CONSENT FOR CANCER RESEARCH

Project Title: CASE 3419; Phase II Study of Rituximab and Acalabrutinib in Newly Diagnosed B Cell Post Transplant Lymphoproliferative Disorder (PTLD)

Sponsor: Case Comprehensive Cancer Center, NCT04337827

Principal Investigators: Deepa Jagadeesh, MD, MPH (Cleveland Clinic)

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC).

This study will also be offered at the University of Wisconsin Carbone Cancer Center and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

One or more of the Investigators conducting this study serve as paid speakers, consultants or advisory committee members for the company that is paying for this research or a company that makes products used in this study. These financial interests are within permissible limits established by the Cleveland Clinic Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask your study doctor or call the Institutional Review Board at 216-444-2924.

Key Information: The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

Why am I being invited to take part in a research study?
We invite you to take part in a research study because you have been diagnosed with B cell post-transplant lymphoproliferative disorder (PTLD). PTLDs are a rare and clinically diverse group of diseases that occur in both solid organ and bone marrow transplant (BMT) patients. You are being asked to participate in this trial because there is currently no approved therapy for PTLD.

What should I know about a research study?
- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?
The purpose of this study is to evaluate how effective rituximab and acalabrutinib are when given as a combination treatment for your cancer. Currently there is no approved therapy for PTLD. Rituximab alone is commonly used. It works in some patients, but in others it does not. In addition, patients with PTLD have trouble tolerating therapies with lots of side effects due to

their health conditions and medications for their transplant. Due to these reasons we are looking for a new treatment with novel targeted agents in order to improve outcomes and to minimize toxicity.

Acalabrutinib is an inhibitor of Bruton Tyrosine Kinase (BTK). BTK is important in B cells and plays a role in the development of PTLD. Acalabrutinib is approved in the US for the treatment of adult patients with indolent lymphoma, mantle cell lymphoma, and is being evaluated to treat other lymphomas.

Rituximab has been approved for the use in lymphomas and rheumatologic conditions (like rheumatoid arthritis). While not approved for PTLD, it has become the mainstay of treatment.

Based on emerging data of clinical efficacy of acalabrutinib in B cell malignancies and an unmet need for novel therapies in PTLD, we propose a study of rituximab and acalabrutinib in patients with newly diagnosed B cell PTLD.

How long will the research last and what will I need to do?
You will receive the study drugs for 4 to 16 weeks depending on how your cancer responds to study treatment. After you finish receiving the study drugs, your doctor will continue to watch you for side effects and follow your condition for up to 3 years.

You will be asked to provide extra blood and urine samples, undergo PET/CT imaging, and record each time you take your medication (acalabrutinib) on a pill diary form.

More detailed information about the study procedures can be found under "What extra tests and procedures will I have if I take part in this study?"

Is there any way being in this study could be bad for me?
There may be discomforts, side effects, and risks to using the rituximab plus acalabrutinib treatment combination that we do not know yet. Sometimes during a study, the sponsor may learn new information about the study drug and the risks, which the study doctor/staff will tell you about in a timely manner. This new information might make you change your mind about being in the study. The study drugs may not be better, and could possibly be worse than the usual approach for your cancer.

More detailed information about the risks of this study can be found under "What possible risks can I expect from taking part in this study?"

What possible benefits can I expect from taking part in this study?

We cannot know if you will have any benefit as a result of your participation in the study; it is possible the study treatment may improve your cancer, which may give you relief from some symptoms, improve your quality of life or prolong your survival. However, it is possible that your condition could worsen. Your participation in this study may help to obtain information about treating subjects with B cell PTLD.

What is the usual approach to my PTLD?
As stated earlier, there is currently no approved therapy for PTLD. Single agent rituximab and combination chemotherapy plus rituximab (R-CHOP) are the treatments often used in clinical practice.

What are my other choices if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer. For example: comfort/palliative care

Detailed Information: The following is more detailed information about this study in addition to the information listed above.

What are the study groups?

All study participants will get the same study intervention. All study participants will get the combination of the study drugs rituximab and acalabrutinib.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there may be some extra blood, urine, and imaging tests that you will need to have if you take part in this study. The full list of exams and procedures are given in the study calendar at the end of this document.

Before you begin the study:
You will need to have the following extra exams, tests, or procedures to find out if you can be in the study:

- Electrocardiogram (EKG)
- Urinalysis
- PET/CT scan of neck, chest, abdomen, and pelvis
- Diagnostic material of your most recent biopsy sent to the Cleveland Clinic
- 20 ml (approximately 4 teaspoons) of blood will be collected for research purposes

Neither you nor your health care plan/insurance carrier will be billed for the collection of the research related blood and tissue that will be used for this study, but will be responsible for standard of care charges.

