CONSENT FOR CANCER RESEARCH

Project Title: An Open-Label, Phase I/II study of ME-401 and R-CHOP in Newly Diagnosed Diffuse Large B-Cell Lymphoma (CASE 1420)

Clinical Trials Registration Number: NCT04517435

Sponsor: Cleveland Clinic/Case Comprehensive Cancer Center

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Cleveland Clinic Foundation
[redacted]

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic 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 currently being offered at Cleveland Clinic (CC).

One or more of the Investigators conducting this study serve as consultants for the company that makes products used in this study. These financial interests are within permissible limits established by the local institutional Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask you study doctor or call the Cleveland Clinic Institutional Review Board at [redacted]

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 a type of cancer known as Diffuse Large B-Cell Lymphoma (DLBCL).

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?

We are studying a drug called ME-401, also known as zandelisib, which is an investigational (experimental) drug being developed to treat certain types of lymphoma and leukemia. ME-401 inhibits, or blocks, a molecule called PI3K delta, which is typically present in normal lymphocytes and lymphoma cells. By blocking PI3K delta, ME-401 was shown to suppress cancer growth in several laboratory studies. ME-401 is experimental because it is not approved by the Food and Drug Administration (FDA).

- The purpose of this study is to evaluate if ME-401 can improve the treatment of patients with diffuse large b-cell lymphoma (DLBCL). Many patients with DLBCL are treated with the standard of care treatment known as R-CHOP. R-CHOP stands for a series of drugs called Rituximab, Doxorubicin, Vincristine, Cyclophosphamide and Prednisone. After receiving R-CHOP many patients go into long-term remission, however, a little less than half of patients will have their cancer come back despite being treated. Once DLBCL comes back, it is much harder to treat and treatment is much more aggressive. This study will combine treatment of ME-401 with R-CHOP.

- There are 2 parts to this study: part 1 is referred to as phase I and part 2 is referred to as phase II.
    - The goal of the phase I study is to find the safest dosing schedule to give patients ME-401 in combination with R-CHOP
    - The goal of phase II is to use the safest dosing schedule (found in phase I) in combination with R-CHOP to see if it decreases the rate of cancer coming back after it is treated.

How long will the research last and what will I need to do?
You will receive the drugs R-CHOP plus ME-401 for 6 cycles. Each cycle lasts 21 days. After you finish the study treatment your doctor will continue to watch you for side effects and follow your condition for up to 24 months.

You will be asked to take a combination of ME-401 and R-CHOP and return to the clinic periodically for routine tests and procedures throughout your time on study.

As mentioned above there are two phases to this study. In each phase patients will be given R-CHOP plus ME-401 for 6 cycles (21 days per cycle) unless there are side effects. R-CHOP is given on day 1. This includes 4 medications that are given into your veins (intravenous). Prednisone is a pill you take by mouth that is given on days 4-5. ME-401 is a capsule taken by mouth given on days 1-4 or days 1-7 of each cycle, depending on which phase of the study you take part in.

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?
The side effects of study treatment may be a minor inconvenience or could be severe enough to be life-threatening or cause death. You will be watched closely for side effects, and the drug will be stopped if unwanted or serious side effects develop.

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. There is no proof that combining ME-401 with R-CHOP will be more useful than the usual treatment (R- CHOP) for the type of cancer that you have. Your participation in this study will help to obtain information about treating subjects with diffuse large b-cell lymphoma (DLBCL).

What is the usual approach to my diffuse large b-cell lymphoma (DLBCL)?
Many patients with DLBCL are treated with the standard of care treatment known as R-CHOP. R-CHOP stands for a series of drugs inserted into your vein (intravenous) called Rituximab, Doxorubicin, Vincristine, and Cyclophosphamide, along with Prednisone that is taken orally.

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?

As mentioned above there are two parts to this study. These parts will be referred to as phase I and phase II. In each phase, patients will be given R-CHOP plus ME-401 for 6 cycles unless there are side effects.

