CONSENT FORM - NCT03788291

Phase II study of acalabrutinib and high frequency low dose subcutaneous rituximab in patients with previously untreated CLL/SLL

Principal Investigator: Paul Barr, MD

This consent form describes a research study, what you may expect if you decide to take part and important information to help you make your decision. Please read this form carefully.

The study staff will also explain this study to you. Please ask questions about anything that is not clear before you agree to participate. You may take this consent form home to think about and discuss with family or friends.

Key Information

- Being in this research study is voluntary – it is your choice.
- You are being asked to take part in this study because you have been diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).
- The main purpose of this research study is to find out if the combination of acalabrutinib and frequent low dose subcutaneous rituximab is safe and effective in patients who have previously untreated CLL/SLL.
- Your participation in the treatment part of the study will last about 2 years. After that, studypersonnel will monitor your health status by checking your medical chart periodically, noting any additional treatments you might receive for CLL/SLL.
- Procedures will include documenting your medical history and physical examination, updating medications being taken, and doing blood tests before starting the medication.
- There are risks from participating.
    - The most common risk is headache or transient diarrhea with starting acalabrutinib or an infusion reaction with the first rituximab administration.
    - One of the most serious risks is an irregular heart rhythm (atrial fibrillation). See the "Risks of Participation" section in this consent form for more information. You should discussthese risks in detail with the study team.
- We do not know if you will benefit from this research study. It is possible that your condition will get better, but it is also possible that there will be no effect on your condition or that your condition will get worse. We can use what we learn from this research study to help other people with the same disease.
- If you do not want to take part in this study, you may discuss other therapy options with your physician. These could include being followed with observation, chemotherapy or ibrutinib.

Description of Study Procedures

Before you begin the research study

You will need to have the following exams, tests or procedures to find out if you can be in the research study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the research study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Physical exam,** which includes vital signs, height, weight, and assessment of disease.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests,** to measure the numbers and types of cells in your blood, test markers to help better understand your CLL disease, test your liver and kidney function, blood clotting, and test for viruses in your blood.
- **Blood pregnancy test** (for women of child bearing potential)
- **An assessment of your tumor** using CT (Computed Tomography) scan of your chest, abdomen, pelvis and neck will be done. This is a tumor assessment to measure the extent of your disease.

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Study Treatment
Treatments are repeated every 28 days. Each period of 28 days is called a cycle.

- You will start treatment with an IV infusion of rituximab on Day 1. An IV is a small plastic tube inserted into a vein in your arm using a needle, the drug will be administered through the tube. Afterwards, you will receive rituximab subcutaneous starting on Day 3, 4, or 5 of cycle 1 and then twice weekly for 6 cycles.
- You will begin acalabrutinib on Day 8 of cycle 1. Acalabrutinib will be taken twice per day by mouth.
- Response assessments including CT will be performed prior to the completion of cycle 12. Based on these results at cycle 12, the study doctor will decide if you will undergo a bone marrow biopsy to confirm complete remission as well as peripheral and bone marrow testing for minimal residual disease (MRD) negativity.
    - If remission is confirmed, you will stop therapy and be followed until disease progression.
    - If not in a complete remission or MRD remains positive/detectable, you will continue acalabrutinib until cycle 24.
- Repeat response assessments will again be performed at 24 cycles of therapy for those continuing on acalabrutinib. Based on these results, the study doctor will decide if you will undergo a bone marrow biopsy to confirm complete remission and minimal residual disease negativity.
    - If remission is confirmed, you will stop therapy and be followed until disease progression.
    - If not in a complete response or MRD remains positive/detectable, will you will continue acalabrutinib at you and your study doctor's discretion.
    - Know that using minimal residual disease testing to guide treatment duration is still considered investigational.

The table below provides further details of study procedures:

Cycle = 28 days	Screening	Cycle 1				Cycle 2-6	Cycle 7-12	Cycles 12-24	Follow up
	D-28 to -1	D1	D3,4 or 5	D8	D15	D1	D1	Every 3 months	
Informed Consent	X								
Medical History	X								
Physical Examination	X	X		X		X	X	X	
Vital Signs	X	X	X	X		X	X	X	
Blood Draw	X	X	X	X	X	X	X	X	
Pregnancy Test	X								
CT imaging (neck, chest, abdomen, pelvis)	X						X	X	
Bone Marrow (BM) aspirate & biopsy							X	X	
Flow cytometry for MRD							X		
Rituximab 50 mg twice weekly		X	X	X	X	X			
Acalabrutinib 100 mg twice a day				X	X	X	X	X	X
Response Assessment							X	X	
Medication Review		X	X	X	X	X	X	X	

Information about your study participation and study results may be included in your electronic health record. If you have concerns about this or to obtain more detail, you should discuss this with the study team.

