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Study Informed Consent Form

Title:	ILyAD (Indolent Lymphoma And Vitamin D): A phase III double blind, prospective randomized trial to evaluate the supplemental effect of vitamin D (cholecalciferol) on progression-free survival in patients with low tumor-burden indolent non-Hodgkin lymphoma treated with rituximab therapy
Sponsor:	National Institutes of Health, National Cancer Institute
Principal Investigator:	Jonathan W. Friedberg, MD, MMSc; University of Rochester
Clinical Trial Number:	NCT03078855
Final Consent Version:	10FEB2021

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CONSENT FORM

ILyAD (Indolent Lymphoma And Vitamin D):
A phase III double blind, prospective randomized trial to evaluate the supplemental effect of vitamin D (cholecalciferol) on progression-free survival in patients with low tumor-burden indolent non-Hodgkin lymphoma treated with rituximab therapy

Principal Investigator: Jonathan W. Friedberg, MD

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

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

- Being in this study is voluntary – it is your choice.
- If you join this study, you can change your mind and stop at any time.
- If you choose not to take part, your routine medical care, will not be changed in any way.
- There are risks from participating and you should understand what these mean to you.

Introduction
You are being asked to take part in this study because you have been diagnosed with indolent (slow growing) non-Hodgkin lymphoma that has not been previously treated.

This study is being conducted by Dr. Jonathan Friedberg of the University of Rochester's Wilmot Cancer Institute.

Purpose of Study
Despite strong evidence suggesting that vitamin D deficiency is associated with undesirable outcomes in patients with numerous cancers, there has never been a thorough study of vitamin D treatment in subjects undergoing treatment for cancer. The purpose of this study is to evaluate whether modification of vitamin D levels in the blood, through supplementation, can improve outcomes.

Description of Study Procedures

You will be treated for your indolent lymphoma with rituximab through an IV infusion or an injection underneath your skin every week for 4 weeks. This is the standard treatment for your type of cancer. You will also undergo routine CT scans and blood testing to see how well you are responding to treatment as part of your standard care.

If you decide to take part in this study and are eligible, in addition to standard treatment, you will be randomized (like flipping a coin) to receive an oral daily dose of either 2,000 IU vitamin D (also called cholecalciferol) supplementation or placebo. A placebo is a substance that looks like the study supplement but doesn't include any active ingredients. Each daily dose will be 1 capsule that you will be asked to swallow whole. The randomization will be 2:1. A 2:1 randomization means for every three people enrolled on the study, two people will receive vitamin D and one person will receive placebo. This study is conducted in a double blind fashion, which means neither you nor your doctor will know which treatment group you are in.

Once you start rituximab treatment, you will begin treatment with oral vitamin D or placebo daily. After treatment with rituximab is completed, you will remain on study to continue with daily vitamin D or placebo for three years or until disease progression. You will be asked to complete study visits every 3 months for the duration of the study. A PET/CT scan will be performed at Week 13 to determine your response to rituximab. If your lymphoma has not responded to treatment you will stop taking vitamin D or placebo and will discontinue study activities.

Four total study blood samples (of 4 mL; approximately 0.8 teaspoons each) will be collected at the following time points for vitamin D evaluation: baseline, 13 weeks, 12 months and at 36 months or end of treatment. Your parathyroid levels will also be checked at baseline with a blood test (of 4 mL). We will also collect a research saliva sample at baseline. Blood and saliva contain genes, which we will use to help us study how small variations in genes might help the body process Vitamin D, and whether these small variations affect outcomes of lymphoma. We will aslo collect available left over biopsy samples from a subset of subjects to study the relationship between vitamin D and immune cells within lymphoma biopsies. We will measure the expression of genes in the biopsy samples to determine how many and what type of immune cells are present.

Number of Subjects

Approximately 210 subjects from 7 study centers across the country will take part in this study. Locally, about 90 will participate at the University of Rochester.

Duration of the Study

Your participation in the study will last approximately 3 years.

