LS138D / 14-003066

The Asymptomatic Follicular Lymphoma (AFL) Trial: A Phase III Study of Single-Agent Rituximab Immunotherapy Versus Zevalin Radioimmunotherapy for Patients With New, Untreated Follicular Lymphoma Who Are Candidates for Observation

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MAYO CLINIC

Name and Clinic Number

Approval Date: **December 9, 2020**
Not to be used after: **July 29, 2021**

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: LS138D: The Asymptomatic Follicular Lymphoma (AFL) Trial: A Phase III Study of Single-Agent Rituximab Immunotherapy versus Zevalin Radioimmunotherapy for Patients with New, Untreated Follicular Lymphoma Who Are Candidates for Observation

IRB#: 14-003066

Principal Investigator: Dr. Witzig and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you get at Mayo Clinic now or in the future if you choose not to participate or discontinue your participation.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.

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CONTACT INFORMATION

You can contact …	At …	If you have questions about …
Principal Investigator: Dr. Thomas Witzig	**Phone:** (507) 284-2511 **Address:** Mayo Clinic 200 First Street SW Rochester, MN 55905	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Mayo Clinic Institutional Review Board (IRB)	**Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681	▪ Rights of a research participant
Research Subject Advocate (The RSA is independent of the Study Team)	**Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu	▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information
Patient Account Services	**Toll Free:** (844) 217-9591	▪ Billing or insurance related to this research study

Other Information:

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

1. Why are you being asked to take part in this research study?

You are being asked to take part in this research study because you have been diagnosed with follicular lymphoma (FL) grade I or II, have undergone staging, and are a candidate for observation. Your doctor has determined that you fall into the category of "asymptomatic follicular lymphoma" (AFL). This means you do not have symptoms of the disease and you do not meet the criteria to receive chemotherapy.

About 128 people will take part in this research study. The plan is to have about 40 people take part in this study at Mayo Clinic.

2. Why is this research study being done?

In this study, we want to compare the effects, good and/or bad, of Zevalin with rituximab on you and your condition to find out which is better. In this study, you will get either the Zevalin regimen which includes two doses of rituximab or rituximab for four doses. You won't get both.

3. Information you should know

Who is Funding the Study?

This research study is being done by the Lymphoma SPORE (Specialized Program of Research Excellence). The Lymphoma SPORE (SPORE) is a group of 2 health care centers, Mayo Clinic Rochester and the University of Iowa that have joined together to research lymphoma and lymphoma treatments. The SPORE is supported by the National Cancer Institute. Mayo Clinic Rochester is the coordinating site for this study.

In addition, Acrotech Biopharma is also providing funding for the study. Acrotech Biopharma will pay the Principal Investigator or the institution to cover costs related to running the study.

4. How long will you be in this research study?

You will be in the study for up to 10 years after you are registered to this study.

5. What will happen to you while you are in this research study?

Before you start treatment, you will begin by completing screening tests that will help to determine if you are able to participate in the study. These tests will include:

- Routine physical exams
- Routine blood tests
- Hepatitis B and C testing
- PET/CT, CT, or MRI scan to document tumor size
- Pregnancy test (only for women able to have children)
- Optional fresh tumor tissue biopsy
- Research blood sample (2½ tablespoons)
- Quality of life (QOL) questionnaire - You will be asked to complete written questionnaires to assess how your cancer affects your daily life and how you are feeling. The questionnaires will be completed in the clinic or doctor's office before any study treatment is given.
- Central review of tissue from the biopsy used to diagnose your AFL
- Optional submission of additional tissue from the biopsy used to diagnose your AFL for research studies

I agree to have additional tissue from the diagnostic biopsy submitted for research studies:

☐ Yes ☐ No Please initial here: _____ Date: _____

If you are eligible for the study, we will assign you by chance (like a coin toss) to the rituximab group or the Zevalin group. You and the Principal Investigator can't choose your study group. You will have an equal chance of being assigned to the one of these groups.

Arm A: Rituximab
If you are assigned to Arm A, you will receive rituximab by intravenous infusion (into a vein in your arm) on days 1, 8, 15, and 22.

Arm B: Rituximab and Zevalin
If you are assigned to Arm B, you will receive rituximab by intravenous infusion (into a vein in your arm) on day 1. You will receive Zevalin and a second dose of rituximab on day 8. You will have routine blood tests done 5, 6 and 7 weeks after treatment with Zevalin.

All Patients

After you complete the treatment, you will be expected to return for the following visits:

3 months after day 1 of treatment
- Adverse event assessment
- Routine blood tests
- QOL questionnaire – The questionnaire will be completed in the clinic or doctor's office before meeting with your doctor.