Number of Subjects

Approximately 40 subjects will take part in this study.

Risks of Participation

There are risks to taking part in any research study. One risk is that you may get a study drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of the study drugs to keep track of your blood counts and the function of vital organs, particularly the kidneys and liver. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Rituximab:

***Very Common (Equal to or greater than 10% of patients)*:**

- Infusion/Administration related reaction (flushing, decreased blood pressure, rash)
- Fever
- Chills
- Infection
- Weakness
- Headache
- Abdominal Pain
- Pain
- Low white blood cell counts (and associated risk of infection)
- Low platelet count (and associated risk of bleeding)
- Night sweats
- Rash
- Pruritus (itching)
- Rash and itching at injection site
- Cough
- Runny nose
- Angioedema (swelling, especially around the nose or mouth)
- Nausea

***Common (1-10% of patients)*:**

- Back pain
- Throat irritation
- Flushing (redness in face or other areas of body)
- Anemia (low hemoglobin leading to fatigue and shortness of breath)
- Hives (itchy red welts)
- Wheezing
- Shortness of breath
- Sinus infection
- Hyperglycemia (high blood sugar causing fatigue, blurry vision in patients with diabetes)
- Peripheral edema (swelling of extremities)
- Diarrhea
- Vomiting
- Constipation
- Dizziness
- Anxiety

- Muscle pain
- Joint pain
- Constriction ('spasm') of muscles in chest
- Hypotension (low blood pressure)
- Hypertension (high blood pressure)

Less Common (less than 1% of patients):
- Progressive multifocal leukoencephalopathy (a brain infection)
- Tumor lysis syndrome (rapid breakdown of the leukemia)

Risks Associated with Acalabrutinib:

***Very Common (Equal to or greater than 10% of patients)*:**
- Infections
- Headache
- Bruising Events including bruises, petechiae (pinpoint red or purple spots on the skin), and increased tendency to bruise
- Diarrhea (frequent or loose stools)
- Musculoskeletal pain
- Nausea
- Constipation (bowel movements that are infrequent or hard to pass)
- Bleeding
- Vomiting
- Abdominal pain
- Rash
- Fatigue (feeling tired)
- Joint pain
- Leukopenia (low white blood cells)
- Dizziness
- Second primary malignancy (development of second cancer)
- Anemia (low red blood cells)

***Common (1-9% of patients)*:**
- Nose bleeds
- Thrombocytopenia (low platelets)
- Asthenia (lack of energy)
- Atrial fibrillation/flutter (a type of abnormal heart rhythm)

Less Common (less than 1% of patients):
- Progressive multifocal leukoencephalopathy (a brain infection)
- Other severe infections
- Irregular heart rhythm (atrial fibrillation)
- Tumor lysis syndrome (rapid breakdown of the leukemia)
- Drug induced liver injury

Risks Associated with Bone Marrow Biopsies:
For this procedure, a numbing drug is injected into the skin over one of your hipbones. A needle is then inserted into the hipbones and a small piece of bone is removed. The risks may include:

- Moderate pain and discomfort
- Bleeding at the biopsy site
- Scarring at the biopsy site
- Rarely, an infection at the biopsy site
- Rarely, nerve injury at the biopsy site

Risks Associated with Bone Marrow Aspiration:
For this procedure, a numbing drug is injected into the skin over the same hipbone. A needle is then inserted into the hipbone and a sample of bone marrow fluid is removed. Risks of this procedure are small, but may include:

- Pain from the needle sticks
- Pain from aspirating the bone marrow with a syringe
- Bleeding
- Infection
- Local nerve damage

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, CT scans may be used to evaluate your disease. The frequency of these exams is similar to what you would receive as standard care. In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

This research study involves exposure to radiation from up to 3 CT scans of the chest, abdomen, pelvis and neck. Please note that this radiation exposure is required to obtain the desired research information.