Risks of Participation

The possible risks of this study, while unlikely to occur, include the following:

- Allergic reaction to cholecalciferol or placebo (very rare). Symptoms of allergic reaction include:
  - Rash
  - Swelling, particularly of face, tongue or throat
  - Dizziness
  - Trouble breathing

- Hypercalcemia associated with vitamin D (cholecalciferol) supplementation. Symptoms of hypercalcemia include:
  - Nausea
  - Vomiting
  - Constipation
  - Decreased appetite
  - Increased thirst
  - Increased urination
  - Mental or mood changes
  - Fatigue (tiredness)
  - Muscle or bone pain
  - Ringing in ears
  - Vertigo (dizziness)
  - Unsteady gait
  - EKG changes (changes in the electrical conduction of your heart)
  - Kidney stones

- Risks associated with blood draws include: lightheadedness, bruising at the site of needle stick, and infection.

Non-Physical Risks

A saliva sample will be collected as part of this study to analyze your genetic information. Genes are made up of DNA, which will be isolated from your saliva to study small variations in the genes that process vitamin D and whether these small variations affect lymphoma outcome. Your sample will be labeled with your study number only and will be kept in a locked lab at the University of Rochester. You will not receive the results of this genetic testing, nor will the results be entered into your medical record.

We will select a subset of patients with available left over diagnostic tissue biopsy samples to study the relationship between vitamin D and immune cells within the lymphoma tissue. If your sample is selected we will measure the expression of genes related to immune cells and compare the results to your vitamin D levels at the beginning of the study. Approximately 12 samples will be selected for additional studies to determine how the expression of these genes change in different locations within the biopsy sample. This technique known as spatial genomics will help us to understand how the lymphoma cells interact with immune cells and if vitamin D levels influence these interactions.

The National Institutes of Health (NIH), who is funding this study, requests that we share the genetic data created as part of this study with other researchers. This is known as Genomic Data Sharing. This information will be stored and shared through an NIH controlled access data repository. This means that data is only available to researchers and companies who apply to the NIH. The NIH will review data requests for good scientific design, methods to protect data, and methods to ensure data will be used for the approved purpose. We will not know what types of health-related research will be done with the data that are shared.

The goal of collecting this information is to allow researchers to look for genetic connections that:

- may increase the likelihood of getting a certain disease (such as asthma, cancer, diabetes, heart disease or mental illness) or a condition (such as high blood pressure)
- may affect the progress of a certain disease or condition
- may affect treatments (for example, medicines) that work for certain diseases in some people, but not in others.

We will remove direct identifiers (such as your name) and assign a random code to your information before sending it to the repository. NIH will never get this code or the identifiers we removed.

We would like to use this data for studies going on right now as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding lymphoma, or other diseases or conditions. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your data you give up any property rights you may have in the data. You will be given the option at the end of this consent form to decide if you would like your de-identified information shared and/or used for future research.

What are the risks to your privacy?
There may be risks to your privacy and the privacy of your relatives from storing your information in the repository. Although the NIH takes measures to protect privacy, we do not know how likely it is that your identity could become re-connected with your genetic and health information. We believe the chance that this will happen is very small, but we cannot make guarantees. If your genetic information were re-identified, personal information about you, your health, and your risk of disease could become known to others. This could present unknown risks. Your privacy and the confidentiality of your data are very important to us; we will make every effort to protect them.

Current federal law called the Genetic Information Non-Discrimination Act, or GINA, will help protect you from genetic discrimination in health insurance and employment. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. To learn more about the GINA Law, please ask the study staff or check the internet.

Are there benefits to sharing your genetic information?
There is no benefit to you from placing your genetic information in the repository.

No blood, saliva or biopsy samples will be stored or banked for future research. Any remaining samples will be destroyed at the end of the study.

Benefits of Participation
You might not benefit from being in this research study.

The potential benefit to you from being in this study might be that if you are vitamin D deficient at the time of study entry, and you are randomized to receive vitamin D supplementation, your vitamin D levels may return to normal at the dose of vitamin D provided.