6 months after day 1 of treatment
- Routine physical exam
- Adverse event assessment
- Routine blood tests
- Bone marrow aspirate and biopsy if your initial biopsy was positive
- PET/CT, CT, or MRI scan
- QOL questionnaire – The questionnaire will be completed in the clinic or doctor's office before meeting with your doctor.
- Research blood sample (2½ tablespoons)

9, 12, 18, 24, 30, 36, 48, and 60 months after day 1 of treatment
- Routine blood tests
- Bone marrow aspirate and biopsy if your initial biopsy was positive
- PET/CT, CT, or MRI scan (months 12, 24, 36, 48, and 60 only)
- QOL questionnaire – The questionnaire will be completed in the clinic or doctor's office before meeting with your doctor.

OPTIONAL FRESH RESEARCH TISSUE BIOPSY

This part of the study is optional. You do not need to take part in this part of the study to be in the treatment part of the study. If you have a tumor that is easy to get to, you may agree to have an optional excisional or tissue core needle biopsy for research purposes. If you have a core needle biopsy, this procedure may be done under CT (X-ray) guidance.

I agree to participate in the optional fresh research tissue biopsy prior to starting treatment:

☐ Yes ☐ No Please initial here: _____ Date: _____

6. What are the possible risks or discomforts from being in this research study?

Rituximab

Likely risks of Rituximab *(events occurring greater than 20% of the time)*

- Fever (Pyrexia)
- Chills or shaking chills (Rigors)
- Low blood lymphocyte count, which could lead to an increased risk of infection
- Feeling sick to your stomach (Nausea)
- Infection
- Infusion related reaction

Less likely risks of Rituximab *(events occurring less than or equal to 20% of the time)*

- Sensation of tongue or throat swelling (Angioedema)
- Cough
- Hives (Urticaria)
- Asthma (Bronchospasm)
- Rash
- Flushing
- Itching sensation (Pruritis)
- Runny nose (Rhinitis)
- Shortness of breath (Dyspena)
- Headache
- Throat irritation (Pharyngitis)
- Throwing up (Vomiting)

- Joint pain (Arthralgia)
- Stiff or aching muscles (Myalgia)
- Sensation of lightheadedness or vertigo (Dizziness)
- Abdominal pain
- Lowered white blood cell count that could lead to an infection (Leukopenia/Neutropenia)
- Low platelet count, which could result in an increased risk of bleeding (Thrombocytopenia)
- Low blood pressure (Hypotension)
- Serious infections with bacteria, fungus or viruses including infection in the bloodstream (Sepsis)
- Impairment in the ability to generate an immune response to a vaccine
- High blood sugar (Hyperglycemia or diabetes)
- Back pain
- Increased levels of phosphorus in the blood (Hyperphosphatemia)
- Increased uric acid in the blood (Hyperuricemia)
- Increased potassium levels in the blood (Hyperkalemia)
- Loose stool (Diarrhea)
- Excessive sweating or night sweats
- Inflammation of the sinuses (Sinusitis)
- Low hemoglobin count (anemia), which could lead to fatigue and shortness of breath
- Swelling of the arms or legs (Edema)
- High blood pressure (Hypertension)
- Anxiety
- Inflammation of the lungs
- Severe allergic reaction (Anaphylactic event)
- Rapid, irregular heart beat
- Pain
- Abnormal physical weakness or lack of energy (tiredness)

Rare but serious risks of Rituximab *(events occurring less than 2-3% of the time)*

- Reduced amount of oxygen supplied to the tissue (Hypoxia) due to a reaction to rituximab
- Difficulty breathing on your own with a need to be put on a ventilator (Acute Respiratory distress)
- Low amount of calcium in the blood that can cause muscle cramps and stomach cramps (Hypocalcemia)
- Worsening of heart problems if you already have a heart condition

- Severe, life threatening skin rash (Toxic epidermal necrolysis, Paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis)
- Reactivation of viral infections with bacteria, fungus or viruses - this can include hepatitis B or C reactivation, herpes simplex virus, the shingles virus (varicella zoster), cytomegalovirus, and the JC virus. This could lead to serious hepatitis, liver failure, and death.
- In very, very rare cases the JC virus has been reactivated which produces a condition called progressive multifocal leukoencephalopathy (PML). PML affects the brain and can lead to memory difficulties and death.
- Kidney damage due to tumor lysis syndrome—this is a situation when the tumor or lymphocytes are destroyed rapidly by the rituximab causing a breakup of tumor cells which can lead to kidney damage
- Obstruction of the bowel and bowel rupture (gastrointestinal obstruction and perforation). This could lead to death because of infection from the bowel contents spilling into the abdomen.
- Chest pain/Heart attack (myocardial ischemia)
- Loss of blood pressure when standing up
- Painful mouth sores (Mucocutaneous reaction)

