Study Protocol

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
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Research Protocol

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

National Clinical Trial Number: NCT03078855

Funded by: National Institutes of Health

Principal Investigator: Jonathan W. Friedberg MD, University of Rochester

Co-Investigators: Jonathon Cohen MD, Emory University
Brad Kahl MD, Washington University
John P. Leonard MD, Weill Cornell
Loretta Nastoupil MD, MD Anderson
Izidore Lossos MD, University of Miami
Brian Link, MD, University of Iowa

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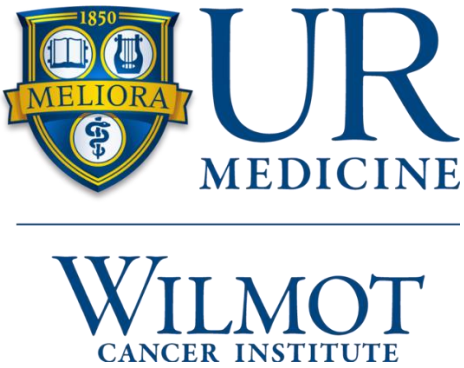

Summary of Changes for Amendment 5

Section	Change
General	- Co-Investigators and study sites updated. - Administrative edits
2.4. End of Treatment (EOT)	- Added systemic treatment for new cancer
5.1. Treatment Dosage and Administration	- Use of approved rituximab biosimilar is permitted.
5.2. Study Procedures and Schedule	- Allowance of telemedicine visits and shipping study drug directly to subjects. - Expanded windows for annual imaging.
5.6. Data & Specimen Banking for Future Research Use	- Tumor biopsy added to NIH Genomic Data Sharing description.
5.7. Genetic/Genomic Research Activities	- New correlative project studying gene expression of tumor infiltrating immune cells described.
9.3. Recording Adverse Events	- Clarification that only clinically significant laboratory abnormalities require reporting.
10.2. Protection Against Risks	- Tumor samples for gene expression added
13.2. Planned Statistical Analysis	- Statistical plan for the correlative gene expression project added.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SUMMARY

Title: ILyAD: 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.

Objectives:
The primary objective of the study is:

Complete a double-blind placebo-controlled randomized trial to evaluate if vitamin D supplementation with oral cholecalciferol 2000 IU daily for three years improves the progression-free survival of patients with indolent lymphoma treated with single agent rituximab.

The secondary objectives of the study are:

- Identify if baseline and restaging Vitamin D levels predict subgroups of patients with indolent lymphoma for whom 2000 IU oral cholecalciferol daily is particularly effective, or particularly ineffective.
- Using whole exome sequencing, determine whether key vitamin D-related germline variations are critical determinants of outcome in the context of cholecalciferol supplementation for patients with indolent lymphoma.

Study Population:

Male and Female, ≥ 18 years of age, with biopsy proven indolent NHL with one of the following histologies: Follicular, SLL, Marginal Zone, MALT. See full inclusion/exclusion criteria in section 3. 2.

Number of Subjects:

210

Description of Study Intervention:

- Arm A: rituximab (weekly x 4) + cholecalciferol (vitamin D3) 2,000 IU daily for 3 years.
- Arm B: rituximab (weekly x 4) + placebo daily for 3 years.

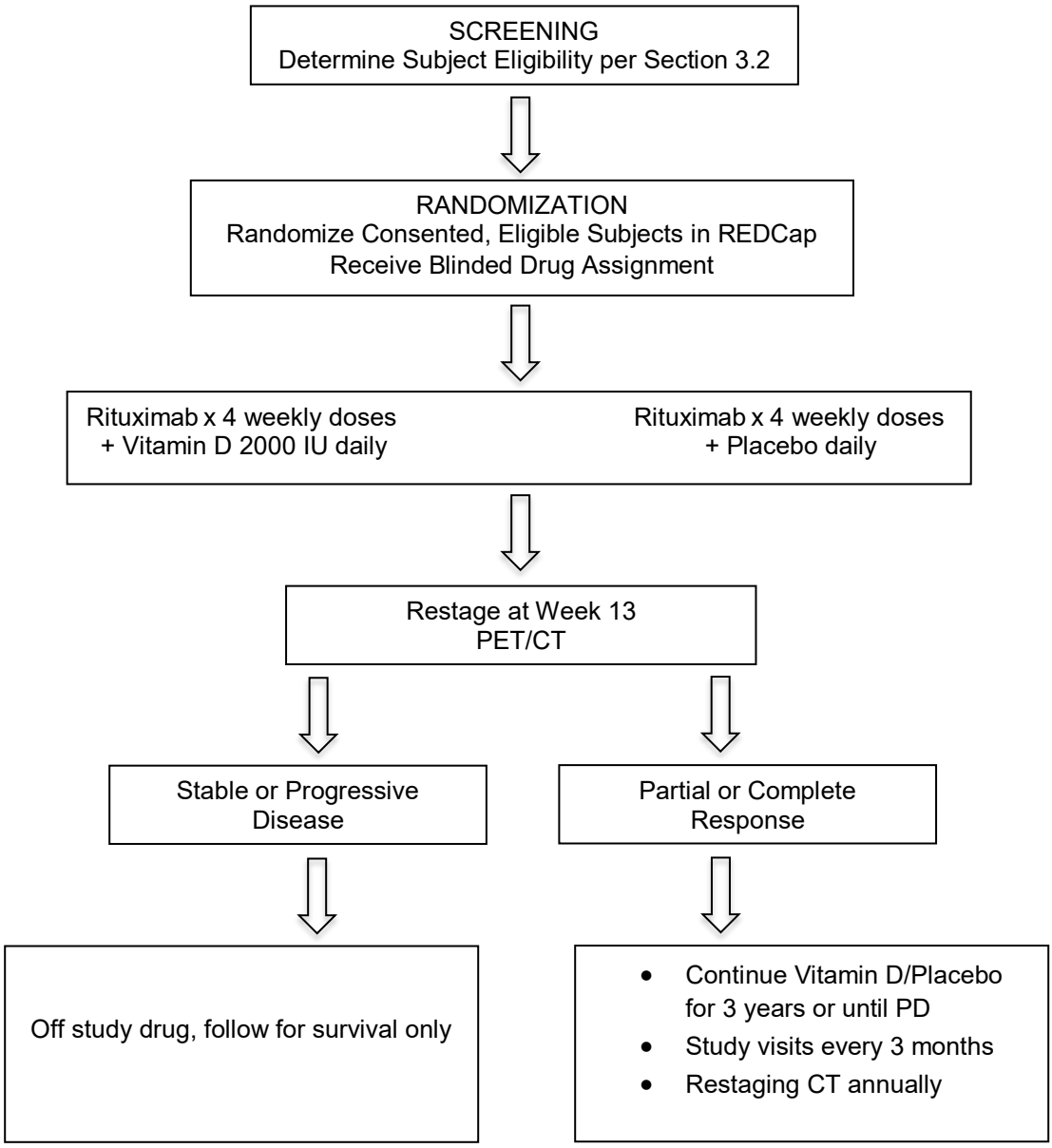
Study Duration:

Approximately 5 years

Participant Duration:

Approximately 3 years

STUDY SCHEMA



1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Purpose of the study

Complete a double-blind, placebo-controlled, randomized trial evaluating if vitamin D supplementation with 2000IU oral cholecalciferol tablets daily for three years improves the progression-free survival of patients with indolent lymphoma treated with single agent rituximab. Completion of these aims will definitively establish whether supplementation with vitamin D improves outcomes in patients with indolent lymphoma treated with rituximab, and, through subgroup analyses, provide insight on mechanisms of vitamin D in this setting. If effective, this will result in a novel, inexpensive, well-tolerated treatment option for patients.

