require surgery • 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 • Blockage of internal organs which may cause shortness of breath, wheezing, vomiting • 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, AND SERIOUS In 100 people receiving rituximab, 3 or fewer may have:
• 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 stops beating

Other Risks of Rituximab

Hepatitis B (HBV) Reactivation: Hepatitis B Reactivation refers to the sudden increase in hepatitis B virus in an individual who has inactive or resolved HBV. In patients with a history of HBV infection, taking rituximab could cause this sudden increase in HBV. If you experience HBV reactivation, we will treat your HBV and monitor you closely while on study.

You should not receive rituximab or any of the study medications if you have active HBV liver disease. We will test you during screening for HBV and monitor you during the study if you have a history of HBV.

You should tell your study doctor immediately if you have any of these symptoms which may suggest hepatitis: worsening of fatigue and yellow discoloration of the skin or eyes.

Risks of Other Procedures

- Blood Samples: Blood draws may cause pain, redness, bruising or infection at the site of the needle stick. Rarely some people faint. The study team member may apply numbing cream to the area so that the needle stick won't hurt as much.
- Imaging:
  - CT scans and FDG PET/CT scans: CT and FDG PET/PET scans expose you to radiation; the amount of radiation you will be exposed to and the risks associated with this radiation are outlined in the section titled, "*What are the risks of radiation from research*?"

    The CT scans and FDG PET/CT scans will involve the use of a contrast agent. There is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely, death. The contrast material may also cause kidney problems. The study doctors will do a blood test prior to the test to confirm that it is safe you to receive the contrast.

    For IV contrast: You may feel discomfort when the contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach. For oral contrast: you may experience vomiting, nausea, cramping, bloating, constipation or diarrhea after drinking the contrast.

    The risks of IV insertion include temporary pain and bleeding or bruising at the site where the IV enters the skin. In placing the IV, there is a small chance of fluid leaking into the tissue surrounding the IV and infection, which may cause some swelling and discomfort. Rarely, the IV site may become infected, which might require treatment with antibiotics.
  - MRI: People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

    In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

    People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing

protection. If the hearing protection comes loose during the scan, you should let us know right away.

There are no known long-term risks of MRI scans.

- Additional risks associated with gadolinium enhanced MRI: The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

  Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

  People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

  Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

- Bone Marrow Aspiration and Biopsy: The bone marrow aspiration and biopsy may cause pain, bruising, bleeding and infection. Soreness near the site may last for a couple of days after the procedure. You may have more pain, risk of bleeding and bruising if you complete both aspiration and biopsy rather than just the aspiration. If your pain is severe or you develop a fever, please contact the study team immediately. Conscious sedation and general anesthesia may be used if you find the risks acceptable. The risks for both are listed further below.
- Tumor Biopsy/Lymph Node Excision: A tumor biopsy or lymph node excision may be performed at the beginning of the study, about 4 weeks after the start of treatment (before starting copanlisib with rituximab) and at the time your disease worsens. The tumor

biopsies are an optional part of the study (unless one is required prior to starting if prior tissue is not available or adequate) and you will only be asked to do so if it is felt to be safe.

- Although the tissue may be sent to pathology for review (such as to confirm if it contains cancer tissue), a routine report may not be done if not needed for your standard care. A tumor biopsy done for research purposes only, will not benefit you. It might help other people in the future. You may agree to tumor biopsies now and change your mind later. If at any time you do not want to have a tumor biopsy done, please tell us, it will not affect your care. If you agree to have the tumor biopsy, you will be asked to sign a separate procedure consent before you have the procedure(s). Conscious sedation and general anesthesia may be used if you find the risks acceptable. The risks for both are listed further below.

The risks for this procedure includes:

- Likely: discomfort or pain, redness, swelling, and/or bruising at the site of the needle insertion.
- Less likely: bleeding from site of the needle insertion.
- Rare: significant infection or bleeding from this procedure, allergic reaction to the anesthetic, formation of a scar at the site of needle entry.

- General Anesthesia: If you need to be sedated for a procedure it will be given by one of the NIH Clinical Center anesthesia specialists. Once the specialists evaluate you, they will discuss the risks of general anesthesia with you. You will be asked to sign a procedure and anesthesia consent.

  The anesthesia specialists will closely monitor your heart rate, blood pressure and breathing during the sedation. They may put a short plastic tube into your mouth to help keep the airway open. They may choose to use a breathing tube instead. They may give you oxygen to breathe while you are under general anesthesia.

  Although rare, any time a patient has general anesthesia there is a risk of a problem occurring. Most problems relate to decreased breathing rates. Using less anesthesia can fix this. Another risk is you can breathe stomach fluids into the lungs. This can result in an infection called pneumonia. We can treat the pneumonia with drugs such as antibiotics.

  People can have a bad reaction to sedative drugs. A severe reaction could include low blood pressure or heart rate problem. In this rare case, the anesthesia specialists may have to put a tube into your mouth and windpipe and use a respirator to breathe for you. They may give medication to increase your blood pressure. Some drugs may increase the chance of a seizure at first use. Please tell us if you or a family member had problems with general anesthesia.

- Conscious Sedation: Alternatively, you may receive conscious sedation before undergoing a biopsy. Conscious sedation is usually given to help someone relax and minimize discomfort. It can be given as a pill, a shot, an IV or even inhaled. You may have to wait up to an hour to start feel the effects depending on how it is given. Once it takes effect, you will be mostly awake, though relaxed or drowsy. The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These

are generally mild and last no more than a few hours. You will be monitored throughout the procedure.

- Electrocardiogram (ECG): An ECG is a tracing of your heart rate and rhythm. This test is very safe and is performed using wires that are briefly placed on the skin of your chest.

- Other: There are no known risks or discomforts with other tests and procedures (e.g., urine or saliva collection, cheek/ buccal swabs)

What are the risks of radiation from research?

During your participation in this research study, you will be exposed to radiation from up to 6 CT scans, 5 [^{18}F] FDG PET/CT scans and 3 CT-guided biopsies in your first year on study. The amount of radiation exposure you will receive from these procedures is equal to approximately 16.2 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The [^{18}F] FDG PET/CT scans and the CT scans that you receive will expose you to the roughly the same amount of radiation as approximately 54 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.6 out of 100 (1.6%) and of getting a fatal cancer is 0.8 out of 100 (0.8%).

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

Privacy Risks Associated with Genetic Testing

It may be possible that genetic information from you could be used by law enforcement agencies or other entities to identify you or your blood relatives

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your

family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumor(s) to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug combination effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study

Please talk to your doctor about these and other options.

STOPPING THERAPY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease worsens or comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines,

information collected on you up to that point may still be provided to Bayer or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed

CONFLICT OF INTEREST

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

The National Institutes of Health and the research team for this study are using copanlisib, developed by Bayer through a joint study with your researchers and the company. The company also provides financial support for this study.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect, use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Genomic Data Sharing

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must

receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you*)* is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. Someone will work with you to provide more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor, Center for Cancer Research, NCI, or their agents.
- Qualified representatives from Bayer Pharmaceuticals, the pharmaceutical company who produces Copanlisib.

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those

disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Mark Roschewski, M.D., at mark.roschewski@nih.gov or 240-760-6183. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.