Zevalin

Likely risks of Zevalin *(events that occur > 20%)*

- Low white blood cell count (can increase risk for infection)
- Low platelet cell count (can increase risk for bleeding and may require transfusion)
- Low red blood cell count [anemia] (can cause fatigue and may require transfusion)
- Infection (for example, infections of the sinuses, lungs or respiratory tract, urinary system or bladder, blood stream, skin)
- Chills
- Nausea (feeling sick to the stomach)
- Asthenia (weakness, lack of energy and strength)

Less likely risks of Zevalin *(events that occur less ≤ 20%)*

- Vomiting (throwing up)
- Abdominal pain or swelling
- Pain or aches in the bones or muscles (arthralgia or myalgia)
- Diarrhea or constipation (loose stools or difficulty passing stools)
- Loss of appetite or weight (Anorexia)
- Fever
- Headache

- Throat irritation
- Back Pain
- Flushing (sweating-feeling hot in the face)
- Low blood pressure (Hypotension)
- Dizziness
- Increased cough
- Shortness of breath (Dyspnea)
- Chest discomfort
- Difficulty falling or staying asleep (Insomnia)
- Rash or itchiness (Pruritus)
- Hives
- Inflammation of the nasal mucous membranes (Rhinitis)
- Spasm of the muscle wall that lines the airways (breathing tubes) of the lung as in asthma. (Bronchospasm). This may cause difficulty breathing.
- Bruising (Ecchymosis)
- Abnormal build up of fluid in ankles, feet, and legs. (Edema)
- Swelling in head, neck, face, lips, floor of the mouth, tongue, and larynx (Angioedema) which can make it difficult to breathe.
- Dyspepsia (heartburn)

Rare but serious risks of Zevalin *(events that occur less than 2-3% of time)*

- Allergic reaction, which can be life threatening
- Fast heart rate over 100 beats per minute (Tachycardia)
- Bleeding in the stomach or bowel
- Fluid on the lungs
- Liver test abnormalities

The following side effects have been reported for patients taking part in other Zevalin research studies. It is not known if these side effects were related to the Zevalin:

- Anxiety
- Blood clots
- Angina or other heart problems
- Liver failure
- Small red or purple spots (Petechia)
- Nosebleeds
- Bleeding gums
- Bone marrow failure (myelodysplasia) or acute leukemia

Pregnancy and Birth Control:
Rituximab can potentially cause harm to the unborn fetus when given to pregnant woman Women of child bearing age should use effective contraceptive methods during and for 12 months after treatment with rituximab. The use of rituximab during breast feeding has not been studied in humans and there are no studies of rituximab in human breast milk. Rituximab is detected in the milk of monkeys. It is recommended that women discuss the risks and benefits with their physicians to weigh the risks vs benefits. .

Procedure Risks:
Blood Samples: Routine needle sticks for blood samples may cause pain, bruising or infection at the site where the needle enters your body. It is also possible that you may feel lightheaded or faint. Please tell the study doctor or study staff if you do not feel well after having your blood drawn.

Optional Tumor Tissue Biopsy: If tumor tissue is a lump in the skin or in a superficial lymph node, you may undergo a biopsy called an excisional biopsy, in which the node will be removed for further evaluation. In an excisional biopsy, a small incision is made in the skin, and the lump or lymph node is removed (excised). In some cases, biopsies of internal tumor tissue may also be performed with a special needle, called a core biopsy needle. When the core biopsy needle is inserted into an area that contains tumor tissue it permits the doctor to remove a small piece of that tissue that can later be evaluated under a microscope. A CT scan will help the doctor locate the internal tumor tissue, avoid vital structures like blood vessels, and place the needle into the tumor tissue. Therefore, unless the tumor tissue is a lump in the skin or in a superficial lymph node just under the skin, the tumor biopsies in this study may be done under CT scan guidance. You will be exposed to radiation if CT guidance is needed for the biopsy procedure. The amount of radiation you will receive has a low risk of harmful effects. The risks of the tumor biopsy procedure are mainly pain, bleeding, and infection.

Your doctor will discuss the risks of the PET/CT scans, CT scans, MRI scans, and bone marrow aspirate and biopsy as these tests and procedures are part of your standard clinical care.

Many side effects go away shortly after the Zevalin or rituximab are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death. Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

Additional costs:
Taking part in this research study may lead to added costs to you. In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research

study. You should check with your insurance company to see what services will be covered and what you will be responsible to pay. If you are on Arm A and your insurance plan will not cover rituximab, your study doctor may be able to give you a medication in place of rituximab, called a rituximab biosimilar substitute. This medication is safe, is very similar to rituximab, and can be used instead of rituximab. Talk to your study doctor about this.

7. Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time:

- if it is in your best interest,
- if you don't follow the study procedures,
- if you have unacceptable toxicities,
- if the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

8. What if you are injured from your participation in this research study?

Where to get help:
If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries:
Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance.

9. What are the possible benefits from being in this research study?

This study may not make your health better. However, your disease may go into remission and it may be awhile before you need chemotherapy treatment. We also hope that information learned from this study may help others in the future.

10. What alternative do you have if you choose not to participate in this research study?

You don't have to be in this study to receive treatment for your condition. Your other choices may include observation without treatment, rituximab immunotherapy, or Zevalin radioimmunotherapy. Talk to the Principal Investigator or your doctor if you have any questions about any of these treatments or procedures.

11. What tests or procedures will you need to pay for if you take part in this research study?

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Central review of your tissue to confirm diagnosis
- Research tests done on your blood and tissue samples
- Excisional or lymph node biopsy if you agree to this optional procedure

However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care. These tests and procedures are:

- Rituximab (or a rituximab biosimilar substitute) and Zevalin
- Routine exams and blood tests

- Pregnancy test for women of childbearing potential
- Bone marrow aspirate and biopsy
- PET/CT, CT, or MRI scans
- Hepatitis B and C tests

You will also be responsible for any co-payments and deductibles.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the "Contact Information" section of this form.

12. Will you be paid for taking part in this research study?

You won't be paid for taking part in this study.

13. What will happen to your samples?

We would like to keep your sample for future research. You can still take part in this current study even if you don't want your sample used for future research. If you agree to give your sample, it will be the property of Mayo Clinic.

Other researchers at Mayo Clinic who aren't involved with this study may ask to use your sample for future research. Researchers at other institutions may also ask for a part of your sample for future studies. Your sample will be sent to researchers in a coded format, which protects your identity.

Some future studies may examine your DNA, which is the genetic information you inherited from your parents (genetic testing). The Principal Investigator may contact you if there are findings which may be useful for your health care. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

Please read the following statements and mark your choices:

1. I permit my sample to be stored and used in future research of lymphoma by the Lymphoma SPORE:

☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my sample to be stored and used in future research by the Lymphoma SPORE to learn about, prevent, or treat any other health problems:

☐ Yes ☐ No Please initial here: _____Date: _____

3. I permit the Lymphoma SPORE to give my sample to researchers at other institutions:

☐ Yes ☐ No Please initial here: _____Date: _____

There is a very small chance that some commercial value may result from the use of your donated sample. If that happens, you won't be offered a share in any profits.

You may request to have your sample destroyed by writing to the Principal Investigator. The address is found in the "Contact Information" section of this consent form.

Because we cannot predict how your sample will be used in the future, we cannot promise that samples can be retrieved and destroyed.

14. How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study. For the purposes of your participation in this study and the protection of your identity, your study doctor will assign you a unique code, such as a series of numbers and/or letters. The study doctor will record the study data collected from you in a report form that uses your assigned code, not your name. This is to protect your study data by making it anonymous for most study purposes.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission.

Health information may be collected about you from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

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

- To do the research.
- To report 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.

Who may use or share your health information?

- Mayo Clinic research staff involved in this study.
- Acrotech Biopharma

With whom may your health information be shared?

- The Mayo Clinic Institutional Review Board that oversees the research.
- Other Mayo Clinic physicians involved in your clinical care.
- Researchers involved in this study at other institutions.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- The sponsor(s) of this study and the people or groups it hires to help perform this research.
- A group that oversees the data (study information) and safety of this research.

In addition, individuals involved in study oversight and <u>not</u> employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you. However, the individuals will not be allowed to record, print, or copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with Mayo Clinic.

You can cancel your permission to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate at: researchsubjectadvocate@mayo.edu

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission lasts until the end of this study, unless you cancel it. Because research is an ongoing process, we cannot give you an exact date when the study will end.

MAYO CLINIC

Name and Clinic Number

Approval Date: **December 9, 2020**
Not to be used after: **July 29, 2021**

ENROLLMENT AND PERMISSION SIGNATURES

Your signature documents your permission to take part in this research.

	/ /	: AM/PM
Printed Name	Date	Time

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

	/ /	: AM/PM
Printed Name	Date	Time

Signature