1.2. Background

Follicular lymphoma is the second most common subtype of non-Hodgkin lymphoma, and the most prevalent lymphoma in the United States. Though outcomes have improved substantially in the modern therapeutic era, this disease is still characterized by a generally incurable clinical course.[1,2] While follicular lymphoma (FL) prognosis is known to be influenced by clinical characteristics and age, modifiable prognostic and predictive factors for this disease in the modern treatment era have been difficult to elucidate. Other less common indolent non-Hodgkin lymphomas include marginal zone and small lymphocytic lymphomas, these often present in a similar fashion to follicular lymphoma, are treated in a similar way, and have similar outcomes.[3,4]

Treatment of indolent lymphoma is generally individualized, and is based on both patient and disease factors at presentation. The most common presentation of indolent lymphomas in the United States is “low tumor burden” disease, defined as asymptomatic disease, non-bulky lymphadenopathy, and no cytopenias, which is the subject of this study. Although patients with low tumor burden disease may be observed for a period of time without treatment, two recent large randomized trials have suggested single agent rituximab is an attractive therapeutic option for these patients, and this approach is supported by expert opinion and consensus guidelines.[5-7] In a registry study conducted in the United States between 2004 and 2007, single agent rituximab was frequently utilized for patients with low tumor burden follicular lymphoma.[8] A randomized trial from the United Kingdom compared early administration of rituximab to observation, and follow-up to date demonstrates significantly improved progression-free survival, and longer time to chemotherapy initiation for the patients treated with rituximab.[9] A recently published United States Intergroup trial (“RESORT” trial) enrolled patients with low tumor burden follicular and other indolent lymphomas, and demonstrated the safety and efficacy of 4 weekly doses of single agent rituximab, with approximately 40% of patients responding to treatment and then remaining progression-free after 3 years.[10,11] This strategy of single agent rituximab administered weekly x 4 has also been shown to be cost-effective in this setting.[12]

Since a link between solar radiation, vitamin D production, and decreased colon cancer mortality was established in the 1980s,[13] animal and human research has been ongoing to investigate the association between vitamin D status and many cancers, including prostate, colon, lung, pancreatic, endometrial, breast, and even skin cancer.[14,15] Obtained mostly through sun exposure, but also available from food sources and dietary supplements[16], vitamin D in humans is metabolized in the liver to 25-hydroxyvitamin D (25(OH)D), and further metabolized in the kidney to its active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).[17] However, there is evidence that many cell types, including immune cells, also express both the 1-α-hydroxylase needed to activate vitamin D and the nuclear vitamin D receptor (VDR)

to which 1,25$(OH)_2$D binds.[17,18] This extra-renal activation of 25(OH)D and binding of the VDR by 1,25$(OH)_2$D leads to transcriptional regulation of hundreds of downstream target genes containing the vitamin D response elements (VDREs)[19], and results in autocrine and paracrine effects biologically relevant to both cancer prevention and slowed progression of existing tumors, including regulation of cell proliferation and induction of apoptosis and differentiation.[17]

A variety of malignant cell types are known to express the VDR[17], and recent published evidence supports a survival benefit in patients with higher vitamin D levels at diagnosis in several malignancies, including melanoma[20], aggressive prostate cancer[21-23], colorectal cancer[24,25], and breast cancer;[26,27] prospective nonrandomized trials evaluating the use of vitamin D in the treatment of advanced prostate cancer, metastatic breast cancer, and colorectal cancer are ongoing.[15] The importance of prospective studies evaluating benefit of vitamin D supplementation in the setting of cancer has been highlighted as a research priority.[28] With regard to lymphoma specifically, several recent studies suggest that increased sun exposure (our major source of vitamin D) is protective against lymphoma, though the literature to date is thus far weak or null with regard to an association between vitamin D status and risk of developing lymphoma.[29] However, evidence of a biologic effect of 1,25(OH)D on lymphoma prognosis has been demonstrated in the laboratory, with observed promotion of differentiation and antiproliferative effects on lymphoma cell lines *in vitro.* [30,31] Season of diagnosis has been demonstrated to be associated with overall survival in patients with diffuse large B-cell lymphoma in Sweden, with improved overall survivals in patients diagnosed in the summer, controlled for age, stage, performance status, extranodal sites, and year of diagnosis, possibly secondary to higher vitamin D level during the summer months.[32]

Moreover, survival benefit with vitamin D sufficiency among patients with newly diagnosed diffuse large B-cell lymphoma (DLCBL)[33,34] and CLL[35] has been recently reported. In a German clinical trial of rituximab and standard chemotherapy of patients with DLBCL, patients with vitamin D deficiency, defined as </= 8 ng/mL and sufficient vitamin D levels more than 8 ng/mL treated with rituximab had 3-year event-free survival (EFS) of 59% and 79% and 3-year overall survival (OS) of 70% and 82%, respectively. These differences were significant in a multivariable analysis adjusting for standard risk factors with a hazard ratio (HR) of 2.1 (P = .008) for event-free survival and 1.9 (P = .040) for OS, and were validated in an independent group of patients.[36] Similarly, in a retrospective analysis of almost 1000 patients treated at Mayo clinic with aggressive lymphomas, after adjusting for known prognostic factors and treatment, 25(OH)D insufficient patients (defined as </=25 ng/ml) with DLBCL had inferior event-free survival (HR 1.41) and OS (HR 1.99).[37] Furthermore, in patients at Mayo clinic with chronic lymphocytic leukemia, another indolent B-cell lymphoproliferative disorder, with a median follow-up of 3 years, time to treatment initiation (HR 1.66; P = .005) and OS (HR 2.39; P = .01) were shorter for 25(OH)D-insufficient patients using yet another threshold to define insufficiency. In their validation cohort, after a median follow-up of 9.9 years, time to treatment (HR 1.59; P = .05) and OS (HR 1.63; P = .06) were again shorter for 25(OH)D-insufficient patients.[38]

There are likely pleotropic mechanisms to explain these associations between low vitamin D levels and inferior outcomes of lymphoma. Vitamin D analogs have been shown to display concentration and time-dependent anti-proliferative actions on both normal B-cells and aggressive lymphoma cell lines in vitro.[39] However, unlike the case in most solid tumors, expression of the VDR is largely absent on lymphoma cell lines, and in clinical samples of lymphomas, particularly indolent lymphomas.[31,40] Indolent lymphoma in general, and follicular lymphoma in particular are challenging diseases to study in the laboratory given lack of cell

lines, and inadequate murine models that accurately replicate the human disease.[41] Gene expression profiling studies have demonstrated the importance of immune-based signatures in the lymph node microenvironment on prognosis in follicular lymphoma[42], and it is therefore likely that micro environmental effects play a disproportionate role in the association between vitamin D and outcomes of lymphoma.

In the setting of diffuse large B-cell lymphoma, the observed association between vitamin D and outcome is strongest in patients treated with rituximab, which is the current standard treatment along with CHOP-based chemotherapy. Antibody-dependent cell-mediated cytotoxicity (ADCC) is the major mechanism of rituximab action in patients with follicular lymphoma.[43] Using an LDH release assay with rituximab as the antibody and the $CD20^+$ Daudi cell line as the target, improved rituximab-mediated cellular cytotoxicity was observed in blood samples of healthy patients with vitamin D deficiency after vitamin D substitution compared with the deficient state.[36] Additionally, activation of the vitamin D signaling pathway on tumor-associated macrophages has been shown to activate anti-lymphoma activity. In a laboratory model of Burkitt lymphoma, treatment of anti-inflammatory M2 macrophages with vitamin D induces production of cathelicidin (an anti-microbial peptide), and triggers anti-lymphoma activity.[44] Moreover, in this model, rituximab-mediated cytotoxicity of vitamin D-treated M2 macrophages is cathelicidin-dependent, which strongly indicates that ADCC against lymphoma in the setting of rituximab is enhanced with vitamin D.

In addition, laboratory studies have demonstrated that vitamin D modulates the activity of CD4+T cells which have previously been shown to promote follicle center cell proliferation, and are critical to maintenance of the malignant microenvironment of follicular lymphoma.[31] These data further support that modifying vitamin D levels through replacement could impact outcome in patients with lymphoma treated with rituximab. Indeed, in a small clinical study of 34 patients with indolent lymphomas, asymptomatic patients were treated with 1 microgram daily of oral alfacalcidol, a vitamin D analogue. Complete response was observed in four patients and a partial response in four patients with an overall response rate of 24%. Median duration of response was 14 months. Disease stabilization was observed in ten additional patients (29%) and in the sub-group of patients with follicular, small-cleaved cell-lymphoma the overall response to treatment was 29%.[45]

In an international collaborative study of newly diagnosed FL patients uniformly treated in the modern era with standard chemotherapy (CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone) plus anti-CD20 therapy, and routinely followed for outcomes per clinical trial protocol, we reported a significant association between low vitamin D levels and FL outcomes in two independent cohorts of patients.[46] The magnitude of the association is stronger than the individual clinical prognostic factors within the FL-IPI score which we currently rely on clinically for this subtype, and may be the strongest association reported to date of a pre-therapy prognostic factor in follicular lymphoma.[47] In the SWOG cohort of patients, with a median follow-up of 5.4 years, vitamin D deficient patients had significantly inferior progression-free survival (HR 2.00, p=0.011) and OS (HR 3.57, p=0.003) as compared to those with higher levels. The magnitude and significance of these associations remained after analyses were stratified by treatment trial and adjusted for prognostic index (IPI), BMI, quarter of enrollment (3/4 vs. 1/2), latitude (≥35°N vs. <35°N), and a quarter by latitude interaction term. Similarly, in the LYSA cohort, after median follow-up of 6.6 years, vitamin D deficient patients had significantly inferior progression-free survival (HR 1.66 p=0.013) as compared to those with higher levels. The magnitude of these associations remained after analyses were adjusted for prognostic index (FLIPI), BMI, quarter of enrollment (3/4 vs. 1/2), latitude (Europe vs. Australia), hemoglobin, performance status, and gender. The Vitamin D levels were

evaluated centrally in the same laboratory, using a gold-standard assay. The strength of our observed association in two independent cohorts of patients, and the lack of multiple comparisons inherent in our study design indicate these findings are unlikely secondary to chance.