- Each cycle is 21 days
- R-CHOP is given on day 1. This includes 4 medications that are given into your veins (intravenous). Prednisone is a pill you take by mouth that is given on days 1-5.
- ME-401 is a capsule taken by mouth given on the following days:
    - Phase I: days 1-4 of each cycle or days 1-7 of each cycle.
    - Phase II: recommended duration established from phase I

The goal of the phase I study is to find the safest dosing schedule to give patients ME-401 in combination with R-CHOP. Different durations of the study drug ME-401 will be given to several study participants. The first several study participants will receive a shorter duration of ME-401, on days 1-4 of each cycle. If the drug does not cause serious side effects, it will be given to other study participants for a longer duration of time, days 1-7 of each cycle.

The goal of the phase 2 study is to use the safest dosing schedule of ME-401 (found in phase I) in combination with R-CHOP to see if it decreases the rate of cancer coming back after it is treated.

Please speak with your doctor about which study phase you will be entering into.

How many people will take part in this study?

- Phase I: This will include 6-12 patients. This will occur at Cleveland Clinic (CC).
- Phase II: This will include approximately 50 patients. This will occur at Cleveland Clinic (CC), University Hospitals (UH), and a few additional centers that are not confirmed at this time.

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

As a participant in this study you will be asked to complete the visits below involving the following tests and procedures:

Screening

This will require a visit to the clinic. At this visit, the following screening procedures will be performed to determine if you can take part in this study. All of the evaluations listed below must be completed $\leq$ 45 days prior to starting the trial. If you have already recieved a dose of R-CHOP and are eligible for the study screening, your screening window will be extended to $\leq$ 60 days.

- Informed Consent
- Demographics collected, such as your age, race, gender, etc.
- Medical History
- Complete Physical Exam
- Height
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- We will ask you if you taking any including prescription medications, over the counter (OTC) medications or natural/herbal supplements
- ECOG Performance Status (this describes how well you are functioning in your daily activities).
- Baseline Symptoms Assessment (An assessment to see what symptoms you are having)
- Blood and urine samples will be collected for safety and diagnostic tests to make sure your organs are functioning well
  -This includes tests for hepatitis, cytomegalovirus (viral infection), and HIV (see risk section below for explanation)
- Correlative Blood Draw (This is an additional blood draw taken for study purposes only and is described in more detail below. Approximately 6 teaspoons of extra blood will be taken for additional study purposes)
- If you are a female who could become pregnant we will have you take a pregnancy test. You will need to provide a urine sample
- EKG (Electrocardiogram – stick pads will be placed on your chest and connected to a machine so we can check the rhythm of your heart)

- MUGA or echocardiogram (see risk section below for explanations)
- CT scan of neck, chest, abdomen and pelvis with oral and IV contrast (neck may be omitted at discretion of treating physician) (see risk section below for explanation)
- PET/CT (see risk section below for explanation)
- Bone Marrow Aspirate and Biopsy (This is standard of care for most patients, even if you are not on this study) (see risk section below for explanation)

Cycle 1, Day 1

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- We will ask you if you taking any including prescription medications, over the counter (OTC) medications or natural/herbal supplements
- ECOG performance status
- We will ask about any symptoms you are having
- Blood samples will be collected to see how well your organs are functioning
- If you are a female who could become pregnant we will have you take a pregnancy test. You will need to provide a urine sample.
- EKG
- R-CHOP administration (for the first treatment this will take approximately 6 hours).
- ME-401 started (given days 1-4 or days 1-7)
    - You will need to keep a drug diary for every dose of ME-401 that is taken. This will include the date, number of ME-401 capsules taken, and the time of the dose.
- Start taking a medication called Trimethoprim/sulfamethoxazole or Pentamidine to help prevent a lung infection called pneumocystis jirovecii. ME-401 may increase your risk of this infection which is why you will take one of these medications.
    1. Trimethoprim/sulfamethoxazole is given by mouth, three days a week.
    2. Pentamidine is inhaled and given once monthly.