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the CT scan. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
The drugs used in this research study may affect a fetus. The effects of the study drug on a developing baby are unknown; therefore while participating in this research study, you should not become pregnant or father a baby and should not nurse a baby.

If you are able to have children, you should use a highly effective method of birth control while taking study treatment, as well as for 4 weeks after you stop taking study treatment, to prevent pregnancy in either

you or your partner. A **"**highly effective method of birth control" is defined as a method that has a low failure rate (i.e. less than 1% per year) when used consistently and correctly and includes implants,

injectables, birth control pills with two hormones, some intrauterine devices (IUDs), sexual abstinence (which is defined as refraining from all aspects of sexual activity) or a sterilized partner. If you are using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (e.g. condoms) must be used. Note: Some birth control pills will not work when you are taking certain drugs. If you have any questions about this, please discuss this with the study doctor.

Be aware that you can still become pregnant even if you use highly effective method of birth control.

If you or your partner becomes pregnant during the study or until 2 days after the last dose of acalabrutinib or 12 months after the last dose of rituximab, you should immediately inform the study staff. If you become pregnant on the study, you must immediately stop taking the study treatment. The Sponsor would like to collect information about the birth of your baby even after treatment is stopped. We can provide counseling about preventing pregnancy for either male or female study participants.

In addition to the risks listed above, there could be unknown or unexpected side effects associated with the use of the study drug. You will be told in a timely manner, verbally and in writing, of any new information, findings, or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

Risks of study data in the Electronic Health Record

The study team may be notified if you receive other health care services at URMC or its Affiliates (e.g., visit to the emergency room). In addition, the following individuals may know you participated in research and may see results of testing conducted for this study:

- Staff at the University of Rochester Medical Center and its Affiliates (e.g., Strong Memorial Hospital, Highland Hospital, URMC primary care, specialist physician offices) who have a reason to access your electronic health record.
- Health care providers who are involved in your care at a facility that is not part of the University of Rochester Medical Center and its Affiliates and who have reason to access your electronic health record.
- Individuals who request a copy of information from your health record for activities such as treatment or payment (e.g., medical insurance companies, worker's compensation).

Benefits of Participation

We do not know if you will benefit from this research study. It is possible that your condition will get better, but it is also possible that there will be no effect on your condition or that your condition will get worse. We may be able to use what we learn from this research study to help other people with the same disease.

Alternatives to Participation

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Compensation for Injury

If you are directly injured by the treatment being studied, or by medical procedures needed because of this study, and you receive medical care for the injury, you may need to pay for that care. You will be reimbursed for reasonable and necessary medical costs for such care, but you might not be reimbursed for care covered and paid for by a third party like your health insurance provider, or costs such as required co-payments or deductibles related to that coverage. No other funds have been set aside to pay for such things as lost wages or expenses due to a current underlying illness or condition.

If your research injury is paid for by the University, we will collect your name, date of birth, gender, and Medicare Health Insurance Claim Number or Social Security Number to determine your Medicare status. This information will be used only in accordance with the law. If you are a Medicare beneficiary, information about the study you are in, and any payments made related to your injury, will be reported to the Centers for Medicare & Medicaid Services (CMS), in accordance with CMS requirements. This information will not be used for any other purpose.

Costs

Acerta Pharma/AstraZeneca will provide the study drug, acalabrutinib, free of charge while you are participating in this study. Tests and procedures that are required only for the study, that are not a part of your regular medical care, will also be provided at no charge.

Rituximab at this dose and frequency is not standard of care and may not be covered by your insurance, you should discuss with your study doctor and insurance company any costs that may be associated with receiving this study drug.

You or your insurance company will be billed for any standard medical care given during this research study. You will be responsible for any co-pays, insurance deductibles and/or co-insurance required by your health insurance carrier for your standard medical care. This standard medical care includes any care that you would receive for the treatment of your type of cancer whether you were participating in a study or not, such as:

- Routine clinic visits with your doctor or nurse practitioner
- Tests (Including but not limited to routine items such as: laboratory blood tests, CT, PET/CT, and/or FDG/PET scans, X-rays, lung function, or cardiac testing.)
- Procedures (Including but not limited to routine items such as: bone marrow biopsies and/or aspirates, other tumor biopsies)
- Medications: other standard medications to treat your cancer. This can include other chemotherapies or non-chemotherapy medications used to treat your cancer, and/or medications to treat or prevent side-effects.