These data strongly support a randomized trial to evaluate whether vitamin D supplementation improves outcome in patients with indolent lymphoma treated with rituximab.

2. STUDY DESIGN

2.1. Overview

We are conducting a multicenter, double-blind, randomized, placebo-controlled Phase III clinical trial: ILyAD (**I**ndolent **L**ymphoma **A**nd vitamin **D**)

Specific treatment groups (2:1 subject allocation):

- Arm A: rituximab weekly x 4 (intravenous 375 mg/m^2 or subcutaneous 1400 mg) + cholecalciferol (vitamin D3) 2,000 IU daily for 3 years*
- Arm B: rituximab weekly x 4 (intravenous 375 mg/m^2 or subcutaneous 1400 mg) + placebo daily for 3 years*

*or until lack of response at Week 13, new treatment or progressive disease thereafter

Anticipated enrollment period: We anticipate meeting enrollment goals within 30 months.

Follow-up period: Patients will be treated and followed on study for 3 years or until disease progression. Patients should be followed for survival until study closure.

Participating sites: University of Rochester, Cornell, Emory, MD Anderson, Washington University, University of Miami, University of Iowa.

2.2. Rationale for Study Design

Despite strong evidence suggesting that vitamin D deficiency is negatively correlated with outcome in patients with numerous cancers, rigorous prospective randomized evaluation of vitamin D as an anti-neoplastic agent is lacking. Our study evaluates a novel approach to the treatment of indolent B-cell lymphoma through a randomized, placebo-controlled, double-blind trial which will definitely address whether modification of vitamin D levels through supplementation can improve outcomes.

2.3. Rationale for Dosage of Rituximab and Vitamin D (Cholecalciferol)

Weekly intravenous rituximab administration at 375 mg/m^2, for four weeks, has been established as a safe and effective therapy in low-tumor burden follicular lymphoma.[10,48] The subcutaneous formulation of rituximab has been shown to be equally effective as intravenous administration at a dose of 1400 mg.[49] Both the intravenous and subcutaneous formulations have been FDA-approved, the route of administration is left to the investigator's discretion and standard institutional practice.

Current recommended dietary allowance for vitamin D ranges from 600-800 IU in adults.[50] However, recent literature suggests that benefits of vitamin D in cancer may necessitate higher doses.[16] A dose of 2,000 IU of vitamin D3 (cholecalciferol) is a standard daily dose that is readily available over the counter. This dose is chosen in an

attempt to supplement serum 25(OH)D levels in subjects while maintaining a substantial margin of safety below the upper level of intake (4,000 IU) at which point the potential risk for harm begins to increase.[50] Our chosen dose of 2,000 IU has been shown to effectively raise 25(OH)D levels over a prolonged period of administration without evidence of toxicity in previous studies,[51] and this strategy and dose of vitamin D has been utilized in many prospective clinical trials, including ongoing NIH studies.[52-56] Moreover, the 2000 IU dose reversed vitamin D deficiency in over 80% of patients in a recently published dose-response study.[55] After comprehensive deliberation, the NCI-sponsored VITAL vitamin D primary prevention study also chose this dose.[57] Oral vitamin D supplementation has been shown to have similar vitamin D area under the curve levels compared with bolus intravenous supplementation,[58] and is chosen in this study for patient convenience given the planned prolonged administration. Our choice for 3 years of vitamin D therapy is based upon previous studies demonstrating the safety of this approach,[59] and the observation that time to maximal response with rituximab is variable. Moreover, to the degree that vitamin D supplementation may affect the indolent lymphoma microenvironment, we feel a prolonged exposure will maximize potential beneficial effects.

2.4. End of Treatment (EOT)

Subjects that have not achieved a response to treatment at Week 13 or have had disease progression thereafter (or new treatment for lymphoma or systemic treatment for another cancer in the absence of progression) should stop taking study drug. These subjects should remain on study and be followed for survival only. Subjects that have had increased calcium above normal reference ranges* should stop taking study drug but continue on study with the planned study procedures according to Table 2. End of treatment study blood should be collected if the EOT visit occurs at a visit where blood has not already been collected.

*At the discretion of the investigator, albumin-corrected calcium or ionized calcium results may be used to confirm true hypercalcemia. If albumin-corrected or ionized calcium levels exceed the laboratory reference range, the subject should be taken off study drug as described above.

2.5. End of Study

Subjects should remain on study for survival follow-up after the completion of procedures in Table 2. Subjects should be followed for survival until study closure.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

Two hundred ten subjects will be enrolled and randomized in a 2:1 fashion; 140 treated and 70 controls.

a. **Gender and Age of Subjects:** Children will not be enrolled in this trial, as the pediatric presentation of follicular lymphoma is extremely uncommon, and has a unique natural history. Both men and women ≥ 18 years of age are eligible for the study. It is anticipated that the cohort will ultimately have 45% women and 55% men, which is the approximate sex distribution for NHL in the United States.

b. **Racial and Ethnic Origin:** At each participating center, we are not excluding any persons on the basis of racial background. The incidence of follicular lymphoma is highest in whites, followed by Hispanic-Americans, then African-Americans; with

non-Hispanic whites having more than double the incidence of this disease compared to African Americans and Hispanic whites.[60] To increase our enrollment of Hispanic-Americans and African-Americans, we have included centers that specialize in the care for these populations, including Miami, Emory and MD Anderson Cancer Center.

c. **Vulnerable Subjects:** Vulnerable subjects should not be enrolled.

3.2. Inclusion and Exclusion Criteria

a) **Inclusion Criteria:** Each of the following criteria must be met in order for a patient to be considered eligible for registration.

- Biopsy proven (with hematopathology review at one of the participating sites to confirm correct histology in accordance with WHO) indolent lymphoma to include the following diagnoses:
  - Grade 1, 2, or 3a follicular lymphoma
  - Small lymphocytic lymphoma (CLL excluded)
  - Marginal zone lymphoma (nodal or splenic)
  - Mucosal-associated lymphoid tissue (MALT)
- Measurable disease defined by Lugano criteria[61]
- No prior anti-lymphoma systemic therapy; prior radiation therapy is allowed
- Age 18 or over
- Ann Arbor stages II, III or IV
- Patients with follicular lymphoma must have PET FDG-avid lymphoma and fulfill low tumor burden by Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria:
  - No mass > 7 cm
  - < 3 distinct masses of greater than 3 cm
  - No B symptoms
  - No splenomegaly > 16 cm by computed tomography (CT) scan
  - No risk of vital organ compression
  - No leukemic phase > 5000/µl circulating lymphocytes (except for in patients with splenic marginal zone diagnosis)
  - No cytopenias (platelets < 100,000/µl, hemoglobin < 10 g/dl, or absolute neutrophil count < 1500/µl)

b) **Exclusion Criteria:** The following criteria will prevent inclusion of an inappropriate subject into the trial:

- Osteoporosis requiring prescription treatment
- Known symptomatic primary hyperparathyroidism
- Hypercalcemia defined as above the institutional normal range (corrected for albumin when albumin levels are below normal)*
- History of calcium-related kidney stones
- Creatinine > 1.5 X above ULN
- Women who are known to be pregnant or who plan to become pregnant while on rituximab treatment

* Albumin corrected calcium = [0.8 x (normal albumin – patient's albumin)] + serum calcium
https://www.ebmconsult.com/app/medical-calculators/calcium-correction-albumin-calculator

NOTE: While we are collecting study serum at baseline, 25(OH)D values will not be released until study analysis. We have chosen to not limit study participation based on baseline serum 25(OH)D levels for a wide variety of reasons, including: 1) The maximum 25(OH)D level in our previous study of Follicular Lymphoma patients was 63 ng/ml[46], minimizing our concern for potential toxicity with our chosen dose of 2000 IU daily; 2) we are excluding patients with other clinical manifestations of low 25(OH)D levels, namely osteoporosis requiring prescription treatment; 3) 25(OH)D levels vary substantially by season[50]; 4) 25(OH)D levels are also known to vary by race and BMI[50,62]; 5) our intention in designing this study is to be as inclusive as possible to maximize generalizability; and 6) Baseline 25(OH)D is an important potential effector modifier that we plan to evaluate in secondary analyses. Moreover, we are planning to evaluate clinical calcium levels at 13 weeks, 12, and 36 months to detect potential toxicity.

Pregnancy while on study treatment is expected to be a very rare event given the demographics of the study population. However, in the event of a pregnancy the subject's continued participation should be discussed with the principal investigator and the event documented in the REDCap database.

All enrolled patients will be strongly encouraged to enroll in the LEO consortium study as well, and over 90% of eligible patients at the participating institutions are enrolling in this companion study. Through the LEO consortium, tissue and blood from these patients will be banked for future analyses; baseline epidemiology surveys and follow-up patient-reported outcome measures, including quality of life instruments will be collected. Patient-reported quality of life is being captured longitudinally (baseline, 1, 2, and 3 years) via validated FACT-G and FACT-Lym instruments. LEO enrollment is not required for participation in the ILyAD study.