  You will take this until 2-6 months after finishing treatment
- Start a medication called Acyclovir that will be taken twice a day.

Cycle 1, Day 2

- Pegfilgrastim administration or ONPRO™ wearable device. This is a medication given to patients who get R-CHOP. It helps increase infection fighting cells (neutrophils) which helps your body's ability to fight infections. It can be given as a subcutaneous injection (just under the skin) in the clinic or you can wear a device on your arm that injects it at home.

Cycle 1, Day 8 (Phase I Only)

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Blood samples will be collected to see how well your organs are functioning
- We will ask you if you are having any concerns or new symptoms.

Cycle 1, Day 15 (Phase I Only)

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Blood samples will be collected to see how well your organs are functioning
- We will ask you if you are having any concerns or new symptoms.

Cycle 2-6, Day 1

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- We will ask you if you taking any including prescription medications, over the counter (OTC) medications or natural/herbal supplements
- ECOG performance status
- We will ask about any symptoms you are having
- Blood samples will be collected to see how well your organs are functioning
    - *Cycle 2 Day 1 only: Additional blood samples to check your uric acid and phosphorous levels (approximately 1-2 teaspoons of blood) will be drawn to examine your organ function
    - *Cycle 4 Day 1 only: Correlative Blood Draw for study purposes (approximately 6 teaspoons of blood)
- EKG *Cycle 3 Day 1 and Cycle 6 Day 1 only
- R-CHOP administration (This will take approximately 4 hours)
- ME-401 started (given days 1-7 or days 1-4)
    - You will need to keep a drug diary for every dose of ME-401 that is taken. This will include the date, number of ME-401 capsules taken, and the time of the dose.

Cycle 2-6, Day 2

- Pegfilgrastim administration or ONPRO™ wearable device

Cycle 3, Day 15-21

- CT of neck, chest, abdomen, and pelvis, with contrast for response assessment given intravenously (through a vein) and orally (by mouth). Neck CT can be omitted if there is no involvement at baseline.

End of Treatment (EOT) Response Assessment – 8 weeks (+/- 7days) after last treatment

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- We will ask you if you taking any including prescription medications, over the counter (OTC) medications or natural/herbal supplements
- Adverse Event Evaluation
- We will ask about any symptoms you are having
- Blood samples will be collected to see how well your organs are functioning
- Correlative Blood Draw for study purposes
- EKG

- Bone marrow biopsy (may be omitted if screening bone marrow biopsy did not show lymphoma).
- PET and diagnostic CT of neck, chest, abdomen, and pelvis with contrast inserted into your vein and by mouth (see below for more details). This test will help us assess if the treatment worked for your lymphoma.

Follow Up

After completion of the study treatment the participants will be followed for a total of 2 years. The follow up visits will be done at 6, 12, 18, and 24 months after the last cycle of therapy. If you are unable to follow up in person, virtual visits may be used to capture applicable procedures during long-term follow up only. Please discuss this option with your study doctor if you think it will be necessary.

- Physical Examination
- Vital signs
- ECOG performance status
- We will ask about any symptoms you are having
- Blood samples will be collected to see how well your organs are functioning
- CT neck, chest, abdomen and pelvis scan will be done at 6, 12 and 24 months to evaluate if the DLBCL is back or still gone
- *Discontinue Trimethoprim/sulfamethoxazole or Pentamidine by 6 month visit (can be stopped between 2-6 months)
- *Discontinue acyclovir at 6 month visit

Patients whose lymphoma comes back after treatment are not required to come into clinic for follow up. They can be called on the phone to discuss the following:

- Disease status
- We will ask you about any symptoms you are having
- Current lymphoma treatment

During the study the following will be additional research procedures:

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 tests that you will need to have if you take part in this study. You will not be charged for any extra tests. Tests and frequency of tests that are solely associated with this study and are not part of routine medical care are listed as follows:

- Urine test- At screening visit
- Test to check for cytomegalovirus infection (a kind of herpes virus that can cause damage to people with weakened immune systems)- At screening visit, Cycle 1 Day 1 visit of every cycle, EOT visit, and all follow up visits
- Pregnancy test (HCG blood draw) for women of childbearing potential- At Cycle 1 Day 1 visit, if applicable
- Correlative Blood Draw- At screening visit, Cycle 4 Day 1, EOT visit, at 1-year follow-up

visit
- Echocardiogram (EKG)- At Cycle 1 Day 1, Cycle 3 Day 1, Cycle 6 Day 1, and EOT visit

Correlative Tests (Extra Tests)

The tissue collection/analysis and additional blood samples are required in order for you to take part in this study because the research on the sample is an important part of the study.

Extra Tissue Collection/Analysis:

- Tests will be done on the lymphoma biopsy sample that was obtained at diagnosis and at the end of treatment visit. These biopsies are part of your typical care and you will not have new or extra biopsies completed solely for this study.

Correlative Blood Draw:

- Four extra tubes of blood, each containing 10ml (the equivalent of about 8 teaspoons of blood) will be collected at the screening visit, at the end of treatment (EOT) visit, and at the 1-year follow-up visit. Only 2 extra tubes (about 4 teaspoons) of blood will be collected prior to treatment of Cycle 4.

The following applies to all correlative tests completed for this research study. Correlative tests are additional samples of blood and tissue collected only for research purposes:

- All samples collected as part of this research study will be labeled with a study identifier or code that is unique to you and will not be labeled or stored with names or other direct links to your identity. This unique identifier will allow us to link information obtained from your samples and your medical information, but will not allow study personnel, to identify you.
- Results from any testing/analysis on your samples will also be labeled with your unique identifier code and will not include your name or other information that could identify you. The confidentiality of any central computer record will be carefully guarded, and no information by which you may be identified will be released or published.
- Your name will not be used in any reports or publications about the research study. No information that may identify you will be released or published.
- The results from these exploratory tests will be used for research purposes only, and will not be shared with you or used in your care. This research will not change the care you receive from your study doctor, but may be useful to guide the treatment of future patients with the study drugs.
- Neither you nor your health care plan/insurance carrier will be billed for the collection or analysis of the tissue or blood that will be used for this study.

The tissue and blood samples collected in the correlative section may contain genetic testing. The privacy of the research information generated from your DNA (gene) sample will be protected as much as possible. If this information were released to you, your family, or third parties, there could be adverse psychological effects for you or your family members. There could also be undesirable effects on you or your family members' ability to obtain a job or insurance. In order to minimize these risks, every effort will be made to keep all genetic research information obtained from your blood sample confidential. But absolute confidentiality cannot be guaranteed.

The results of the analysis of your DNA done as part of this study will not be given to you. Your DNA (genes), or your cells that can be used to make your DNA, will be stored for research purposes.

Your DNA samples may be used for any scientific purpose involving this project and/or any other project.

At any time, you may ask to have your samples that were collected for research testing be destroyed by contacting the study doctor. If you do this, all of the remaining samples will be destroyed so that no more research can be done. However, any information collected from your samples before your request to destroy them will be kept by the Cleveland Clinic. If you decide to stop participating in the study, but do not request destruction of your samples, Cleveland Clinic may continue to use your samples for this project as well as any other projects.

Genetic Information Nondiscrimination Act (GINA)

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

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

You may have all, some, or none of the known side effects described in the following sections. There is also a risk that other rare or unknown side effects may occur. Your doctors and nurses will check you closely for side effects, and may give you medicines or other treatments to stop or reduce some of these effects. Some side effects may go away soon after the study medication is stopped, but in some cases, side effects may be serious, long lasting, and/or permanent. There is even a chance that a side effect may cause 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.

ME-401 Risks and Side Effects:

- ME-401 is an investigational drug and it has not been combined with chemotherapy. It is not possible to predict all of the risks and unwanted effects that might happen if you take ME-401. The following tables describe the side effects that have been seen in previous patients taking ME-401 and side effects that could be of concern.
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COMMON, SOME MAY BE SERIOUS In 100 people receiving ME-401, more than 10 and up to 100 may have:
• Diarrhea • Nausea (unease and discomfort in the stomach, often with the urge to vomit) • Fatigue (feeling tired) • Neutrophil count decreased (decrease in certain white blood cells that help fight infections) • AST increased • Platelet count decreased (blood cells that control bleeding) • Rash maculopapular (rash with bumps)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ME-401, 1 and up to 10 may have:
• Neutropenia (decrease in certain white blood cells that help fight infections) • Anemia (low number of red blood cells or hemoglobin in the blood) • Abdominal (stomach) pain • Constipation • Stomatitis (mouth sores)

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving ME-401,
1 and up to 10 may have:

- Colitis (inflammation of the colon)
- Gastroesophageal reflux disease (GERD, or heartburn)
- Abdominal distension (swollen abdomen)
- Dyspepsia (indigestion)
- Dry mouth
- Vomiting
- Flatulence (gas)
- Oral pain
- Fever
- Edema peripheral (swelling of hands and lower legs)
- Asthenia (feeling tired, weak)
- Pneumonia
- Upper respiratory tract infection
- Sinusitis (sinus infection)
- Herpes zoster (shingles)
- Conjunctivitis (eye infection)
- Cytomegalovirus infection (CMV)
- ALT increased (liver enzymes)
- Leukopenia (low white blood cell count)
- Blood creatinine increased (a waste product from kidneys, may indicate decreased kidney function)
- Weight decreased
- Blood alkaline phosphatase increased (liver enzyme)
- Lymphocyte count decreased or increased (a type of white blood cell)
- Electrocardiogram qt prolonged (irregular fast heart beat)
- Blood bilirubin increased
- Decreased appetite
- Hyperkalemia (high levels of potassium in the blood)
- Dehydration
- Tumor lysis syndrome (rapid death of cancer cells) within 1 to 2 days after starting treatment, which if not properly treated can cause severe medical complications, including death. You may need to be admitted to the hospital for the prevention or treatment of tumor lysis syndrome
- Arthralgia (joint pain)
- Myalgia (muscle pain)
- Muscle spasms
- Muscular weakness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ME-401, 1 and up to 10 may have:
• Headache • Dizziness • Dysgeusia (abnormal taste) • Insomnia • Acute kidney injury • Cough and/or productive cough • Dyspnea • Nasal congestion (stuffy nose) • Oropharyngeal (throat) pain • Pneumonitis (you will be prescribed a medication to help prevent a possible lung infection) • Upper-airway cough syndrome • Rash • Pruritis • Dermatitis acneiform (skin inflammation) • Dry skin • Drug eruption (skin reaction) • Erythema (redness) • Hypertension (high blood pressure)

A potentially **RARE AND SERIOUS** condition, cardiomyopathy (a condition where the heart muscle can become enlarged and weak and is less able to pump blood through the body. This could potentially lead to heart valve problems, irregular heartbeats, and heart failure) was reported in 1 study participant in a different study.

Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP)

- R-CHOP is standard of care for patients with newly diagnosed DLBCL.

Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) Risks and Side Effects:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP), more than 20 and up to 100 may have:

- Hair loss
- Constipation, nausea, vomiting, loss of appetite
- Sores in mouth
- Infection, especially when white blood cell count is low
- Absence of menstrual period which may decrease the ability to have children
- Blood in urine
- Red colored urine, saliva, or sweat
- Pain or redness at the site of injection or area of previous radiation
- Numbness and tingling of fingers or toes
- Headache, jaw pain and/or muscle pain
- Weakness and difficulty walking
- In children and adolescents: decreased height
- Loss of bone tissue
- Mood swings
- Skin changes, acne
- Swelling of the body, tiredness, bruising
- Swelling of lower legs
- High blood pressure which may cause headaches, dizziness, blurred vision
- Pain in belly
- Increased appetite and weight gain
- Weight gain in the belly, face, back and shoulders

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP),
from 4 to 20 may have:

- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- Damage to the bone which may cause joint pain and loss of motion
- Loss or absence of sperm which may lead to an inability to father children
- Stuffy nose
- Fluid around the heart
- Heart failure or heart attack which may cause shortness of breath, swelling of ankles, cough or tiredness which may occur years after the dose
- Swelling of the body which may cause shortness of breath
- Swelling and redness at the site of the medication injection or area of previous radiation
- Sores in the throat or stomach
- Diarrhea
- Hepatitis (inflammation of liver) which may cause yellow eyes and skin
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Cancer of the bone marrow (leukemia) caused by chemotherapy
- Damage to organs which may cause infection, bleeding, may require transfusions
- Darkening of the nail beds or skin or hands and feet
- Loss of nails
- Anemia which may cause tiredness, or may require transfusion
- Drooping eyelids
- Hoarseness
- Cloudiness of the eye, visual disturbances
- Glaucoma (condition damaging the nerves in the eye)
- Non-healing wound
- Diabetes
- Kidney stones
- Heartburn

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP), 3 or fewer may have:
• Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • A new cancer including cancer of bone marrow (leukemia) caused by chemotherapy • Swelling of the brain which may cause dizziness and confusion • Scarring of the lungs • Infection, especially when white blood cell count is low • Bruising, bleeding • Severe blood infection • Seizure • Bleeding from sores in the stomach • Broken bones

Rituximab Risks and Side Effects

COMMON, SOME MAY BE SERIOUS Side effects that have been seen in patients who have received Rituximab include:
• Fever • Headache • Vomiting • Asthenia (feeling weak and having no energy) • Angioedema (swelling that affects deeper layers in your skin) • Pulmonary infiltrates (substances that linger in the lungs) • Myocardial infarction (heart attack) • Neutropenia (condition in which the number of white blood cells, called neutrophils, is abnormally low) • Chills • Nausea • Rhinitis (nasal inflammation) • Hypotension (low blood pressure) • Hypoxia (a decrease of oxygen reaching body tissues) • Acute respiratory distress syndrome (a severe, life-threatening medical condition characterized by widespread inflammation in the lungs) • Tumor lysis syndrome (Tumor lysis syndrome is caused by rapid killing of tumor cells during treatment. When the tumor cells die, they release their contents into the bloodstream. If cell killing is very rapid, this can affect blood chemistries and the kidneys. In severe cases, this can lead to shutdown of kidney function requiring dialysis) • Marrow hypoplasia (a condition where you bone marrow contains very few blood cells) • Increased risk of infection

Potential Risk or Discomfort from Research Procedures

Blood Samples
Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or get an infection with redness and irritation at the place where the needle enters your vein.

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.

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.

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

ECHO or MUGA Scan
Echocardiograms (ECHOs) and MUGA (multigated acquisition) scans are two tests that evaluate heart function. You and your doctor may choose either one of these to be done during this study. You do not need to have both.

- There are no known risks from an echocardiogram because the test uses only sound waves to evaluate your heart. These high-frequency sound waves have not been shown to have any harmful effects. A microphone is rubbed across the chest on top of a lubricating gel to produce the pictures. Some coldness of the gel and pressure from the microphone might be felt.
- In a MUGA scan an injection of a small amount of a radioactive material is made into a vein and then pictures are made of the heart's pumping action. You may feel some discomfort from the needle inserted into your vein during the MUGA scan. This test involves exposure to radiation. The total amount of radiation that you will receive from one MUGA scan is about 5.18 mSv (millisievert) or 518 mrem (millirem). This is approximately equivalent to a whole body exposure of 630 days (1.726 years) of exposure to natural background radiation. This use involves minimal risk. Persons

participating in this research will have 2 MUGA scans, although some could have 3. You are allowed to choose to have an echocardiogram instead of a MUGA scan if you prefer and you may discuss this with your doctor.

Risks of CT and PET/CT scans

If you take part in this research, you will have one or more medical imaging studies which use radiation. The imaging studies will include a CT scan and PET/CT scans. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. This research gives your body the equivalent of about 2 extra years' worth of this natural 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.

- CT scan of neck, chest, abdomen and pelvis with oral and IV contrast: This is an imaging test that takes several x-rays of your body and then allows us to look for areas of cancer. You will get contrast (a special dye to make the images easier to read) injected in your vein and you will drink contrast. Some people have allergic reactions to the dye but this is rare.
- PET/CT: This is an imaging test like the CT discussed above however instead of contrast, you get a radioactive substance injected into your vein. This is basically sugar that is then taken up by your body. Areas of cancer take up more of this sugar so we can see where the cancer is in your body.

Bone Marrow Aspirate and Biopsy

A bone marrow aspirate is the removal of a small amount of liquid from the soft tissue inside your bone, called the bone marrow. A bone marrow biopsy is when a small amount of the solid bone marrow tissue is collected.

There are also risks associated with taking samples of your bone marrow. Your study doctor will insert a needle into your hip or breast bone to withdraw a sample of fluid containing bone marrow cells. The risks of bone marrow sampling commonly include discomfort, pain, redness, swelling, and/or bruising where the sample is taken from your hip or chest. Sometimes bleeding can occur at the place where the sample is drawn. Fainting and infection can happen, but rarely. Many patients also experience soreness or stiffness in the hips for several days after the procedure.

Though not common, there may be side effects of having a bone marrow aspiration and biopsy such as the following:

- Pressure and/or pain when the needle is inserted, as well as when the bone marrow is removed with a syringe (aspiration)
- Bleeding where the needle is inserted into the skin and tissue over the bone
- Bruising where the needle is inserted into the skin and tissue over the bone
- Pain where the needle is inserted into the skin and tissue over the bone
- Infection where the needle is inserted into the skin and tissue over the bone

Rare side effects may include the following:

- Infection of the bone
- Extensive bleeding at the biopsy site

Reproductive Risks

- You should not get pregnant, breastfeed, or father a baby while in this study. The ME-401 used in this study could be very damaging to an unborn baby. Women must not donate eggs during the study. If you are a woman who can have children (not surgically sterile or post-menopausal), you will have a pregnancy test before you can be in this study. If you are pregnant, you cannot be in this study. Tell your study doctor right away if you suspect that you have become pregnant while in the study. If you become pregnant during this time, you may be asked to withdraw from the study and the study doctor will ask to collect information about the pregnancy and its outcome.

- Women of child-bearing potential and men must agree to use adequate contraception (double barrier method of birth control or abstinence) 2 weeks prior to initiation of treatment, for the duration of study participation and for 3 months after completing treatment. Methods of birth control you can use include intrauterine device (IUD), hormonal (birth control pills, injections, implants), condoms, diaphragm, tubal ligation ("tubes ties"), vasectomy (for males), or complete abstinence. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. Your doctor can talk to you about these and other birth control options.

- Should a woman become pregnant or suspect that she is pregnant while she or her partner is participating in this study, she should inform the treating physician immediately.

- If you are a man, you must agree to refrain from sperm donation for at least 90 days after the last dose of ME-401. If your partner becomes pregnant during this time, the study doctor will ask to collect information about the pregnancy and its outcome. Your partner will be asked to sign a consent form if this occurs.

Unknown Risks

Side effects that are not yet known may also occur. The side effects of study treatment may be a minor inconvenience or could be severe enough to be life-threatening or cause death. You will be watched closely for side effects, and the drug will be stopped if unwanted or serious side effects develop.