New Study Findings
If we discover anything that might make you change your mind about continuing in the study, we will let you know.

Alternatives to Participation
You are eligible for standard of care treatment regardless of whether you choose to participate in this study. Standard of care treatment may include observation without therapy, or single agent rituximab treatment, as determined by you and your doctor.

Sponsor Support
The University of Rochester is receiving payment from the National Institutes of Health (NIH) for conducting this research study.

Costs
This study will provide the study agent (vitamin D or placebo) free of charge while you are participating in this study. Tests and procedures that are required only for the study, that are not a part of your regular medical care, will also be provided at no charge. Research testing on this study includes 4 blood draws to check your vitamin D levels, the baseline test of your parathyroid hormone levels, and a saliva sample for gene analysis.

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

- Routine clinic visits with your doctor or nurse practitioner
- Tests (Including but not limited to routine items such as: laboratory blood tests, CT, PET/CT, and/or FDG/PET scans, X-rays, lung function, or cardiac testing.)

- Procedures (Including but not limited to routine items such as: bone marrow biopsies and/or aspirates, other tumor biopsies)
- Medications: other standard medications to treat your cancer. This can include other chemotherapies or non-chemotherapy medications used to treat your cancer, and/or medications to treat or prevent side-effects.

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

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

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

Circumstances for Dismissal
You may be withdrawn from the study if:
- You do not keep appointments for study visits or if you cannot complete study activities.
- The calcium level in your blood becomes too high.
- Your disease becomes worse or if your doctor feels that staying in the study is harmful to your health.

Early Termination
If you end your participation in the study early, any remaining study supplements or placebo will be collected and destroyed.

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

If your research injury is paid for by the University, we will collect your name, date of birth, gender, and Medicare Health Insurance Claim Number or Social Security Number to determine your Medicare status. This information will be used only in accordance with the law. If you are a Medicare beneficiary, information about the study you are in, and

any payments made related to your injury, will be reported to the Centers for Medicare & Medicaid Services (CMS), in accordance with CMS requirements. This information will not be used for any other purpose.

University Of Rochester Statement On Access To Information About Your Study Participation In Your Electronic Health Record

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

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

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

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes

The University of Rochester makes every effort to keep the information collected from you private. In order to do so, we will ensure that only approved research staff have access to your research data. Sometimes, however, researchers need to share information that may identify you with people that work for the University, regulators or the study sponsor.

To help us further protect your privacy, the investigators have a Certificate of Confidentiality from the Department of Health and Human Services (DHHS).

With this Certificate, the investigators cannot be forced (for example, by court subpoena) to disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, other proceedings, or be used as evidence. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes, or to other government agencies related to communicable diseases.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your consent to receive research information, then the investigator may not use the

Certificate to withhold that information. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

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

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

- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Past and present medical records related to the study
- Results of medical tests

Who may use and give out information about you?

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

Your information may be given to:

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

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

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

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

What if I decide not to give permission to use and give out my health information?

- Then you will not be able to be in this research study.

May I review or copy my information?

- Yes, but only after the research is over.

How long will this permission be valid?

- This permission will last indefinitely.

May I cancel my permission to use and disclose information?

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

May I withdraw from the study?

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

Is my health information protected after it has been given to others?

- No. There is a risk that your information will be given to others without your permission.

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

Contact Persons

For more information concerning this research or if you feel that your participation has resulted in any research related injury, emotional or physical discomfort, please contact**:** Dr Jonathan Friedberg at (585) 275-5863 (24 hours).

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

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

Voluntary Participation

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

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SIGNATURE/DATES

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

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

Consent To Future Use and Sharing of Information

May we use your genomic and health information for future studies?

Yes _____ No _____

May we share your de-identified genomic data and health information with other researchers?

Yes _____ No _____

Subject Consent

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

_____

Subject Name (Printed by Subject)

_____ _____

Signature of Subject Date

Person Obtaining Consent

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

information. I have given the subject adequate opportunity to read the consent before signing.

_____
Name and Title (Print)

_____ _____
Signature of Person Obtaining Consent Date