3.3 **Discussion of Subject Population**

Follicular lymphoma is the second most common subtype of non-Hodgkin lymphoma, and the most prevalent lymphoma in the United States. Though outcomes have improved substantially in the modern therapeutic era, this disease is still characterized by a generally incurable clinical course.[1,2] While follicular lymphoma (FL) prognosis is known to be influenced by clinical characteristics and age, modifiable prognostic and predictive factors for this disease in the modern treatment era have been difficult to elucidate. Other less common indolent non-Hodgkin lymphomas include marginal zone and small lymphocytic lymphomas, these often present in a similar fashion to follicular lymphoma, are treated in a similar way, and have similar outcomes.[3,4]

The most common presentation of indolent lymphomas in the United States is "low tumor burden" disease, defined as asymptomatic disease, non-bulky lymphadenopathy, and no cytopenias, which is the subject of this study. The inclusion criteria define this population.

To minimize risk of vitamin D therapy, patients with osteoporosis requiring prescription treatment, known symptomatic primary hyperparathyroidism, hypercalcemia (> normal), history of calcium-related nephrolithiasis, or creatinine > 1.5 X normal will be excluded.

4. SUBJECT IDENTIFICATION, CONSENT AND RANDOMIZATION

4.1. Method of Subject Identification and Recruitment

Eligible patients will be identified through patient scheduling, medical and pathology records, and other systems specific to each participating site, all of which involve clinicians actively involved in the clinical care and research with NHL patients.

4.2. Process of Consent

Invitation to participate will be extended by clinicians and details on study participation and informed consent will be conducted by members of the clinical research team at each site. The investigator or designee is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB approved informed consent document and for ensuring patients are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each subject by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

4.3. Subject Enrollment/Randomization

After consent is obtained and screening procedures are complete, eligible subjects will be randomized within 1 week of planned study drug start.

- Each site will receive access to the study-specific, REDCap database. Site users will enter subject demographic information and stratification factors directly into REDCap to receive a blinded bottle assignment in real time as eligible patients are registered. One unblinded URMC statistician will also have the randomization schema and will be able to communication urgent randomization results to sites in cases of REDCap login issues or system failure.

  It is the expectation that all eligibility data has source documentation available at the enrolling sites. Site personnel will be responsible for entering subject data regularly into this database.

- Randomization Procedures: Study statisticians will prepare a randomization assignment with the strata indicated below. This randomization scheme will be uploaded into the Randomization module in REDCap.

- Stratification Factors:
  - Histology: FL vs. all other histologies
  - FLIPI for FL patients (High vs. Low and Intermediate)

5. METHODS AND STUDY PROCEDURES

5.1. Treatment Dosage and Administration

- Table 1 indicates the planned treatment regimen, dosing, and administration.

Table 1. Treatment Dosage and Administration

Agent	Dose	Route	Schedule	Cycle Length
Arm A				
Rituximab (or approved biosimilar)*	375 mg/m^2 intravenous or 1400 mg subcutaneous	Per Site Standard of Care	Weekly	Every week for 4 weeks
Cholecalciferol	2,000 IU	PO	Daily	Continuous for 3 years**
Arm B				
Rituximab (or approved biosimilar)*	375 mg/m^2 intravenous or 1400 mg subcutaneous	Per Site Standard of Care	Weekly	Every week for 4 weeks
Placebo	N/A	PO	Daily	Continuous for 3 years**

*Sites may follow local policy regarding the use of approved biosimilar rituximab products, with deference to institutional standards regarding product selection based on formulary guidance and reimbursement concerns.
**Or until lack of response at week 13, new treatment or disease progression thereafter.

5.2. Study Procedures and Schedule

At screening, patients will be reviewed for eligibility. A PET/CT scan is required within 8 weeks prior to beginning study drug. A physical exam should be performed and local labs drawn within 4 weeks to determine calcium and creatinine levels. LDH and hematology labs should be obtained as needed to determine FLIPI score and GELF criteria for patients with follicular histology. Hepatitis B serology testing is strongly recommended as per institutional practice; patients who are positive for Hepatitis B surface antigen or core antibody will be allowed on study as long as appropriate prophylaxis measures are taken as per institutional practice. These will be documented on the case report forms.

At Day 1 baseline, patients who fulfil eligibility criteria will have study blood drawn and saliva collected as detailed below and in the laboratory manual. Study blood should be shipped same day as collection for central analysis at URMC Labs. Saliva samples will be stored ambient on site and batched shipped for central analysis at the URMC Genomics Core. Pre-paid shipping labels for batched saliva samples can be obtained by email request from: ILyAD_Trial@urmc.rochester.edu

Vitamin D or Placebo will be dispensed through the URMC Clinical Materials Services Unit (CMSU) to the study sites. Subjects will receive a 3-month supply of medication, with instructions to take one capsule daily. If a dose is missed, it should be made up as soon as possible on the same day with a return to the normal schedule the following day. If doses are missed for a day (or several days), dosing should restart at the usual dose without an attempt to 'make-up' any missed doses. Empty bottles or leftover capsules should be returned at the next clinic visit. Rituximab or approved biosimilar will be administered as per institutional practice.

All randomized-treated subjects will be evaluated for treatment response at Week 13. Subjects without PET FDG-avid disease at baseline can have either a PET/CT or a CT at Week 13. Subjects with PET FDG-avid disease at baseline should have a PET/CT at Week 13. Subjects who have not responded with at least a partial response by Lugano criteria will be counted as events, taken off study medication and followed subsequently only for overall survival.

Subjects who have achieved at least a partial response will remain on study and will continue with daily oral cholecalciferol or placebo for three years or until disease progression. Subjects will be seen every three months for physical exam, drug distribution, drug reconciliation, and history. In response to the declared public health emergency for COVID-19 and with the safety of all subjects and research staff as a priority, telemedicine visits can be performed in place of in-person visits when deemed appropriate by site investigators and when in accordance with local institutional and IRB guidelines. Study labs should continue to be collected whenever possible and when determined not to pose additional safety risks to subjects. When study labs are not collected due to concerns for subject safety, the missed labs will be documented in the study REDCap database. Study drug can be shipped directly to subjects as dictated by local, state or federal guidance and/or local or subject preference. CT scans will be performed (of C/A/P and neck if previously involved) annually at year 1, year 2 and year 3. Calcium will be checked annually. If at any time calcium is above the institutional limit of normal*, patients will be taken off study drug but should remain on study with assessments every 3 months for 3 years or until progression.

*At the discretion of the investigator, albumin-corrected calcium or ionized calcium results may be used to confirm true hypercalcemia. If albumin-corrected or ionized calcium levels exceed the laboratory reference range, the subject should be taken off study drug as described above. Subjects may continue taking study drug if albumin-corrected or ionized calcium levels are within the normal laboratory reference range.

Table 2 indicates the timing of all study procedures.

Table 2. Schedule of Study Procedures

Visit	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13
Study Visit	**≤4 weeks of study drug start**	**Day 1 Baseline**	**13 Week**	**6 Month**	**9 Month**	**12 Month**	**15 Month**	**18 Month**	**21 Month**	**24 Month**	**27 Month**	**30 Month**	**33 Month**	**36 Month/ EOT**
Visit Window (Weeks)		**-**	**±2**	**±2**	**±2**	**±4**	**±2**	**±2**	**±2**	**±4**	**±2**	**±2**	**±2**	**±4**
Obtain Informed Consent	X													
Confirm Eligibility	X													
Randomize/Enroll[1]	X													
History and Physical Exam[8]	X		X	X	X	X	X	X	X	X	X	X	X	X
Local Labs: -CBC with differential -Creatinine -LDH (if required for FLIPI) -Hepatitis B testing[2]	X													
-Blood Calcium	X		X			X				X				X
-Blood Albumin	X													
FLIPI Assessment (Follicular histology only)	X													
PET/CT	X[3]		X[7]											
CT (C/A/P; neck if involved)						X				X				X
Study Drug Dispensed		X	X	X	X	X	X	X	X	X	X	X	X	
Study Drug Reconciliation			X	X	X	X	X	X	X	X	X	X	X	X
Study Blood Draw[4]		X[5]	X			X								X
Saliva Collection for SNPs		X												
Rituximab treatment[6]		X												

[1]After eligibility is confirmed, sites will use REDCap to obtain a blinded bottle number. Subjects should begin treatment within 1 week of randomization.
[2]Recommended as per institutional standard
[3]PET/CT within 8 weeks of study drug start.
[4]Study blood labs include: PTH (Day 1 only), $25(OH)D_2$ and $25(OH)D_3$.
[5]Study blood should be drawn prior to dosing.
[6]Rituximab will be administered weekly for 4 weeks per institutional practice. Rituximab can be administered within 5 business days of Day 1.
[7]CT is permitted in place of PET/CT in subjects without PET FDG-avid disease at baseline.
[8]Physical Exam is not required if telemedicine visits are performed.