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra exams, tests, or procedures. They are not part of the usual approach for your type of cancer.

During the study the following will be additional research procedures:

- At each time point (see study calendar at the end of this document), about 20 ml (approximately 4 teaspoons) of blood will be collected for research purposes
- Complete a monthly drug diary that will document your twice daily doses of acalabrutinib. You should bring a completed diary with you when you return for each appointment. Acalabrutinib will be taken twice per day on days 1-28 of each cycle.

What possible risks can I expect from taking part 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 be asked sensitive or private questions which you normally do not discuss

The drug combination 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.

There is also a risk that you could have side effects from the study drug(s)/study approach.

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 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.

Possible side effects of **rituximab**, which is the usual approach for this type of cancer:

COMMON, SOME MAY BE SERIOUS In 100 people receiving rituximab, more than 20 and up to 100 may have:
• fatigue • infusion reactions (including low blood pressure, fever, chills, flushing, headache, and/or shortness of breath). Infusion reactions tend to happen more commonly during the first infusion and the risk is somewhat higher the higher the white blood cell count is. To help prevent infusion reactions, your study doctor may administer anti-histamines and steroids, and may also split the dose of rituximab over two days.

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving rituximab, from 4 to 20 may have:
• anemia (which may require blood transfusions) • bruising • bleeding • infections, potentially associated with lowered white blood cell counts • diarrhea • vomiting • pain • cough • stuffy nose • rash • itching • hives • high blood sugar • dizziness • anxiety

RARE, AND SERIOUS There are some very rare but serious side effects that can occur as well in people taking rituximab (may happen in less than 1% of patients). Some of these include:
• severe skin rash (with blisters and peeling that can involve the mouth and other body parts) • severe life-threatening damage to the lungs • abnormal heartbeat • tear or a hole in the stomach, or an obstruction in the stomach that may require surgery. Furthermore, severe reactions may occur during rituximab infusions including allergic reactions (e.g. a fast heart rate, wheezing, low blood pressure, sweating, swelling of the throat and face) and may occur within minutes of treatment (may happen in less than 1% of patients). Giving medications and slowing the rate of rituximab infusion have generally controlled these reactions. This reaction generally becomes less severe as the drug is given during future treatments.

As of October 2020, over 1000 patients who received acalabrutinib as a single agent in clinical trials for the treatment of blood cell cancers, have been evaluated for safety.
Acalabrutinib side effects considered caused by the drug are provided in the table below.

Very Common (at least 10% of patients)	**Common (at least 1% but less than 10% of patients)**
• Infections • Headache	• Thrombocytopenia (low platelets) • Nose bleeds

• Diarrhea *(frequent or loose stools)* • Bruising events *(including bruises, petechiae (pinpoint red or purple spots on the skin)), and increased tendency to bruise* • Musculoskeletal pain • Nausea • Fatigue (feeling tired) • Rash • Joint pain • Leukopenia (low white blood cells) • Constipation *(bowel movements that are infrequent or hard to pass)* • Anemia (low red blood cells) • Dizziness • Vomiting • Abdominal pain • Bleeding • Second primary malignancy (development of second cancer)	• Asthenia (lack of energy) • Atrial fibrillation/flutter (a type of abnormal heart rhythm)

Tumor Lysis Syndrome (TLS)

TLS can occur when a drug kills a large amount of cancer cells at the same time causing the contents of the cancer cells to spill into the blood stream. This can lead to parts of your body not working which can be life-threatening if not monitored and treated promptly. Cases of TLS (including one case of TLS caused by acalabrutinib) have occurred in patients receiving acalabrutinib. If your study doctor thinks you are at risk for TLS, you will be closely monitored during the study.

Potential Risk or Discomfort from Research Procedures

Blood Draws

The insertion of the needle to draw blood is painful; however, the discomfort is usually brief. For most people, needle punctures to get blood do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

CT Scans

If you take part in this research, you will have one or more medical imaging studies which use radiation. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may have received or will receive from other tests. The CT scan that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the sun and the environment. This type of radiation is called "background radiation." No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including

causing a new cancer. The amount of radiation that scientists think can cause harmful side effects equals more than 15 times the amount of extra radiation you would receive from being in this study. Also, scientists believe the number of people who would be at risk for developing a second cancer from being exposed to large amounts of radiation to be about 1 out of every 1,000.

Electrocardiogram (ECG)
Some people's skin reacts to the sticky patches that attach the electrodes to the chest and extremities for the ECG. This skin irritation usually disappears when the patches are removed. Some men may have some chest hair shaved.

Hepatitis testing
The state of Ohio and applicable regulations require laboratories to report new cases of Hepatitis B, and Hepatitis C infection to governmental agencies. The reports may include the patient's name, social security number, and other identifying information. Information about these new infections is used to track these diseases statewide and nationwide. Other than this required reporting, your results will be treated confidentially by the research study staff.