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study prior to enrolling on a research study. Depending on how your insurance company pr**o**cesses payments for standard medical care given during a research study, you might have unexpected expenses from being in this study. If your insurance company does not pay for your standard medical care, you will be billed for those charges.

Ask your study doctor to discuss the specific costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

Payments
You will not be paid for participating in this study.

Financial Interest
The Investigator, Dr. Barr, receives payment for consulting activities from the Study Sponsor, AstraZeneca. Please feel free to ask Dr. Barr or other study staff any questions you may have about his role as a consultant for the sponsor.

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes
The University of Rochester makes every effort to keep the information collected from you private. In order to do so, we will maintain your information in a password protected database where only study investigators and coordinators will access. Sometimes, however, researchers need to share information that may identify you with people that work for the University. If this does happen we will take precautions to protect the information you have provided. Results of the research may be presented at meetings or in publications, but your name will not be used.

If you have never received a copy of the University of Rochester Medical Center (URMC) and Affiliates Notice of Privacy Practices, please ask the investigator for one.

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Research records
- Records about phone calls made as part of thisresearch
- Records about your study visits
- Past and present medical records related to the study, including records of external providers that are available via your electronic health record at URMC & Affiliates
- Results of medical tests

Who may use and give out information about you?

- The study doctor and the study staff
- URMC and Affiliates

Your information may be given to:

- The Department of Health and HumanServices
- The University of Rochester
- The U.S. Food and Drug Administration (FDA) may also need to inspect study records at some point during the study or even after it has been completed. In the event that this should occur, every effort will be made to keep identifying information about youprivate.

Why will this information be used and/or given to others?

- To do the research
- To study the results
- To see if the research was done correctly

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

How long will this permission be valid?
This permission will last indefinitely.

May I cancel my permission to use and disclose information?
Yes. You may cancel your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. Upon receiving the written notice, the study team will no longer use or disclose your health information and you will not be able to stay in this study. Information that has already been gathered may need to be used and given to others for the validity of the study.

May I withdraw from the study?
Yes. If you withdraw your permission to be in the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
No. There is a risk that your information will be given to others without your permission.

Future Use of Information/Samples
Your information might be distributed or used for future research studies without additional informed consent. All identifiers will be removed before your information is used or distributed.

Circumstances for Dismissal
The study doctor may stop you from taking part in this research study at any time if he/she believes it is in your best interest; if you do not follow the research study rules; or if the research study is stopped.

Early Termination
You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

New Study Information
If we discover any new information that might make you change your mind about continuing in the study, we will let you know.

Return of Research Results

In general, we will not give you any individual results from your participation in the study. If we find something of urgent medical importance to you, we will inform you, although we expect that this will bea very rare occurrence.

Contact Persons

For more information concerning this research or if you feel that your participation has resulted in any research related injury, emotional or physical discomfort, please contact**:** Dr. Paul Barr at 585-275-5863.

Please contact the University of Rochester Research Subjects Review Board at 265 Crittenden Blvd., CU 420628, Rochester, NY 14642, Telephone (585) 276-0005 or (877) 449-4441 for the following reasons:

- You wish to talk to someone other than the research staff about your rights as a research subject;
- To voice concerns about the research;
- To provide input concerning the research process;
- In the event the study staff could not be reached.

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 website at any time.

Voluntary Participation

Taking part in this study is voluntary. You are free not to take part or to withdraw at any time, for whatever reason. No matter what decision you make, there will be no penalty or loss of benefit to which you are entitled. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

SIGNATURES/DATES

After reading and discussing the information in this consent form you should understand:

- Why this study is being done;
- What will happen during the study;
- Any possible risks and benefits to you;
- Other options you may have instead of being in the study;
- How your personal information will be protected;
- What to do if you have problems or questions about this study.

Subject Consent

I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a signed copy of this form for my records and future reference.

_____

Subject Name (Printed by Subject)

_____ _____

Signature of Subject Date

Person Obtaining Consent

I have read this form to the subject and/or the subject has read this form. I will provide the subject with a signed copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information. I have given the subject adequate opportunity to read the consent before signing.

_____

Name and Title (Print)

_____ _____

Signature of Person Obtaining Consent Date