5.3. **Efficacy Assessments**

Response assessment will be determined by Lugano criteria at 13 weeks (PET/CT) and annually for 3 years (CT of the chest/abdomen/pelvis and neck if involved at baseline). A CT scan may be used in place of the Week 13 PET/CT in subjects without PET avid disease at baseline. Assessments will be performed by the treating physician at enrolling sites. Study data will be captured and entered into REDCap by each site. See Appendix 2 for Lugano Criteria.

Clinical or telemedicine evaluation will be performed every 3 months for 3 years by the treating physician at enrolling sites.

5.4. **Safety Assessments**

Blood calcium levels will be measured at baseline, week 13 and annual visits to monitor for hypercalcemia. Calcium levels above the institutional limit of normal will result in discontinuation of vitamin D/placebo. At the discretion of the investigator, albumin-corrected calcium or ionized calcium may be used to confirm true hypercalcemia. Patients will continue on study for the duration of the study.

5.5. **Assessment of Subject Compliance**

Study drug will be dispensed at Day 1. Subjects should return all unused pills and empty bottles at each visit for site reconciliation. We will also be able to retrospectively assess compliance with vitamin D levels at 13 weeks, 12 months and end of study.

5.6. **Data & Specimen Banking for Future Research Use**

No samples will be stored or banked for future research.

In accordance with the National Institutes of Health Genomic Data Sharing policy, anonymized genomic sequence data derived from saliva samples and tumor biopsies will be shared by depositing the data in the database of Genotypes and Phenotypes, dbGaP, a controlled-access data repository funded by NIH. Prior to submitting the data, direct identifiers will be removed according to the standards set forth in the HHS Regulations for the Protection of Human Subjects and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule to ensure that the identities of research subjects cannot be readily ascertained with the data. A random code will be assigned to the data before sending it to the repository. The University of Rochester will maintain the key to the code and study identifiers. Controlled-access data in NIH-designated data repositories are made available for secondary research only after investigators have obtained Internal Review Board approval to use the requested data for a particular project. The genotype data will be made publicly available no later than the date of initial publication. Consent to share the data and future use of data will be obtained from each subject with IRB approval and prior to submission to the dbGaP.

5.7. **Genetic/Genomic Research Activities**

At baseline, we will collect germline DNA in all patients with a saliva sample, using Oragene DNA self-collection kits (DNA Genotek, Ottawa, Canada). Whole exome sequencing will be conducted in the URMC Genomics Research Center. Genomic DNA (gDNA) is extracted from Saliva samples using the PrepIT-L2P purification kit (DNA Genotek). Extracted gDNA is quantified by Qubit Flourometer Quant-iT assay (LifeTechnologies, Carlsbad, CA) and DNA quality determined with Agilent TapeStation 2200 (Agilent Technologies, Santa Clara, CA). For SNP genotyping analysis, samples are processed using the GRC's standard WES operating procedure utilizing SureSelectXT Whole Exome v5 (+UTRs) (Agilent Technologies, Santa Clara, CA) based on previously published methods. Briefly, 500ng of genomic DNA is sheared with Covaris S2 (Covaris, Woburn, MA) to an average peak size of 250bp followed by end repair, poly adenylation,

Illumina adaptor ligation, and purification with AmpureXP (Beckman Coulter, Brea, CA). Library amplification is carried out with 250ng of purified DNA with 4 cycles of PCR followed by AmpureXP purification (Beckman Coulter, Brea, CA). Exome probe hybridization capture is performed per manufacturer's protocols. Exome target enriched samples are quantified using the Qubit Flourometer (ThermoFisher, Waltham, MA) and library sizing is assessed with the high sensitivity Bioanalyzer 2100 DNA assay (Agilent Technologies, Santa Clara, CA). Whole exome libraries are normalized, pooled and 2x100 pair end sequencing is performed with the HiSeq2500 (Illumina, San Diego, CA).

A subset of up to 65 subjects with available banked formalin fixed paraffin embedded (FFPE) diagnostic biopsy samples will be used to study whether vitamin D deficiency is correlated with a low immune tumor infiltration pattern defined by PD-L2 expression and RNA sequencing, and whether this is a biomarker of response to supplementation. RNA will be isolated using RNeasy FFPE RNA purification kit (Qiagen) and quality control will be performed using Bioanalyzer 2100 RNA assay (Agilent Technologies) to determine quality and quantity. Samples will be analyzed for PD-L2 expression using a Taqman real-time assay in combination with several endogenous control targets with qPCR (Thermofisher). Preliminary analysis will be conducted by standard relative expression using delta-delta-Ct analysis as well as with using the HTqPCR R package to determine statistically significant PD-L2 relative expression between low vs high vitamin D. RNA sequencing (RNA-Seq) will be used to measure lymphoma relevant gene expression as well as genes expressed in immune infiltrating cells, macrophages and stromal cells. This panel will include immune effector (CD137, CD4, CD7, TNF-alpha) immune checkpoint (PD-1, PD-L1, PD-L2, TIM3, FOXP3) and macrophage (CD68) molecules. Total RNA will be subjected to ribosomal RNA depletion rather that polyA enrichment using TruSeq Total RNA-Seq library (Illumina, Inc.). Illumina libraries will be sequenced on the NovaSeq 6000 platform at a depth of 50 million read pairs per library. Sequence data will be processed and analyzed for differential transcript expression using DeSeq2 and feature counts, along with pathway enrichment analysis. To determine gross diversity for the infiltrating immune cells we will use CIBERSORT[63] to identify and characterize the immune populations from the bulk RNA-Seq data. We will focus on the genes that are predictive of immune infiltration, such as known genes representing cytotoxic T-cells, tumor associated macrophages, neutrophils and dendritic cells.

Up to 12 samples (6 from the lowest decile of Vitamin D levels and 6 from the highest decile of Vitamin D levels) will be selected for additional gene expression analysis by spatial genomics. Slide-mounted tissue sections will be incubated with morphology markers and a cocktail of high-plex oligo-labeled RNA probes corresponding to over 1600 immune-oncology RNA targets (Cancer Transcriptome Atlas, NanoString Technologies). This new high-plex RNA expression profiling panel provides a more informed view of the cancer transcriptome, with particular attention to immune-oncology biology. The morphology markers allow the generation of a fluorescent image of the tissue morphology to guide region of interest selection. After imaging the slides, regions of interest (ROI) are selected. ROIs are exposed to ultraviolet illumination, leading to release of oligos into the aqueous layer above the tissue slice. The oligos are collected via microcapillary aspiration and stored in an individual well of a microtiter plate. Oligos are hybridized to optical barcodes to permit digital quantification of analytes from the selected ROIs. Digital counts are incorporated into the image data for each ROI to create highly multiplexed, spatially resolved expression datasets.

We will identify malignant B cells from microenvironmental cells using protein and gene expression profiles. The cellular composition of the non-malignant microenvironment will be characterized in the scanned slides using de novo clustering procedures recently developed and described for single cell RNAseq data. We will explore spatial relationships of each cell

subpopulations by characterizing area and spatial entropy at various scales. Spatial correlation between cell subpopulations will be assessed using spatial cross-correlograms. These spatial genomic studies will allow us to address fundamentally important functional questions about immune infiltration in the setting of sufficient or insufficient Vitamin D, and more importantly we may uncover previously unexpected cellular interactions that are modulated by Vitamin D.

5.8. Costs to the Subject

The patient and/or their health plan/insurance company will need to pay for some or all of the costs of treating their cancer in this study. Rituximab is commercially available. All restaging and follow-up assessments are standard of care, and therefore, taking part in this study will not cost the patient or their insurance company more than the cost of getting regular cancer treatment.

Administration of the study drug (cholecalciferol or placebo) will be provided free of charge. The parts of the research consisting of keeping research records, central study drug assays, saliva collection kits and SNPs evaluation will be covered by the study.

5.9. Payment for Participation

Patients will not be compensated for their participation.

5.10. Return of Individual Results

Study results are not reported back and are not entered into the medical record.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

Participants will be asked to avoid taking vitamin D outside of this trial. However, given the increased publicity regarding potential benefits of this supplement, daily personal use of up to 1,000 IU of vitamin D will be permitted but discouraged. The daily combined dose of vitamin D from supplements and multivitamins should not exceed 1,000 IU.

7. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Written withdrawal of consent can be submitted to the participating site investigator / treating physician, after which point no further data will be collected on these patients.

8. STUDY DRUG ADMINISTRATION/ASSIGNMENT

8.1. Study Drug / Placebo

- Rituximab (or approved biosimilar) is commercially available and will be obtained via standard methods by each participating site.

- Cholecalciferol and placebo will be obtained from Bio-Tech Pharmacal, Inc. Study drug will be sent in bulk at study initiation to URMC Clinical Materials Services Unit (CMSU) for packaging, labeling, and distribution to the participating sites.

Frequency of distribution to enrolled subjects: Study drug or placebo will be distributed to patients in 3 month supplies at clinical visits.