HIV testing
As part of this protocol, you will be tested for HIV (human immunodeficiency virus, which is the virus that causes the acquired immunodeficiency syndrome (AIDS). You will be notified of the results of the testing, and counseled as to the meaning of the results, whether they are positive or negative. If the test indicates that you are infected with HIV, you will receive additional counseling about the significance for your medical care and possible risks to other people. We are required to report all positive results to the Ohio State Board of Health. The test results will be kept confidential to the extent permissible under the law. If you do not want to be tested for HIV, then you should not agree to participate in this study.

Reproductive risks
You should not get pregnant, breastfeed, or father a baby while in this study. The drug combination used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What happens to the information collected for the research?
If identifiers are removed from your identifiable private information or identifiable samples that are collected during this research, that information or those samples could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent.

Can I stop taking part in this study?
Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect

your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.
- If you become pregnant.

What are my rights in this study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

What are the costs of taking part in this study?
Your involvement in this research study is voluntary and you will not be paid for your participation.

The study agent, acalabrutinib, will be provided free of charge by AstraZeneca, while you are participating in this study. Rituximab will not be covered by the study and will be charged to your insurance provider. Neither you nor your insurance provider will be responsible for the costs of any research-only tests or procedures. The blood work for research purposes will not be charged to you. It will be paid for by the research study.

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study (i.e., medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, rituximab infusions, hospitalizations, x-rays and/or scans for tumor measurement). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

What happens if I am injured or hurt because I took part in this study?
If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor.

If injury occurs as a result of your involvement in this research, medical treatment is available from Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost

wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924.

HIPAA AUTHORIZATION
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Deepa Jagadeesh, MD and the research study staff at Cleveland Clinic for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition..

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Cleveland Clinic, its study monitors and representatives
- Funding/Drug Support: AstraZeneca
- Case Comprehensive Cancer Center members and collaborators
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

Deepa Jagadeesh, MD
Case Comprehensive Cancer Center
Cleveland Clinic

9500 Euclid Ave.
Cleveland, OH 44195

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Questions about the Research
If you have any questions, you can ask the Principal Investigator and/or research staff: Dr. Deepa Jagadeesh at Cleveland Clinic, 216-444-0857.

Emergency or after-hours contact information
You should contact the page operator at (216) 444-2200 or toll free at (800) 223-2273, and ask for the oncologist (cancer doctor) that is on call.

Where Can I Get More Information?
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-2924.

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if applicable, 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.

Signature
Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____	_____	_____
Signature of Participant	Date	Printed Name of Participant

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____	_____
Signature of Person Obtaining Consent	Date

_____
Printed Name of Person Obtaining Consent

Procedures	Screening	Cycle 1					Cycles 2-4[a]	End of Treatment	Long Term Follow Up (± 14 days)[b]				
	Day -28 to Day 1	Day 1	Day 8 (± 2)	Day 15 (± 2)	Day 22 (± 2)	Day 42 (- 3)	Day 1	8 weeks ± 7 days after treatment completion	6 Months	12 Months	18 Months	24 Months	36 Months
Physical Exam	X	X					X	X	X	X	X	X	X
Blood Sample for research	X					X		X					
Pregnancy Test[c]	X												
Blood testing[d]	X	X	X	X	X		X	X	X	X	X	X	X
Urinalysis	X												
Hepatitis Panel	X												
HIV testing	X												
EBV test	X					X[e]		X[e]	X[e]	X[e]		X[e]	
Electrocardiogram	X												
CT Neck/Chest/ Abdomen/Pelvis[f]	X					X		X	X	X		X	
PET Scan	X							X					
Bone marrow biopsy/aspiration	X[g]							X[g]					
Acalabrutinib[h]		X					X						
Rituximab		X	X	X	X		X						

a. For patients with a complete response after cycle 1, rituximab will be administered weekly for 4 additional weeks. Patients with a partial response will receive rituximab every 4 weeks for 3 additional cycles. Patients with stable or progressive disease will discontinue drug therapy and proceed into long term follow up.
b. Patients with disease progression only need to have survival follow-up and current lymphoma treatment captured. Virtual visits may be used to capture applicable procedures if the patient is unable to follow up in person.
c. Pregnancy test to be done within 72 hours of starting the study drug. This only applies to women of childbearing potential.
d. Sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT], CBC w/ differential, INR/PTT, LDH, uric acid, phosphorous (not all tests will be done at every timepoint)
e. Epstein-Barr Virus (EBV) test if positive at baseline
f. Neck CT can be omitted at the discretion of the physician if there is no involvement
g. Bone marrow aspiration and biopsy if there is suspicion of involvement
h. Acalabrutinib taken on days 1-28