There may also be other unknown effects that could harm you (or your embryo or fetus, if you become pregnant or father a child) during the time you take part in the study or after the study has been completed.

Psychological or Social Risks Associated With Loss of Privacy

- Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all the safety measures that we will use, we cannot guarantee that your identity will never become known.
- While neither the public nor the controlled-access databases developed for this project will contain information that is traditionally used to identify you, such as your name, address, telephone number, or Social Security number, people may develop ways in the future that would allow someone to link your medical information in our databases back to you. It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.
- There also may be other privacy risks that we have not foreseen.

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

Taking part in this study may or may not make your health better. There is no proof that combining ME-401 with R-CHOP will be more useful than the usual treatment (R- CHOP) for the type of cancer that you have. Information from this study will help doctors learn more about ME-401 as a treatment for patients with Diffuse Large B- Cell Lymphoma. This information could help future cancer patients.

What happens to the information collected for the research?

Your information will be kept in a coded form and not attached to your name. We will store the code in a secure area and allow only the study team (the researchers, research nurse and other study staff) to have access to this code. We will keep this code in order to maintain a link between your name and the information about you created and collected during this study. The coded information, without your name attached, may be shared with others outside 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 and you may still be treated at your hospital or clinic. Tell your study doctor if you are thinking about stopping or decide to stop. You should talk to the doctor about leaving the study before you decide so that he/she can find out if you are having any side effects from study treatment. Another reason to tell your doctor that you are thinking about stopping is so that he/she can talk to you about any other treatments that could be helpful to you. 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.

If you decide to stop being in this study, you will still be asked to come back to the hospital or clinic for the end of treatment tests as described. You may also be asked to take part in follow-up

phone calls and/or visits. This information is important to make sure that there are no lasting side effects from the study treatment and to see if your cancer got better, stayed the same, or got worse after treatment.

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.

The study doctor may stop you from taking part in this study at any time if he/she thinks it is in your best interest, or if you do not follow the study rules. Your study doctor may decide to stop this study for either medical or other reasons at any time without your consent. Your study doctor will tell you if this happens and will talk to you about other treatment options.

What are my rights in this study?

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.

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, ME-401 will be provided free of charge by the drug supplier MEI Pharma, while you are participating in this study. 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. The section called "during the study the following will be additional research procedures" also refers to study procedures outside of your typical standard of care.

The following tests are outside of your standard treatment and will be paid for by the research study:

- Study drug ME-401
- Urine test- At screening visit
- Test to check for cytomegalovirus infection (a kind of herpes virus that can cause damage to people with weakened immune systems)- At screening visit, Cycle 1 Day 1 visit of every cycle, EOT visit, and all follow up visits
- Pregnancy test (HCG Quantitative blood draw) for women of childbearing potential- At Cycle 1 Day 1 visit, if applicable
- Correlative Blood Draw- At screening visit, Cycle 4 Day 1, and EOT visit
- Echocardiogram (EKG)- At Cycle 1 Day 1, Cycle 3 Day 1, Cycle 6 Day 1, and EOT visit
- Patient Parking for each visit

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, x-rays and/or scans for tumor measurement). You or your health insurance company will be billed for parts of the study that are standard care for your disease. Your health insurance company may or may not pay for these charges. 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.

Cleveland Clinic has not set aside any money to pay you or to pay for your treatment if you suffer a research related injury as a result of being in the study. 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 [redacted].

What else do I need to know?
Your information and samples may be used to create products or to deliver services, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

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, MPH 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:

- Case Comprehensive Cancer Center, its study monitors and representatives
- Case Comprehensive Cancer Center members, collaborators, and licensees
- MEI Pharma, its licensees 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, MPH
Case Comprehensive Cancer Center
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195
[redacted]

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 at [redacted].

Emergency or after-hours contact information
Cleveland Clinic patients should contact the page operator at [redacted] or toll free at [redacted], 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 [redacted].

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