Method of distribution to enrolled patients while maintaining the double blind: The CMSU will label all bottles with arm code and a unique bottle number. The procedure for distribution to sites will be as follows:

- CMSU will send bulk supplies of study drug to each site at study initiation and as needed throughout the study.
- Eligible patients will be entered into the REDCap system at each site. After the stratification factors are entered, the randomization assignment will be revealed in blinded fashion. A randomization number matching a study drug bottle already in stock at the site will be provided by the REDCap system and will be reported back to CMSU for treatment assignment and inventory tracking.
- REDCap will be used by site staff at each dispensing visit to generate a number corresponding to a bottle containing a 3-month supply of study drug.

8.2. Dosage of Study Drug/Biologic

Rituximab or approved biosimilar: 375 mg/m^2 intravenous or 1400 mg subcutaneous
Cholecalciferol: 2,000 IU PO daily (supplied by Bio-Tech Pharmacal)

8.3. Accountability of Investigational Supplies

The University of Rochester CMSU will be responsible for receipt, storage, dispensing and re-supply to investigator sites. This includes maintaining accurate records of supplies received, used and returned. CMSU will be the unblinded third party that will know which coded bottles contain vitamin D versus placebo, and will maintain contact with the sites to keep them supplied as needed throughout the study.

Investigator site staff and pharmacies will be responsible for obtaining the REDCap assigned bottle code and dispensing to patients. Compliance will be monitored on study source documents. Site pharmacies will maintain logs to track receipt and dispensing of study drug. Returned and expired drug can be destroyed after proper documentation according to each site's standard of practice.

8.4. Subject Withdrawal of Study Drug

At any time, if a patient is removed from the trial either by choice or by protocol, remaining drug will be collected by the study site for reconciliation and destruction.

8.5. Emergency Drug Disclosure

If it is deemed necessary for medical reasons to disclose whether a patient is on drug or placebo, the Data Safety Monitoring Board (DSMB) chair will be alerted, and vet the disclosure only to the providers on site. This is an exceedingly unlikely occurrence given the nature of the agent under study (Vitamin D).

Requests for unblinding should be made via email to: ILyAD_Trial@urmc.rochester.edu.

9. SAFETY AND REPORTABLE EVENTS

9.1. Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to study drug.

9.2. Serious Adverse Events

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;

- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

9.3. **Recording Adverse Events**

At each subject visit the site study staff will assess adverse events by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since his/her last visit.

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, the relationship to investigational product (i.e., drug or device), contributing factors, and any action taken with respect to the study drug/device.

The following attribution scale will be used:

- Definite: AE is clearly related to the investigational agent
- Probable: AE is likely related to the investigational agent
- Possible: AE is possibly related to the investigational agent
- Unlikely: AE is doubtfully related to the investigational agent
- Unrelated: AE is clearly not related to the investigational agent

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents and in the REDCap database. Laboratory abnormalities determined to be clinically significant by providers should be documented in REDCap. Events will be monitored from the first dose of study treatment until 30 days following the completion of study dosing or withdrawal from participation. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.4. **Responsibilities for Reporting Adverse Events**

All serious adverse events should be reported in the REDCap database within 5 business days of learning of the event. SAE reports are expected to include sufficient detail so that the DSMB can determine the severity, toxicity grade, expectedness and treatment. The report should be updated to document resolution or any sequelae. The Coordinating Center will report an aggregate listing of all AEs and SAEs for review at the regular DSMB meetings. The board will review these reports and determine if further action is required.

Serious Adverse Events that are determined to be related AND unexpected require expedited reporting to the REDCap database in addition to notification by email to: ILyAD_Trial@urmc.rochester.edu.

The Coordinating Center will report these events to the DSMB in addition to sending a formal notification describing the event to all investigators. Each investigator must then notify his or her IRB of the event according to local regulations.

Table 3. SAE Reporting Requirements

EVENT	REPORTING TIMELINE	RESPONSIBLE PARTY
SAE	Report within 5 days to REDCap	Site Staff
Related and Unexpected SAEs	Report within 5 days to REDCap and ILyAD_Trial@urmc.rochester.edu	Site Staff

10. RISK/BENEFIT ASSESSMENT

10.1. Potential Risks

The potential physical and psychosocial 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 cholecalciferol supplementation. Symptoms of hypercalcemia include:
  - Nausea
  - Vomiting
  - Constipation
  - Decreased appetite
  - Increased thirst
  - Increased urination
  - Mental or mood changes
  - Fatigue
  - Muscle or bone pain
  - Ringing in ears
  - Vertigo
  - Unsteady gait
  - EKG changes
  - Kidney stones

- Risks associated with venipuncture include vasovagal episodes, ecchymoses at the site of blood removal, and extremely rare instances of infection.

- Psychosocial risks associated with any research involving DNA, as well as any risks associated with a breach in confidentiality with regard to those data. This has never occurred in previous studies by these investigators, and will be safeguarded as described below.

In addition, treatment with rituximab (a standard treatment modality for this clinical situation) may cause serious side effects, some of which can be life-threatening or cause death, including the following, listed according to their frequency/risk:

Very Common (≥10% of patients) – The most common side effects (>10%) observed with rituximab treatment in patients with cancer of the blood, include:

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

Common (>5-10% of patients) - Common side effects (>5-10%) observed with rituximab treatment in patients with cancer of the blood, include:

- Back pain
- Throat irritation
- Flushing (redness in face or other areas of body)
- Anemia (low hemoglobin)
- Hives (itchy red welts)
- Wheezing
- Shortness of breath
- Sinus infection
- Hyperglycemia (high blood sugar)
- Peripheral edema (swelling of extremities)
- Diarrhea
- Vomiting
- Constipation
- Dizziness
- Anxiety
- Muscle pain
- Joint pain
- Constriction ('spasm') of muscles in chest
- Hypotension (low blood pressure)
- Hypertension (high blood pressure)

10.2. **Protection Against Risks**

We have carefully selected the 2,000 IU daily dose of cholecalciferol to maintain a substantial margin of safety below the upper level of intake (4,000 IU) at which point the potential risks for harm begin to increase. However, to ensure safety of continued supplementation, calcium levels will be checked at

week 13 and annually; any level above the institutional limit of normal will result in discontinuation of vitamin D or placebo. A DSMB will be charged with ensuring safety of patients enrolled on this trial.

Saliva samples for DNA analysis and FFPE tumor biopsy samples for gene expression will be labeled with study number only, and will be kept in a locked lab. Although there are presently no known medical conditions associated with the genetic polymorphisms under study, participants will be informed during the informed consent process that they will not receive the results of this genetic testing or the gene expression, nor will the results be entered into their medical record.

10.3. **Potential Benefits to Subject**

Subjects enrolled in this trial have the potential of receiving vitamin D supplementation. If they are vitamin D insufficient at study entry, we anticipate that they will reach sufficiency with the supplementation doses provided. This could benefit their bone health, and should our hypothesis prove true, these subjects will also enjoy an improved progression-free survival period. There will be no financial compensation of subjects for participation in this research.

10.4. **Alternatives to Participation**

Patients are eligible for standard of care treatment regardless of whether they participate in this study, which may include observation without therapy, or single agent rituximab treatment, as per enrolling physician.

11. **CONFIDENTIALITY OF DATA AND INFORMATION STORAGE**

Study specific forms within REDCap will be used for web-based data management. Information abstracted from patient care records is obtained for research purposes only. Privacy is maintained by institutional procedures, which require formal review by appropriate committees prior to any written or telephone correspondence with patients or families. Procedures are in place for maintaining confidentiality of all information collected as part of this study. Access to medical records and the REDCap study database is limited to the investigative staff. Data are managed by study number and will be analyzed anonymously. All reports are of a summary nature and no individual patients are identified. Non-computerized medical records are kept in a locked filing cabinet. Access to personal identifiers is based on a “need to know” basis, and this access is reviewed and documented by each center PI. In order to maintain the treatment blind, only one staff statistician at the University of Rochester and the study drug allocation team at URMC CMSU will be aware of treatment assignment.

11.1. **Data Management Procedures**

CRF completion guidelines for eCRF data entry will be provided. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

11.2**. Access to Source Data**

The investigator will permit the PI or representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect patient confidentiality are to be employed during monitoring. The CRFs and related source documents will be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm information contained in the CRFs, such as past history, secondary diagnoses, disease assessment records, adverse events, and concomitant medications. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by

representatives of the FDA or other regulatory agencies

11.3. **Accuracy and Reliability of Data**

Steps to be taken to assure the accuracy and reliability of data include:
• The selection of qualified investigators and appropriate study centers.
• Review of protocol procedures with the investigators and associated personnel prior to the study.
• Remote monitoring where permitted by the coordinating site.
• CRFs will be reviewed for accuracy and completeness by the designated monitor(s)
• Any discrepancies will be resolved with the investigator or designees as appropriate.

11.4. **Data Handling**

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained. Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data handling procedures for this trial have been designed to permit data changes so that they are documented by an audit trail. Data changes may only be made by those individuals so authorized.

11.5. **Investigator Record Retention**

The investigator shall retain study drug disposition records and all source documentation (such as laboratory reports, inpatient or office patient records) for the maximum period required by the country and Institution in which the study will be conducted. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred.

12. **RESEARCH INFORMATION IN MEDICAL RECORDS**

Results from this research will not be entered into the patient medical records.

13. **DATA ANALYSIS AND MONITORING**

13.1. **Sample Size Determination**

We expect 70% of our enrolled patients to have follicular lymphoma, and 30% to have other indolent subtypes; based upon results of RESORT we estimate the 3-year event-free survival (EFS) in our control arm to be 40%. We hypothesize that cholecalciferol supplementation will reduce the relative hazard of lack of response, progression or death by 45%. For our planned study, HR = 0.55 corresponds with an increase in 3-year EFS from 40% to 60.41%. Assuming a 10% loss to follow-up, a 2:1 randomized trial with 140 patients in the treated group and 70 patients receiving placebo, or a total of 210 randomized patients (with an expected 88 events, 50 and 38 respectively), provides 81% power to detect HR = 0.55 at a two-sided $\alpha = 0.05$ significance level. As HR ranges from 0.50-0.60 (and 3-year EFS varies from 57.71-63.25 in the treatment arm), power varies from 69-90%.

13.2. **Planned Statistical Analysis**

Lack of response to treatment at week 13 (time of the first response assessment) will be counted as an event, as will initiation of a new treatment, and thus the term event-free survival (EFS) more accurately describes the primary endpoint and will be used in place of progression-free survival (PFS). Event-free survival will be defined as the time from randomization to an event of progression, death, no response to treatment at week 13, or initiation of a new treatment in the absence of progression. EFS will be right-censored by the time of last follow-up. The primary analysis will include all treated subjects, data will also be analyzed in an intent-to-treat fashion. PFS and EFS over three years are

standard endpoints for studies in indolent lymphoma, and PFS is the endpoint which resulted in the approval of rituximab maintenance in the high tumor burden setting of this disease.[64] Randomization in our trial will be stratified by histology and by the FL-IPI score[47] within FL, resulting in 3 strata: FL-high, FL-intermediate/low, non-FL. Within each stratum, participants will be 2:1 block-randomized with random block sizes to maintain treatment:control balance and preserve blinding. Since participants will be monitored by clinical evaluation for progression every 3 months, the EFS data will be coarsened to this discrete time grid to fit a grouped relative risk model for the primary analysis as previously described.[65] Otherwise, the hazard ratio (HR) for treatment would be expected to be biased toward the null value of 1, since a standard continuous time Cox model would inappropriately use random ordering of progressions and deaths between monitoring times that would be a function of the random visit dates for each participant. The primary analysis will be based on a stratified grouped relative risk (Cox) model, stratified by the 3 randomization strata, thus allowing for separate baseline hazard functions for FL-high, FL-intermediate/low, and non-FL. This offers a stronger adjustment than a parametric adjustment for the strata, as the proportional hazards assumption is relaxed.

Although it is unnecessary to adjust for covariates in a randomized clinical trial, and thus it is also not critical to optimally model their functional forms, precision and power can be improved by controlling for covariates strongly associated with EFS. The primary histology-stratified grouped Cox model will be further parametrically adjusted for the following 2 covariates: enrolling site (5-df for 6 sites) and participant age at randomization (1-df, assuming linearity in the log-hazard). Given the planned parametric adjustment for pre-specified covariates, inference will be based on the robust sandwich estimator of variance, in order to guarantee control of the Type I Error rate, even if the model is misspecified. The primary analysis will be based on a 1-df robust Wald test of treatment in the histology-stratified grouped Cox model, adjusted for site and age. The adjusted HR for vitamin D supplementation, along with a robust 95% confidence interval (CI) and associated robust Wald p-value will be reported. As a secondary analysis, the histology-stratified grouped Cox model will also be fit without any parametric adjustments for site or age, with no need for a robust sandwich estimator of the variance of the treatment effect. The likelihood ratio test of the treatment effect from this reduced model is thus asymptotically equivalent to a stratified logrank test but with the advantage that the model also yields an estimated HR along with 95% CI. Kaplan-Meier EFS curves by treatment group will be used as a graphical summary, recognizing that they fail to account for strata or covariates, and thus do not correspond directly with the primary analysis model. EFS data will not be coarsened to 3-month intervals for the purposes of Kaplan-Meier curve estimation.

Secondary endpoints will include response at 13 weeks (binary), and overall survival (time from randomization to death from any cause, right-censored by time of last follow-up). Planned subset analyses will include correlative endpoints by genotype (see below), and a subset analysis of patients with follicular lymphoma. Additional planned subset analyses will be performed by sex (given some data on differential outcome by sex[66] in follicular lymphoma treated with rituximab), and based upon vitamin D status and PTH levels, detailed below.

Correlative study: Vitamin D and PTH:
Starting with the grouped histology-stratified Cox model used to test for treatment effect in Aim 1, adjusted for site and age, we will further adjust for baseline Vitamin D level and its interaction with treatment. Baseline vitamin D level will be modeled via a parametric cubic spline with 2 knots located at the tertiles of baseline vitamin D level. This 5-df piecewise cubic function is sufficiently flexible to capture a wide range of potential smooth functional relationships yet sufficiently parsimonious to fit with the expected event rate. Interacting this with the treatment indicator will cost 5-df, so the full interaction model will have 10-df more than the primary analysis model. We will plot the estimated HR for treatment as a function of baseline vitamin D level, along with pointwise 90% robust confidence intervals (CI; Figure 4) so we will have 95% confidence that the true HR falls below the upper bound. Baseline

vitamin D levels for which the estimated treatment HR > 1 will be considered the subgroup of patients for whom cholecalciferol supplementation appears least effective. Baseline vitamin D levels for which the entire 90% robust CI (95% upper bound) for the treatment HR < 1 will be considered the subgroup of patients for whom cholecalciferol supplementation appears most effective. Since it is possible that the treatment effects depend more on achieved rather than baseline vitamin D level, we will repeat these analyses at 13-weeks. As an alternative, lower order (piecewise quadratic, linear, and constant) splines will be explored in secondary analyses since they might improve stability via reduction in parameters from 10 to 8, 6, and 4.

In addition to estimating a smooth HR for treatment as a function of baseline vitamin D, a pre-specified subgroup-type analysis will be performed to estimate the HR for treatment for those with baseline PTH values above the upper limit of normal and a separate HR will be estimated for those with PTH values in the normal range. Rather than fit separate models to each subgroup (which implicitly allows interactions of baseline PTH with *all* variables in the model), the primary analysis model will be enriched by adding an indicator for baseline PTH > ULN, along with its interaction with treatment, resulting in a piecewise constant (histo) spline model with a single knot. This dichotomous interaction model will have just 2-df more than the primary analysis model. The HR for treatment in elevated and normal baseline PTH groups will be reported (along with robust 90% CI) and compared via a 0.10 level 1-df robust Wald test of interaction. We will also plot the HR for treatment as a function of all possible dichotomization thresholds, and display the HR corresponding to subgroups excluding low PTH (in one graph) and excluding high PTH (in a separate plot), for all definitions of "low" and "high". Nominal robust 90% CI will be plotted to depict variability of estimated HR for each subgroup.

Correlative study: Genotyping
Interactions between cholecalciferol supplementation and each of the following four common vitamin D related genetic variants will be considered: **1)** *VDR* BsmI: W/W: 0, W/V:1, V/V:2; **2)** *VDR* TaqI: W/W:0, W/V:1, V/V:2; **3)** VDR FokI W/W: 0, W/V:1, V/V:2; **4)** *DBP* phenotype: DBP1F:0, DBP2:1, DBP1S:2. As is common in many SNP analyses, we plan to assume the additive model structure, whereby each ordinal (0,1,2) genetic variant will be modeled linearly in the log-hazard. This implicitly assumes that the HR for 2 vs. 1 is identical to the HR for 1 vs. 0, and thus the HR for 2 vs. 0 is the square of that for 1 vs. 0. By spending only 1-df on the functional form of the genetic variant, and estimating a common "per allele" HR, we will maximize power for genetic variants for which (a) the additive assumption is at least approximately true or (b) there are very few subjects at level 2 (so the additive assumption is nearly indistinguishable from the dominant model comparing 0 vs. 1+). The interaction of treatment with each genetic variant will be modeled similarly with 1-df, via the product of the treatment indicator and the count (treated as if it were continuous).

The primary histology-stratified grouped relative risk model from Aim 1, adjusted for site and age, will be enriched by further including main effect terms for all four genetic variants detailed above after confirming that these variants are not highly collinear (measured by pairwise correlations as well as condition index of the genetic sub-matrix). This genetic variant main-effect model will have 4-df more than the primary analysis model, or fewer if one or more variants are removed due to collinearity. The full genetic variant interaction model will further include all 4 treatments x genetic variant interaction terms, and will thus have up to 8-df more than the primary analysis model in Aim 1. The full genetic variant interaction model will be compared to the genetic variant main-effect model via a 4-df test of the null hypothesis that the treatment effect does not depend upon any of the four genetic variants. If this overall 4-df test of interactions is statistically significant at the 0.05 level, we will conclude that treatment varies by at least one of the four genetic variants. This testing paradigm is more efficient and powerful than separately testing each interaction term and then Bonferroni-correcting the four separate p-values for multiple comparisons, as it accounts for dependence between variants. But if we find

evidence of interaction via the 4-df test, we will go on to test individual interaction terms via separate 1-df robust Wald tests. Furthermore, we plan to estimate the treatment effect as a function of each genetic variant, along with robust 90% CI. This is analogous to our investigation in Aim 2. Moreover, we will also compare EFS by variant among just the N=140 treated patients, using a grouped relative risk model, replacing the treatment indicator by genetic variants.

Furthermore, we plan to perform whole exome sequencing (WES) and apply specializations of the Sequence Kernel Association Test (SKAT) to explore effects of additional variants. Variants of interest in a region (e.g. a gene) are combined through a kernel function and then related to outcomes. While the kernel provides flexibility in choosing how variants are related to outcomes, the optimal kernel depends on the true, unknown nature of the underlying biology. Therefore, we will use multi-kernel SKAT (MK-SKAT), which controls the Type I error while maintaining high power by simultaneously considering more than one kernel; this approach has been shown to be useful in smaller WES studies. These SKAT-based methods could identify potentially meaningful genes worthy of further study.

Correlative study: Tumor Gene Expression
The primary aim of the tumor gene expression study is to assess the relationship between vitamin D level at baseline and PD-L2 (as a marker of immune infiltration). The outcome will be continuous PD-L2 (possibly transformed, e.g. by log), linearly modeled as function of continuous baseline Vitamin D. The first step will be to estimate the density of each variable using kernel density estimators. If the distribution of PD-L2 appears strongly skewed, PD-L2 will be transformed (e.g. via log or square root) to a more approximately symmetric distribution. Vitamin D levels are expected to be approximately normal, but that will be investigated as well, and transformations considered. Following potential data transformation, the relationship between the variables will be visualized using a scatterplot with the least squared line superimposed. Inference will be based on a 2-sided 0.05 level test of correlation. A sample size of 56 (50-65) patients with complete data will provide 85% (80-90%) power to detect R^2 = 15% (NCSS PASS v15).

We conjecture that we will be able to identify malignant B cells from healthy cells using protein and gene expression profiles in the spatial genomics analysis. We will characterize the cellular composition of non-malignant cells in the scanned slides using de novo clustering procedures developed for single cell RNA-Seq data. We will explore spatial relationships of each cell subpopulation by characterizing area and spatial entropy at various scales. We will explore spatial correlation between cell subpopulations using spatial cross-correlograms.

13.3. **Data and Safety Monitoring**

For the current randomized double blind Phase III trial, we have assembled an independent Data and Safety Monitoring Board and will follow the Data and Safety Monitoring Plan (DSMP) according to the procedure guidelines set forth by the Wilmot Cancer Institute Protocol Review Committee and Wilmot Cancer Institute Data and Safety Monitoring Committee at the University of Rochester. The DSMP and DSMB procedure guidelines are designed to adhere to Good Clinical Practice (GCP) based on Code of Federal Regulations, FDA policy, International Conference on Harmonization guidelines, and institutional RSRB policies. Compliance with GCP ensures that safety of human subjects is not compromised, the study is carefully conducted, protocol is strictly adhered to, and adverse events are properly reviewed and reported. According to GCP guidelines, responsibility for the protection of human subjects and proper conduct of clinical trials is shared among the principal investigator, clinical trial sponsor, institutional RSRB, and the independent DSMB.

Overall Framework for Safety Monitoring

Regular assessment of data quality (audit reports and accrual progress reports) and toxicities will enable the DSMB to assess whether significant risks are occurring that would warrant study closure. Study progress reports will be reviewed to determine whether accrual projections are being met and to determine if the trial should be continued based upon the likelihood of timely completion. Cumulative reports of adverse events including SAE's previously reported for expedited review and any new serious or non-serious adverse event are also reviewed. Discussion of these results will be held during a closed session of the DSMB Meetings in order to maintain confidentiality.

Data Quality Control: We will utilize both auditing/quality assurance review and review of accrual and cumulative events to ensure that our patient data are of the highest quality. Reports of these quality control activities will be reviewed in monthly meetings with the study PI, study manager, and study statistician, and will also be submitted and discussed at the semi-annual DSMB meetings. These two reports will also be submitted with recommendations for follow-up or corrective action to the PI after DSMB review. The PI reviews the reports, communicates as needed with the study sites, implements corrective action, and notifies the Chair of the DSMB of these actions.

Internal Audit / Quality Assurance Review: Data monitoring assures the quality of study execution at the level of the investigator. The primary objective of our trial audit plan is to verify the accuracy of the data by comparing submitted data to source records at the member institutions. We will be subject to review from our local URMC Research Subjects Review Board. In addition, our study team (the program manager) will be responsible for auditing the participating sites, in person, once each during the three-year recruitment period. The audit procedure is a formal, comprehensive, source document review. Ten percent or a minimum of 3 charts from each site will be selected for review in advance of the audit visit. The audit will be scheduled at a mutually agreed upon time. The following elements will be reviewed:

1. Source document verification of eligibility, response, treatment compliance, and toxicity.
2. Regulatory review of IRB compliance and external reporting requirements.
3. Drug accountability and handling.
4. Completeness and quality of data.
5. Compliance with reporting procedures (including adverse events requiring expedited reporting).

In advance of the visit, each participating sites will prepare for the scheduled audit by gathering all source documentation pertaining to each selected case. The following items are considered (but not limited to) source documentation:

- Inpatient and outpatient medical records (progress notes, diagnostic reports, laboratory data, etc.
- Study flow sheets, data forms that are signed and dated where indicated
- Appointment books, calendars
- Enrollment tracking forms
- Subject diaries, calendars
- Drug dispensing logs
- Informed consents and IRB documents (including initial IRB study approval, annual re-approvals with study progress reports, study amendment approvals, etc.)

The pharmacy must be alerted that the auditors will conduct an on-site inspection of investigational agent storage and records. All records regarding the disposition of investigational study agents (including copies of drug orders, return receipts and the NCI Drug Accountability Records) must be made available to the audit team.

The auditors will review specific data related to the research and regulatory requirements. The exercise will consist of reviewing and evaluating:

- conformance to IRB and informed consent requirements
- the pharmacy and use of NCI Drug Accountability Record Forms or the institutional equivalent
- individual patient cases.

At the conclusion of the audit visit, the audit team will conduct an exit interview with the responsible investigator(s) and staff. Preliminary findings will be discussed and recommendations made. This interview allows an opportunity for immediate feedback and/or clarification of any deficiencies found by the auditors.

Where permitted the program manager may be granted remote access to subject electronic medical records. Source document review and data verification will be performed remotely in addition to the in-person visit.

Frequency of Monitoring, interim analysis and stopping rules

The planned frequency of independent DSMB monitoring will be semi-annually, commensurate with the relative risks and complexity of our clinical trial.

Interim Analysis: No interim analyses are planned for this trial, and there is no planned sample size re-estimation.

Individuals and Groups Responsible for Trial Monitoring

a) **PI:** will ensure that the trial is conducted according to protocol, review AE an SAE grading and attribution, and will communicate all DSMB recommendations to the participating sites.

b) **Trial Manager:** will be responsible for daily accrual and safety monitoring, preparing summary reports for DSMB meetings (together with the statistician), and monitoring of data and regulatory integrity through site audits.

c) **Data and Safety Monitoring Board:** Monitoring activities will be conducted by experts in all scientific disciplines needed to interpret the data and ensure patient safety. We have assembled a Board which includes clinical trials experts, a biostatistician, and clinicians knowledgeable about the disease and treatment under study. All members are from outside the institution. Members will be tasked with viewing themselves as representing the interest of patients and not that of the institutions. Investigators directly involved with the conceptual design or analysis of the particular trial will not serve on the DSMB.

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15. **APPENDICES**

Appendix 1

Deauville Score	
Score 1	No uptake
Score 2	Uptake ≤ mediastinum
Score 3	Uptake > mediastinum but ≤ liver
Score 4	Moderately increased uptake > liver
Score 5	Markedly increased uptake > liver and/or new lesions related to lymphoma
X	New areas of uptake unlikely to be related to lymphoma

Appendix 2

Lugano Classification:
Revised Criteria for Response Assessment

Response Criteria	PET/CT-Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete Radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5-point scale. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤1.5 cm in longest dimension No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extra-lymphatic sites	Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5mm x 5mm as the default value. When no longer visible, 0mm x 0mm. For a node > 5 mm, but smaller than normal, use actual measurement
Non-measured sites	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an	Not applicable

Response Criteria	PET/CT-Based Response	CT-Based Response
	interval scan	
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: longest dimension >1.5 cm and increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤2cm, 1.0 cm for lesions >2cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement