

A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia
during R-CHOP chemotherapy
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC # 98317

Principal Investigator:

Rakhee Vaidya, MD
Department of Internal Medicine
Hematology and Oncology
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157



Biostatistician:

Janet Tooze, PhD
Department of Biostatistical Sciences
Wake Forest Baptist Comprehensive Cancer Center
Wake Forest School of Medicine
Medical Center Blvd
Winston-Salem, NC 27157



Participating Institution(s):

WFBCCC

Version Date:

05/11/2018

Amended:

06/03/2021; 09/22/2025

Confidential

Table of Contents

SCHEMA.....	5
1.0 Introduction and Background	6
2.0 Objectives	7
2.1 Primary Objective.....	7
2.2 Secondary Objective(s).....	7
2.3 Exploratory objectives	8
3.0 Patient Selection	8
3.1 Inclusion Criteria	8
3.2 Exclusion Criteria	8
3.3 Inclusion of Women and Minorities.....	9
4.0 Registration Procedures.....	9
5.0 Study Outcomes and Study Measures	10
5.1 Primary Outcome	10
5.2 Secondary Outcomes.....	10
5.3 Exploratory Outcomes.....	11
6.0 Treatment Plan	11
6.1 Study-Related Activities	11
6.2 Treatment Administration	12
6.3 General Concomitant Medication and Supportive Care Guidelines	13
6.4 Duration of Therapy	14
6.5 Duration of Follow Up.....	14
6.6 Additional Study Activities	14
6.7 Criteria for Removal from Study	14
7.0 Dosing Delays/Dose Modifications	15
7.1 Dosage with toxicity	16
8.0 Measurement of Effect.....	18
8.1 Antitumor Effect – Hematologic Tumors	18
9.0 Adverse Events List and Reporting Requirements	19
9.1 Adverse Event List for Prednisone	19
9.2 Adverse Event List for doxorubicin	21
9.3 Adverse Event List for vincristine	23
9.4 Adverse Event List for rituximab.....	25

9.5	Adverse Event List for cyclophosphamide	29
9.6	Adverse Events List for Filgrastim	35
9.7	Adverse Event Characteristics	37
9.8	DSMC SAE Reporting Requirements	37
9.9	WFUHS IRB AE Reporting Requirements	37
10.0	Pharmaceutical Information.....	38
10.1	Pharmaceutical Accountability.....	38
10.2	Rituximab	38
10.3	Prednisone.....	39
10.4	Vincristine	40
10.5	Cyclophosphamide.....	41
10.6	Doxorubicin	43
11.0	Correlative/Special Studies	46
11.1	Laboratory Correlative Studies	47
12.0	Data Management	48
13.0	Statistical Considerations	48
13.1	Analysis of Primary Objective.....	48
13.2	Analysis of Secondary Objective	48
13.3	Analysis of Exploratory Analysis.....	49
13.4	Power and Sample Size	49
13.5	Estimated Accrual Rate:.....	50
13.6	Estimated Study Length	50
	References	51
	Appendix A – Eligibility Checklist	53
	Appendix B – Protocol Registration Form	55
	Appendix C - Race & Ethnicity Verification Form	56
	Appendix D – Mandatory DSMC SAE Reporting Guidelines	57
	Appendix E – Adverse Event Log	63
	Appendix F - Lymphoma Response Form	64
	Appendix G – FACT-Lym.....	67
	Appendix H – FACT - GOG/NTX-4, v4	72
	Appendix I – PROMIS 29.....	73
	Appendix J – Baseline (Pre-Treatment) Data Collection Form.....	75

Appendix K- Hyperglycemia Outcomes 76

Appendix L - R-CHOP Cycle Form 77

Appendix M - CRU Processing Laboratory Requisition 79

Appendix N – Prednisone Diary..... 80

Appendix O – Off-Study Form..... 82

Appendix P– Drug Inserts 84

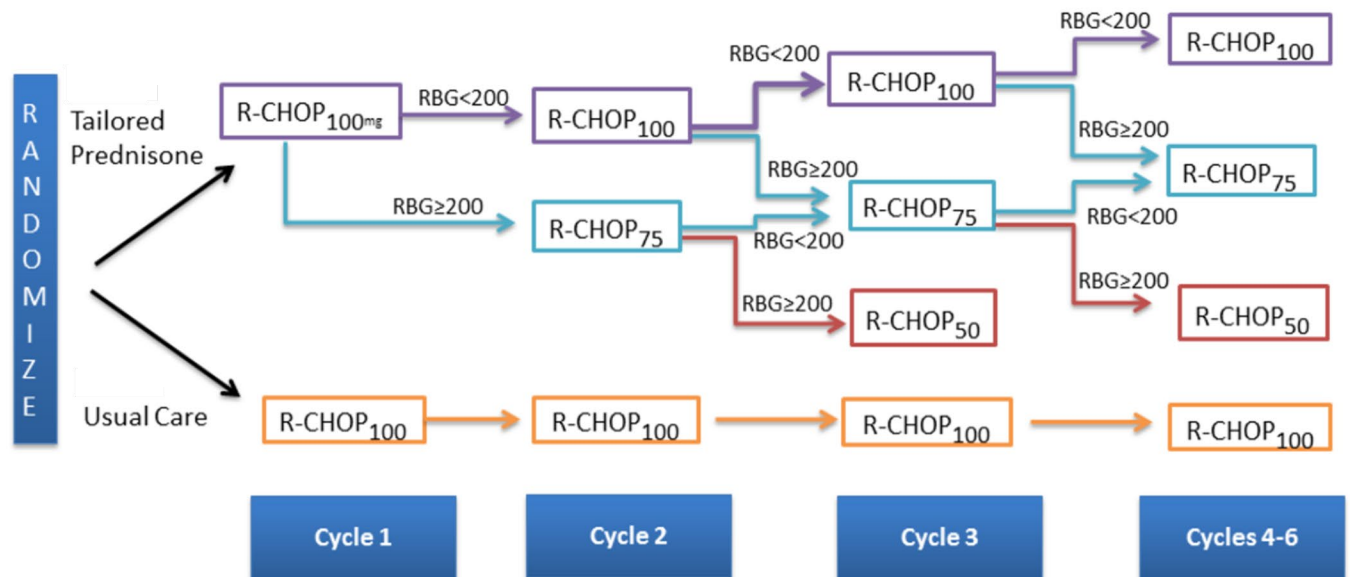
Appendix Q – PRO-CTCAE 85

Appendix R – 30-day Treatment Follow-up Form..... 87

SCHEMA

Patients planned for R-CHOP therapy will be randomized to standard or prednisone tailored groups as illustrated below. Cycles 4-6 will continue dose reductions in the tailored arms as illustrated in the previous cycles. Prednisone doses will not decrease below 50 mg unless directed by the treating physician.

R-CHOP schema



Prednisone in R-CHOP is given once daily in mg

1.0 Introduction and Background

Adult survivors of non-Hodgkin lymphoma (NHL) are increasing, but have late excess mortality: NHL is the 7th most common type of cancer, with nearly 72,000 new cases diagnosed each year.¹ Advances in treatment over the last 40 years have significantly improved survival rates – relative 5-year survival is now over 70%.¹ Nonetheless, patients with aggressive NHL subtypes have late excess mortality compared to the general population, even after 5 years of survivorship.^{2,3} While increased rates of post-chemotherapy cardiovascular disease represent a significant source of late excess mortality, the effects of other adverse events such as hyperglycemia and diabetes mellitus (DM) are not well understood and should be explored further. This study will provide baseline information for future studies on that topic. Retrospective data from our institution demonstrate that 47% of 160 patients treated with first line rituximab, cyclophosphamide, vincristine and prednisone (R-CHOP) or dose adjusted R-EPOCH between 2012 and 2015 had at least one episode of hyperglycemia (glucose ≥ 200 mg/dL. On multivariate analysis those with hyperglycemia were more likely to have chemotherapy delays or dose reductions of chemotherapy ($p = 0.028$; OR 2.2, 95% CI 1.1 – 4.6).

Prednisone and similar glucocorticoids can lead to hyperglycemia, which can cause or worsen diabetes.⁴⁻⁶ The National Comprehensive Cancer Network (NCCN) recommends using the lowest dose of prednisone for the shortest possible time because of the myriad of negative adverse effects in supportive care treatment for elderly patients. Despite this, there are not data evaluating optimal prednisone dosing or scheduling during treatment with R-CHOP or R-EPOCH.⁷ In landmark randomized clinical trials establishing R-CHOP as standard of care in NHL, adverse events directly attributable to prednisone, such as hyperglycemia or prednisone induced DM were not characterized and prednisone doses varied from 100 mg to 100 mg/m² daily for 5 days each cycle.^{8,9} In another landmark R-CHOP trial “severe non-compensated diabetics” were excluded.¹⁰ The study builds on retrospective data showing that over 30% of non-diabetic NHL patients will develop steroid induced diabetes¹¹ and observational based studies in aggressive NHL showing increased chemotherapy related toxicity and worsened overall survival with a comorbidity such as DM.^{12,13}

Pre-DM and DM are epidemics. According to the Centers for Disease Control (CDC), 29 million people in the US have DM and 86 million have pre-DM costing nearly \$250 billion in health care expenditures, lost work and wages. Further, up to 33% of those with pre-DM will develop type 2 DM within 5 years.¹⁴ Up to 25% of US adults who have diabetes are unaware.¹⁵ Appropriate interventions can prevent the onset of type 2 DM in those with pre-DM,^{16,17} but these data are lacking in those with concurrent NHL. Observational studies have shown that dose reduction of all components of R-CHOP is feasible, particularly in older patients, although there are *not data looking specifically at prednisone reduction.*^{18,19}

The American Diabetes Association defines pre-DM or DM using fasting blood glucose (FBG), hemoglobin A1c (HbA1c) or an oral glucose tolerance test. Retrospective studies evaluating prednisone induced hyperglycemia, including ours, evaluated random blood glucose (RBG) because this is drawn as a standard part of labs during chemotherapy. The ideal glycemic measure to diagnose DM or pre-DM during R-CHOP is unknown.

One of the major limitations of HbA1c, the gold standard for pre-DM or DM diagnosis, is that it may be an inaccurate measure of long-term glucose control in patients with disordered hematopoiesis, anemia, those that have been transfused and in certain minority populations.²⁰ Fructosamine, is an alternative glycemic measure and is not altered by anemia or disordered hematopoiesis.^{21,22} The short and long-term consequences of hyperglycemia are known, the rates of DM and pre-DM represent a public health crisis, and high dose prednisone remains a mainstay of R-CHOP chemotherapy without data to discriminate on whether the benefits outweigh the toxicity in high-risk NHL patients. The proposed study will contribute to a better **understanding of how to prevent or reduce prednisone induced hyperglycemia during standard or tailored R-CHOP may improve chemotherapy delivery and could impact long-term outcomes.** We will explore whether tailored prednisone reduction results in decreased rates of hyperglycemia as compared to standard prednisone dosing and whether alternative glucose measures will impact the incidence of hyperglycemia. Although limited to lymphoma, this study could be a model for at-risk patients with solid and hematologic malignancies.

2.0 Objectives

The objectives in this study aim to address the incidence of hyperglycemia in non-Hodgkin lymphoma patients receiving standard and tailored prednisone dosage R-CHOP chemotherapy.

2.1 Primary Objective

- 2.1.1 To compare the cumulative incidence of hyperglycemia after 3 cycles of treatment between standard or tailored R-CHOP chemotherapy

2.2 Secondary Objective(s)

- 2.2.1 To compare the cumulative incidence of hyperglycemia after 6 cycles of treatment and at 6 months post-treatment between standard or tailored R-CHOP chemotherapy
- 2.2.2 To compare response rates after 6 cycles of treatment as measured by Cheson's criteria²³ between standard or tailored R-CHOP chemotherapy
- 2.2.3 To compare cumulative rates of grade III or higher adverse events using CTCAE criteria between standard or tailored R-CHOP chemotherapy from cycle 1 through cycle 6.
- 2.2.4 To compare severity of prednisone related adverse events using the PRO-CTCAE form between standard or tailored R-CHOP chemotherapy from cycle 1 through cycle 6
- 2.2.5 To compare health related quality of life (HRQOL) between standard or tailored R-CHOP chemotherapy at baseline, cycle 4 day 1 and after cycle 6

2.3 Exploratory objectives

- 2.3.1 To evaluate the alternative glucose measures of FBG, HbA1c, fasting insulin and fructosamine to estimate hyperglycemia.
- 2.3.2 To compare health related quality of life (HRQOL) in those with and without hyperglycemia after 3 cycles, 6 cycles, and 6 months post R-CHOP chemotherapy.
- 2.3.3 To compare glycemic variability between the standard and tailored prednisone arms at Day 1 of each cycle
- 2.3.4 To determine the ability of patients in the standard or tailored prednisone R-CHOP groups to complete all six cycles of chemotherapy
- 2.3.5 To compare overall survival (OS) between standard or tailored R-CHOP chemotherapy

3.0 Patient Selection

3.1 Inclusion Criteria

- 3.1.1 Diagnosis of B cell Non-Hodgkin lymphoma confirmed by WHO criteria
- 3.1.2 Planned treatment with R-CHOP chemotherapy
- 3.1.3 18 years of age or older
- 3.1.4 ECOG performance status of 0 - 3
- 3.1.5 Life expectancy of greater than 3 months with chemotherapy
- 3.1.6 The effects of R-CHOP on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately
- 3.1.7 Ability to understand and the willingness to sign an IRB-approved informed consent document.

3.2 Exclusion Criteria

- 3.2.1 Uncontrolled HIV, CD4 count < 50
- 3.2.2 Diagnosis of Primary CNS lymphoma
- 3.2.3 Unable to receive R-CHOP chemotherapy.
- 3.2.4 History of severe (i.e. anaphylactic) allergic reactions attributed to compounds of similar chemical or biologic composition to glucocorticoids and other component of R-.
- 3.2.5 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection not controlled with antibiotics, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia that cannot be rate controlled with medications, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.6 Pregnant women are excluded from this study because R-CHOP includes D Class agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with R-CHOP, breastfeeding should be discontinued if the mother is treated with these agents.

3.3 Inclusion of Women and Minorities

Women of all races and ethnicity who meet the above-described eligibility criteria are eligible for this trial.

The study consent form will also be provided in Spanish for Spanish-speaking participants. Based on WFBCCC population estimates, we expect approximately 40% of participants to be women. Translating this to our sample size estimate of 80, we plan to enroll at least 32 women. Similarly, we expect approximately 3.3% of study participants to be Hispanic/Latino (N = 2). We plan to enroll at least 5% Black or African American (N = 4). Due to population estimates in our catchment area we do not expect recruitment of individuals of American Indian/Alaska Native or Asian ancestry but these patients will not be excluded if they meet the criteria listed in eligibility section. Should we not meet or exceed these estimates, Dr. Vaidya will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist ([Appendix A](#))
2. Complete the Protocol Registration Form ([Appendix B](#))
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.



*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- randomize the patient
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

- 5.1.1 The cumulative incidence of hyperglycemia of standard or tailored R-CHOP after 3 cycles of chemotherapy

5.2 Secondary Outcomes

- 5.2.1 The cumulative incidence of hyperglycemia of standard or tailored R-CHOP at baseline, 6 cycles and at 6 months after completion of chemotherapy
- 5.2.2 Response rates after 6 cycles of standard or tailored R-CHOP as measured by Cheson's criteria²³
- 5.2.3 Rates of grade III or higher adverse events using CTCAE criteria from standard or tailored R-CHOP
- 5.2.4 Severity of prednisone related adverse events using the PRO-CTCAE form between standard or tailored R-CHOP chemotherapy from cycle 1 through cycle 6

5.2.5 Health related quality of life (HRQOL) scores using the FACT-Lym, FACT GOG-Ntx additional concerns and PROMIS 29.

5.3 Exploratory Outcomes

5.3.1 FBG, HbA1C, fasting insulin and fructosamine levels.¹

5.3.2 Health related quality of life (HRQOL) scores in those with and without hyperglycemia after 3 cycles, 6 cycles, and 6 months post R-CHOP chemotherapy.

5.3.3 Glycemic variability

5.3.4 Percentage of patients in the standard and tailored prednisone R-CHOP arms complete all six cycles of chemotherapy

5.3.5 OS as the duration from enrollment to the date of death due to death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

6.0 Treatment Plan

6.1 Study-Related Activities

	Pre-Treatment ^a	Day 1 of each cycle	Cycle 4, Day 1 and 1 st visit after cycle 6 ⁱ	6 months post R-CHOP completion	Follow-up ^j
Informed consent	X				
Demographics, Medical history	X				
Concurrent meds	X	X			
Physical exam ^h , Vital signs, Weight, M ² Performance Status ^h	X	X		X	
IPI Score	X				
Imaging PET* or CT scan/ tumor measurements	X		X	X	
CBC / Serum chemistry	X	X		X	
B-HCG ^b	X				
Random Blood Glucose ^c	X	X	X	X	

HbA1c, fasting blood glucose ^f , fasting insulin and fructosamine	X		X	X	
Adverse event evaluation for prednisone ^e	X	X	X		
Documentation of time and contents of last meal		X		X	
Store blood for future studies (remaining serum sample from FBG and fructosamine draws)	X		X	X	
Health related quality of life using PROMIS measures, FACT GOG Ntx, and FACT- Lym	X		X	X	
PRO CTCAE	X	X ^g	X ^g		
Collection of survival data ^j					X

^a Pre-treatment requirements listed in table must be completed **within** 28 days of cycle 1 day 1 except imaging (PET or CT) must be completed within 42 days of cycle 1 day 1..

^b Serum pregnancy test (women of childbearing potential).

^c Random blood glucose to be drawn twice on Day 1; of each cycle prior to chemotherapy, and then, a minimum of 2 hours after infusion begins

* PET or CT can be done any time after cycle 3 treatment is complete but prior to start of cycle 4. Pet is required for the end of treatment (after cycle 6) imaging

^e Evaluate during entire cycle

^f Sent out for testing. Keep results unavailable until end of study

^g For cycle 1 day 1, no need to repeat PRO CTCAE if done at screening within the past 14 days. PRO CTCAE will be obtained on day 1 of all other cycles as well as at the end of cycle 6.

^h Physical examination, performance status may be performed within 5 days of day 1 of the cycle. Treatment delays are allowed per physician discretion for up to 5 days

ⁱ Completion of all therapy or the labs should be drawn once chemotherapy has finished on cycle 6 day 1

^j Annually for 5 years from date of enrollment.

6.2 Treatment Administration

Our study propositions that high dose prednisone increases rates of hyperglycemia and a tailored reduction of prednisone will result in reduced rates of hyperglycemia and adverse events without impacting response rates. We also propose that hyperglycemia may be underdiagnosed using RBG. We will enroll 80 adults ≥ 18 years of age undergoing chemotherapy with R-CHOP for NHL. At baseline all subjects will have testing to measure HbA1c, FBG, RBG and fructosamine. Patients will be randomized prior to starting R-CHOP to either usual care or tailored prednisone reduction combined with usual care. RBG will be drawn on day 1 of each cycle of chemotherapy at the following times: pre-infusion, post-infusion. Patients will receive prednisone at a dose of 100 mg daily on days 1-5 (R-CHOP₁₀₀) during the first cycle. The remaining components will be given as follows unless cause for dose modifications ([Section 7](#)) occurs:

***rituximab** 375 mg/m² IV Day 1 or (subcutaneous per package insert starting with cycle 2), **vincristine** (Round to nearest 0.1 mg; Max 2 mg)1.4 mg/m² IV Day 1, **doxorubicin** (Round to nearest 1 mg) 50 mg/m² IV Day 1,

cyclophosphamide (Round to nearest 10 mg) 750 mg/m² IV Day 1. The cycle is 21 days. The regimen will continue for 6 cycles. *Note Rituximab hycela may be used at physician discretion for cycles 2-6 per the package insert and institutional guidelines. Adverse event related to prednisone dosing should be collected at each cycle on the R-CHOP Cycle form ([Appendix L](#)).

- 6.2.1 Tailored prednisone Arm: If a participant has a RBG of ≥ 200 mg/dL prior on day one of any cycle of R-CHOP (as indicated by either the pre- or post-chemotherapy draws), then prednisone will be reduced by 25% from baseline (R-CHOP₇₅ [once daily]) in the subsequent cycle. If RBG is ≥ 200 mg/dL in subsequent cycles then prednisone will be further reduced to 50% (R-CHOP₅₀ [once daily]) from baseline in the following cycles. Once a prednisone reduction has occurred then the participant will complete therapy at the reduced dose unless a subsequent hyperglycemic episode occurs. There will not be prednisone reductions below 50% (R-CHOP₅₀ [once daily]).
- 6.2.2 Control Arm: Prednisone dosing in the control arm will not change from R-CHOP₁₀₀ (once daily). Participants will receive a maximum of six cycles of R-CHOP₁₀₀ (once daily). Usual care is defined as the provider's standard practice for managing hyperglycemia during R-CHOP (i.e. continued monitoring, referral to specialists, prescriptions or medications recommended, counseling, etc) will continue in both arms of the study. Prednisone dose reductions are not allowed for this arm unless intolerable side effects occur or physician discretion.

6.3 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, growth factor, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

For patients receiving R-CHOP with the following risk factors (below) growth factor support should be considered:

- Prior chemotherapy or radiation therapy
- Persistent neutropenia
- Bone marrow involvement of lymphoma
- Recent surgery and/or open wounds
- Liver dysfunction (bilirubin >2.0)
- Renal dysfunction (creatinine clearance < 50)
- Age > 65 years receiving full chemotherapy dose intensity

6.4 Duration of Therapy

If the participant is removed from study treatment when any of the criteria listed in [Section 6.4](#) applies, the participant will be followed for a minimum of 30 days as described in [Section 6.5](#) for adverse events. If the participant is removed from study treatment, they will be followed for intention to treat analysis; however, they will not receive the study treatment regimen.

In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.5 Duration of Follow Up

Patients will be followed for a minimum of 30 days after the last study drug is administered for adverse events monitoring. If the patient has not come in for a clinical appointment, phone contact with the patient should be made to record any adverse events and recorded on [Appendix R](#).

Study follow-up for incidence of hyperglycemia will be for 6 months post completion of R-CHOP.

Follow-up for survival will be annually for up to 5 years.

6.6 Additional Study Activities

6.6.1 Blood Draws

6.6.1.1 Blood is drawn per the study calendar schedule in [Section 6.1](#). The description for blood processing is detailed in [Section 11](#). Location to store research blood and processing of research blood draws is also found in this section.

6.6.2 PROs

6.6.2.1 PROs (PROMIS 29, FACT-Lym, FACT GOG-Ntx, and PRO-CTCAE) will be administered per the study calendar schedule in [Section 6.1](#). Descriptions of the PROs are found in [Section 11](#).

6.7 Criteria for Removal from Study

Participants will remain on study until 5 years from enrollment. Reasons a participant may be removed from the study early include, but are not limited to:

- Participant non-compliance with study participation, in the opinion of the investigator

- The participant or legal representative (such as a parent or legal guardian) withdraws study consent from all study activities.
- The participant is lost to follow-up (defined as 4 unsuccessful attempts to reach the participant, with the initial attempts via phone every 2 weeks x 3 and last attempt in writing)
- Investigator's decision to remove the participant
- Participant death
- Early study termination

When participants are removed from the study, the reason for study removal and date the participant was removed should be documented.

Participants that are Off Study will not participate in any study related procedures, including prospective data collection.

7.0 Dosing Delays/Dose Modifications

Dose modifications for prednisone for the prednisone-dose-adjusted arms will include a reduction by 25% every time the patient has a random blood glucose test of 200 mg/dL or higher on day 1 of each cycle until the dose reaches 50% from baseline. Dose modifications for prednisone based on random blood glucose in the standard therapy arm of R-CHOP treatment will be at the discretion of the treating physician.

Additional information and section referenced below related to the drugs can be found in the drug inserts in [Appendix P](#).

7.1 Dosage with toxicity

7.1.1 Hematologic and Non-Hematologic Toxicities:

Toxicity	Doxorubicin ¹ (% previous dose)	Vincristine ¹ (% previous dose)	Cyclophosphamide ¹ (% previous dose)	Rituximab ^{1,2} (% previous dose)
Grade 4 hematological $\geq$ 7 days, febrile neutropenia, bleeding	75%, or G-CSF for low ANC	100%	75%, or G-CSF for low ANC	100%
Grade 3 nonhematological toxicity	75%	100%	75%	100% or delay
Grade 4 organ toxicity	Discontinue	Discontinue	Discontinue	Discontinue
Neurotoxicity	100%	Grade 1: 75% of dose; Grade 2: Hold until recovery, then ↓ 50%; Grade 3 or higher: Discontinue	100%	100%
- Severe rash - Serious/life threatening cardiopulmonary events - PML/RPLS; Reactivation of TB or hepatitis B - Evidence of active hepatitis	Discontinue	Discontinue	Discontinue	Discontinue
Grade 1-2 infusion related				Stop or slow infusion; exclude respiratory symptoms; treat symptomatically. Re-start at

				50% previous rate after resolution of symptoms.
≥Grade 3 Infusion related/ pulmonary				Discontinue; Manage appropriately; monitor patient until complete resolution.

¹Prior to retreatment, major organ toxicity should have recovered to ≤ grade 2 and ANC to ≥ 1000/mcL and platelets ≥ 100 x 10⁹/L (unless at physician discretion).

²Missed or delayed doses may be administered at a later time point, based on physician's discretion

7.2 Hepatic Impairment

Consider dose modification for doxorubicin and vincristine for severe increase in transaminases.

Bilirubin	Doxorubicin (% previous dose)	Vincristine (% previous dose)	Cyclophosphamide (% previous dose)	Rituximab (% previous dose)
1 – 2 X ULN	50%	50%	100%	No adjustment required
2 – 4 x ULN	25%	25%	Caution	No adjustment required
> 4 ULN	Discontinue	Discontinue	Caution	No adjustment required

7.2.1 Renal Impairment

Creatinine Clearance (mL/min)	Doxorubicin (% previous dose)	Vincristine (% previous dose)	Cyclophosphamide (% previous dose)	Rituximab (% previous dose)
30-50	No adjustment required	No adjustment required	per clinician discretion	No adjustment required
10-30			consider dose reduction	
< 10			consider dose reduction	

8.0 Measurement of Effect

8.1 Antitumor Effect – Hematologic Tumors

Response will be determined by Cheson's criteria

Cheson et al., 2014 Response Definitions:

Response	Site	PET-CT-Based Response	CT-Based Response
Complete Response		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 5PS [†]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LD _i
		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	No extralymphatic sites of disease
Nonmeasured 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

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Partial Response	Partial metabolic response	Partial remission (all of the following):
Lymph nodes and extralymphatic sites	Score 4 or 5 [†] with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	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 interval scan	Not applicable

† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma

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
Nonmeasured 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

9.0 Adverse Events List and Reporting Requirements

Additional information on all drugs used in this study and any sections referenced in section 9 can be found in the drug inserts in [Appendix P](#)

9.1 Adverse Event List for Prednisone General

The most commonly reported adverse effects associated with corticosteroid use include fluid retention, alteration in glucose tolerance, high blood pressure, behavior and mood changes, increased appetite and weight gain. Occurrence is often associated with dose and duration of therapy; long-term effects include HPA suppression, Cushingoid appearance, cataracts and increased intraocular pressure/glaucoma, osteoporosis and vertebral compression fractures.

Metabolic

Frequency not reported: Decreased carbohydrate and glucose tolerance, increased requirements for insulin or oral hypoglycemic agents in diabetics, lipid abnormal, negative nitrogen balance caused by protein catabolism, hypokalemia, hypokalemic alkalosis, metabolic alkalosis, potassium loss, sodium retention with resulting edema, increased appetite and weight gain, anorexia and weight loss, hypertriglyceridemia, hypercholesterolemia

Cardiovascular

Frequency not reported: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, ECG changes caused by potassium deficiency, edema, fat embolism, hypotension, hypertension or aggravation of hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, necrotizing angiitis, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis

Endocrine

Frequency not reported: Adrenal insufficiency associated symptoms including arthralgias, buffalo hump, amenorrhea, postmenopausal bleeding or menstrual irregularities, development of cushingoid state, hyperthyroidism, hypothyroidism, moon face, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress as in trauma, surgery, or illness), increased or decreased motility and number of spermatozoa

Ocular

Frequency not reported: Blurred vision, cataracts (including posterior subcapsular cataracts) central serous chorioretinopathy, secondary bacterial, fungal, and viral infections, exophthalmos, glaucoma, increased intraocular pressure

Gastrointestinal

Frequency not reported: Abdominal distention, abdominal pain, constipation, diarrhea, gastric irritation, nausea, oropharyngeal candidiasis, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis, vomiting

Immunologic

Frequency not reported: Immunosuppression, aggravation/masking of infections, decreased resistance to infection

Musculoskeletal

Frequency not reported: Arthralgia, aseptic necrosis of femoral and humeral heads, increased risk of fracture, loss of muscle mass, muscle weakness, myalgias, osteopenia, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture (particularly of the Achilles tendon), vertebral compression fractures, suppression of growth in pediatric patients

Hypersensitivity

Frequency not reported: Anaphylaxis, angioedema, allergic reactions

Nervous system

Frequency not reported: Arachnoiditis, benign intracranial hypertension, convulsions, dementia, dizziness, EEG abnormalities, impaired cognition, increased intracranial pressure with papilledema, increased motor activity,

ischemic neuropathy, severe tiredness or weakness, meningitis, neuritis, neuropathy, paraparesis/paraplegia, sensory disturbances

Psychiatric

Frequency not reported: Amnesia, anxiety, delirium, depression, emotional instability and irritability, euphoria, hallucinations, severe psychiatric symptoms, insomnia, long-term memory loss, mania, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychiatric disorders including steroid psychoses or aggravation of preexisting psychiatric conditions, restlessness, schizophrenia, verbal memory loss, withdrawn behavior

Hematologic

Frequency not reported: Anemia, neutropenia, febrile neutropenia, moderate leukocytosis, lymphopenia, eosinopenia, polycythemia

Dermatologic

Frequency not reported: Acne, acneiform eruptions, allergic dermatitis, alopecia, angioedema, angioneurotic edema, atrophy and thinning of skin, dry scaly skin, ecchymosis and petechiae (bruising), erythema, facial edema, hirsutism, impaired wound healing, increased sweating, lupus erythematosus-like lesions, perineal irritation, purpura, rash, striae, subcutaneous fat atrophy, suppression of reactions to skin tests, telangiectasis, thin fragile skin, thinning scalp hair, urticaria, hypertrichosis

Hepatic

Frequency not reported: ALT, AST and alkaline phosphatase elevations (usually reversible upon discontinuation), hepatomegaly

Respiratory

Frequency not reported: Hiccups, pulmonary edema

Oncologic

Frequency not reported: Kaposi's sarcoma

Other

Frequency not reported: Vertigo, pyrexia, abnormal fat deposits, malaise

9.2 Adverse Event List for doxorubicin

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity. Other reactions reported are:

Cardiotoxicity - Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m² of doxorubicin, 3 to 5% at a dose of 400 mg/m², 5 to 8% at 450 mg/m² and 6 to 20% at 500 mg/m². The risk of developing CHF increases rapidly with increasing total cumulative doses of

doxorubicin in excess of 400 mg/m². Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk of cardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present. Pediatric patients are at increased risk for developing delayed cardiotoxicity.

Cutaneous - Reversible complete alopecia occurs in most cases. Hyperpigmentation of nailbeds and dermal creases, primarily in pediatric patients, and onycholysis have been reported in a few cases. Radiation recall reaction has occurred with doxorubicin administration. Rash, itching, or photosensitivity may occur.

Gastrointestinal - Acute nausea and vomiting occurs frequently and may be severe. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur within 5 to 10 of beginning therapy, and most patients recover from this adverse event within another 5 to 10 days. The effect may be severe leading to ulceration and represents a site of origin for severe infections. The dosage regimen consisting of administration of doxorubicin on three successive days results in greater incidence and severity of mucositis. Ulceration and necrosis of the colon, especially the cecum, may occur leading to bleeding or severe infections which can be fatal. This reaction has been reported in patients with acute non-lymphocytic leukemia treated with a 3-day course of doxorubicin combined with cytarabine. Anorexia, abdominal pain, dehydration, diarrhea, and hyperpigmentation of the oral mucosa have been occasionally reported.

Hematologic - Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) has been reported in patients treated with anthracyclines, including doxorubicin. The occurrence of refractory secondary AML or MDS is more common when anthracyclines are given in combination with DNA-damaging anti-neoplastic agents or radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. The rate of developing secondary AML or MDS has been estimated in an analysis of 8563 patients with early breast cancer treated in 6 studies conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), including NSABP B-15. Patients in these studies received standard doses of doxorubicin and standard or escalated doses of cyclophosphamide (AC) adjuvant chemotherapy and were followed for 61,810 patient years. Among 4483 such patients who received conventional doses of AC, 11 cases of AML or MDS were identified, for an incidence of 0.32 cases per 1000 patient years (95% CI 0.16-0.57) and a cumulative incidence at 5 years of 0.21% (95% CI 0.11-.41%). In another analysis of 1474 patients with breast cancer who received adjuvant treatment with doxorubicin-containing regimens in clinical trials conducted at University of Texas M.D. Anderson Cancer Center, the incidence was estimated at 1.5% at 10 years. In both experiences, patients who received regimens with higher cyclophosphamide dosages, who received radiotherapy, or who were aged 50 or older had an increased risk of secondary AML or MDS. Pediatric patients are also at risk of developing secondary AML.

Hypersensitivity - Fever, chills and urticaria have been reported occasionally. Anaphylaxis may occur. A case of apparent cross sensitivity to lincomycin has been reported.

Neurological - Peripheral neurotoxicity in the form of local-regional sensory and/or motor disturbances have been reported in patients treated intra-arterially with doxorubicin, mostly in combination with cisplatin. Animal studies have demonstrated seizures and coma in rodents and dogs treated with intra-carotid doxorubicin. Seizures and coma have been reported in patients treated with doxorubicin in combination with cisplatin or vincristine.

Ocular - Conjunctivitis, keratitis, and lacrimation occur rarely.

Other - Malaise/asthenia have been reported.

9.3 Adverse Event List for vincristine

In general, adverse reactions are reversible and are related to dosage. The most common adverse reaction is hair loss; the most troublesome adverse reactions are neuromuscular in origin.

When single, weekly doses of the drug are employed, the adverse reactions of leukopenia, neuritic pain, and constipation occur but are usually of short duration (ie., less than 7 days). When the dosage is reduced, these reactions may lessen or disappear. The severity of such reactions seems to increase when the calculated amount of drug is given in divided doses. Other adverse reactions, such as hair loss, sensory loss, paresthesia, difficulty in walking, slapping gait, loss of deep-tendon reflexes, and muscle wasting, may persist for at least as long as therapy is continued. Generalized sensorimotor dysfunction may become progressively more severe with continued treatment. Although most such symptoms usually disappear by about the sixth week after discontinuance of treatment, some neuromuscular difficulties may persist for prolonged periods in some patients. Regrowth of hair may occur while maintenance therapy continues.

The following adverse reactions have been reported:

Hepatic veno-occlusive disease has been reported in patients receiving vincristine, particularly in pediatric patients, as part of standard combination chemotherapy regimens. Some of the patients had fatal outcomes; some who survived had undergone liver transplantation.

Hypersensitivity – Rare cases of allergic-type reactions, such as anaphylaxis, rash and edema, that are temporally related to vincristine therapy have been reported in patients receiving vincristine as a part of multidrug chemotherapy regimens.

Gastrointestinal – Constipation, abdominal cramps, weight loss, nausea, vomiting, oral ulceration, diarrhea, paralytic ileus, intestinal necrosis and/or perforation, and anorexia have occurred. Constipation may take the form of upper-colon impaction, and, on physical examination, the rectum may be empty. Colicky abdominal pain coupled with an empty rectum may mislead the

physician. A flat film of the abdomen is useful in demonstrating this condition. All cases have responded to high enemas and laxatives. A routine prophylactic regimen against constipation is recommended for all patients receiving vincristine sulfate injection.

Paralytic ileus (which mimics the “surgical abdomen”) may occur, particularly in young pediatric patients. The ileus will reverse itself with temporary discontinuance of vincristine sulfate injection and with symptomatic care.

Genitourinary – Polyuria, dysuria, and urinary retention due to bladder atony have occurred. Other drugs known to cause urinary retention (particularly in the elderly) should, if possible, be discontinued for the first few days following administration of vincristine sulfate injection.

Cardiovascular – Hypertension and hypotension have occurred. Chemotherapy combinations that have included vincristine sulfate, when given to patients previously treated with mediastinal radiation, have been associated with coronary artery disease and myocardial infarction. Causality has not been established.

Neurologic – Frequently, there is a sequence to the development of neuromuscular side effects. Initially, only sensory impairment and paresthesia may be encountered. With continued treatment, neuritic pain and, later, motor difficulties may occur. There have been no reports of any agent that can reverse the neuromuscular manifestations that may accompany therapy with vincristine sulfate.

Loss of deep-tendon reflexes, foot drop, ataxia, and paralysis have been reported with continued administration. Cranial nerve manifestations, such as isolated paresis and/or paralysis of muscles controlled by cranial motor nerves including potentially life-threatening bilateral vocal cord paralysis, may occur in the absence of motor impairment elsewhere; extraocular and laryngeal muscles are those most commonly involved. Jaw pain, pharyngeal pain, parotid gland pain, bone pain, back pain, limb pain, and myalgias have been reported; pain in these areas may be severe. Convulsions, frequently with hypertension, have been reported in a few patients receiving vincristine sulfate. Several instances of convulsions followed by coma have been reported in pediatric patients. Transient cortical blindness and optic atrophy with blindness have been reported. Treatment with vinca alkaloids has resulted in both vestibular and auditory damage to the eighth cranial nerve. Manifestations include partial or total deafness which may be temporary or permanent, and difficulties with balance including dizziness, nystagmus, and vertigo. Particular caution is warranted when vincristine is used in combination with other agents known to be ototoxic such as the platinum-containing oncolytics.

Pulmonary - Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin-C and may require aggressive treatment, particularly when there is preexisting pulmonary dysfunction. The onset of these reactions may occur minutes to several hours after the vinca alkaloid is injected and may occur up to 2 weeks following the dose of mitomycin. Progressive

dyspnea requiring chronic therapy may occur. Vincristine sulfate should not be readministered.

Endocrine – Rare occurrences of a syndrome attributable to inappropriate antidiuretic hormone secretion have been observed in patients treated with vincristine sulfate. This syndrome is characterized by high urinary sodium excretion in the presence of hyponatremia; renal or adrenal disease, hypotension, dehydration, azotemia, and clinical edema are absent. With fluid deprivation, improvement occurs in the hyponatremia and in the renal loss of sodium.

Hematologic – Vincristine sulfate injection does not appear to have any constant or significant effect on platelets or red blood cells. Serious bone-marrow depression is usually not a major dose-limiting event. However, anemia, leukopenia, and thrombocytopenia have been reported. Thrombocytopenia, if present when therapy with vincristine sulfate injection is begun, may actually improve before the appearance of bone marrow remission.

Skin – Alopecia and rash have been reported.

Other – Fever and headache have occurred.

9.4 Adverse Event List for rituximab

Infusion reactions
Tumor lysis syndrome
Mucocutaneous reactions
Progressive multifocal leukoencephalopathy
Hepatitis B reactivation with fulminant hepatitis
Infections
Cardiac arrhythmias
Renal toxicity
Bowel obstruction and perforation

The most common adverse reactions of Rituxan (incidence $\geq 25\%$) observed in clinical trials of patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia.

The most common adverse reactions of Rituxan (incidence $\geq 25\%$) observed in clinical trials of patients with CLL were: infusion reactions and neutropenia.

Clinical Trials Experience in Lymphoid Malignancies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Rituxan in 2282 patients, with exposures ranging from a single infusion up to 6–8 months. Rituxan was studied in both single-agent and active-controlled trials ($n = 356$ and $n = 1926$). The population included 679 patients with low-grade follicular lymphoma, 927 patients

with DLBCL, and 676 patients with CLL. Most NHL patients received Rituxan as an infusion of 375 mg/m² per infusion, given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. CLL patients received Rituxan 375 mg/m² as an initial infusion followed by cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

Infusion Reactions

In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first Rituxan infusion. Infusion reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion.

Infections

Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%).

In randomized, controlled studies where Rituxan was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who received Rituxan. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received Rituxan.

Cytopenias and hypogammaglobulinemia

In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituxan therapy occurred during the single-arm studies.

In studies of monotherapy, Rituxan-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

Relapsed or Refractory, Low-Grade NHL

Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of

Rituxan administered as a single agent. Most patients received Rituxan 375
²
mg/m² weekly for 4 doses.

Table 1 Incidence of Adverse Reactions in ≥ 5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituxan (N = 356) ^{a,b}		
	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Reactions	99	57
<u>Body as a Whole</u>	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
<u>Heme and Lymphatic System</u>	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
<u>Skin and Appendages</u>	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1
<u>Respiratory System</u>	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
<u>Metabolic and Nutritional Disorders</u>	38	3
Angioedema	11	1

Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Table 1 (cont'd) Incidence of Adverse Reactions in $\geq 5\%$ of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituxan (N = 356) ^{a,b}		
	All Grades (%)	Grade 3 and 4 (%)
<u>Digestive System</u>	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
<u>Nervous System</u>	32	1
Dizziness	10	1
Anxiety	5	1
<u>Musculoskeletal System</u>	26	3
Myalgia	10	1
Arthralgia	10	1
<u>Cardiovascular System</u>	25	3
Hypotension	10	1
Hypertension	6	1

^a Adverse reactions observed up to 12 months following Rituxan.

^b Adverse reactions graded for severity by NCI-CTC criteria.

In these single-arm Rituxan studies, bronchiolitis obliterans occurred during and up to 6 months after Rituxan infusion.

Previously Untreated Low-Grade NHL

In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more frequently ($\geq 5\%$) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%).

In Study 5, the following adverse reactions were reported more frequently ($\geq 5\%$) in patients receiving Rituxan following CVP compared to patients who received no further therapy: fatigue (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or 4 adverse reaction that occurred more frequently ($\geq 2\%$) in the Rituxan arm compared with those who received no further therapy (4% vs. 1%).

DLBCL

In Studies 6 and 7, [see *Clinical Studies (14.4)*], the following adverse reactions, regardless of severity, were reported more frequently ($\geq 5\%$) in patients age ≥ 60 years receiving R-CHOP as compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

In Study 7, a review of cardiac toxicity determined that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs. 1.0% for CHOP).

The following Grade 3 or 4 adverse reactions occurred more frequently among patients in the R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%). Other Grade 3 or 4 adverse reactions occurring more frequently among patients receiving R-CHOP were viral infection (Study 7), neutropenia (Studies 7 and 8), and anemia (Study 8).

CLL

The data below reflect exposure to Rituxan in combination with fludarabine and cyclophosphamide in 676 patients with CLL in Study 9 or Study 10. The age range was 30–83 years and 71% were men. Detailed safety data collection in Study 9 was limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

Infusion-related adverse reactions were defined by any of the following adverse events occurring during or within 24 hours of the start of infusion: nausea, pyrexia, chills, hypotension, vomiting, and dyspnea.

In Study 9, the following Grade 3 and 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion reactions (9% in R-FC arm), neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and pancytopenia (3% vs. 1%).

In Study 10, the following Grade 3 or 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion reactions (7% in R-FC arm), neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%), thrombocytopenia (11% vs. 9%), hypotension (2% vs. 0%), and hepatitis B (2% vs. < 1%). Fifty-nine percent of R-FC-treated patients experienced an infusion reaction of any severity.

9.5 Adverse Event List for cyclophosphamide

The following adverse reactions are discussed in more detail in other sections of the **labeling** (see [Appendix P for the link](#)).

Hypersensitivity

Cyclophosphamide is contraindicated in patients who have a history of severe hypersensitivity reactions to it, any of its metabolites, or to other components of the product. Anaphylactic reactions including death have been reported with cyclophosphamide. Possible cross-sensitivity with other alkylating agents can occur.

Hematologic

Myelosuppression, Immunosuppression, Bone Marrow Failure, and Infections. Cyclophosphamide can cause myelosuppression (leukopenia, neutropenia, thrombocytopenia and anemia), bone marrow failure, and severe immunosuppression which may lead to serious and sometimes fatal infections, including sepsis and septic shock. Latent infections can be reactivated (see information below).

Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician. In case of neutropenic fever, antibiotic therapy is indicated. Antimycotics and/or antivirals may also be indicated.

Monitoring of complete blood counts is essential during cyclophosphamide treatment so that the dose can be adjusted, if needed. Cyclophosphamide should not be administered to patients with neutrophils $\leq 1,500/\text{mm}^3$ and platelets $< 50,000/\text{mm}^3$. Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop a serious infection. G-CSF may be administered to reduce the risks of neutropenia complications associated with cyclophosphamide use. Primary and secondary prophylaxis with G-CSF should be considered in all patients considered to be at increased risk for neutropenia complications. The nadirs of the reduction in leukocyte count and thrombocyte count are usually reached in weeks 1 and 2 of treatment. Peripheral blood cell counts are expected to normalize after approximately 20 days. Bone marrow failure has been reported. Severe myelosuppression may be expected particularly in patients pretreated with and/or receiving concomitant chemotherapy and/or radiation therapy.

Urinary Tract and Renal Toxicity

Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide. Medical and/or surgical supportive treatment may be required to treat protracted cases of severe hemorrhagic cystitis. Discontinue cyclophosphamide therapy in case of severe hemorrhagic cystitis. Urotoxicity (bladder ulceration, necrosis, fibrosis, contracture and secondary cancer) may require interruption of cyclophosphamide treatment or cystectomy. Urotoxicity can be fatal. Urotoxicity can occur with short-term or long-term use of cyclophosphamide. Before starting treatment, exclude or correct any urinary tract obstructions.

Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of urotoxicity and/or nephrotoxicity. Cyclophosphamide should be used with caution, if at all, in patients with active urinary tract infections. Aggressive hydration with forced diuresis and frequent bladder emptying can

reduce the frequency and severity of bladder toxicity. Mesna has been used to prevent severe bladder toxicity.

Cardiotoxicity

Myocarditis, myopericarditis, pericardial effusion including cardiac tamponade, and congestive heart failure, which may be fatal, have been reported with cyclophosphamide therapy.

Supraventricular arrhythmias (including atrial fibrillation and flutter) and ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported after treatment with regimens that included cyclophosphamide.

The risk of cardiotoxicity may be increased with high doses of cyclophosphamide, in patients with advanced age, and in patients with previous radiation treatment to the cardiac region and/or previous or concomitant treatment with other cardiotoxic agents. Particular caution is necessary in patients with risk factors for cardiotoxicity and in patients with preexisting cardiac disease. Monitor patients with risk factors for cardiotoxicity and with pre-existing cardiac disease.

Pulmonary Toxicity

Pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease and other forms of pulmonary toxicity leading to respiratory failure have been reported during and following treatment with cyclophosphamide. Late onset pneumonitis (greater than 6 months after start of cyclophosphamide) appears to be associated with increased mortality. Pneumonitis may develop years after treatment with cyclophosphamide.

Monitor patients for signs and symptoms of pulmonary toxicity.

Secondary Malignancies

Cyclophosphamide is genotoxic. See nonclinical toxicology below:

Cyclophosphamide administered by different routes, including intravenous, subcutaneous or intraperitoneal injection, or in drinking water, caused tumors in both mice and rats. In addition to leukemia and lymphoma, benign and malignant tumors were found at various tissue sites, including urinary bladder, mammary gland, lung, liver, and injection site.

Cyclophosphamide was mutagenic and clastogenic in multiple in vitro and in vivo genetic toxicology studies.

Cyclophosphamide is genotoxic in male and female germ cells. Animal data indicate that exposure of oocytes to cyclophosphamide during follicular development may result in a decreased rate of implantations and viable pregnancies, and in an increased risk of malformations. Male mice and rats treated with cyclophosphamide show alterations in male

reproductive organs (e.g., decreased weights, atrophy, changes in spermatogenesis), and decreases in reproductive potential (e.g., decreased implantations and increased post-implantation loss) and increases in fetal malformations when mated with untreated females.

Secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported in patients treated with cyclophosphamide-containing regimens. The risk of bladder cancer may be reduced by prevention of hemorrhagic cystitis.

Veno-occlusive Liver Disease

Veno-occlusive liver disease (VOD) including fatal outcome has been reported in patients receiving cyclophosphamide-containing regimens. A cytoreductive regimen in preparation for bone marrow transplantation that consists of cyclophosphamide in combination with whole-body irradiation, busulfan, or other agents has been identified as a major risk factor. VOD has also been reported to develop gradually in patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide. Other risk factors predisposing to the development of VOD include preexisting disturbances of hepatic function, previous radiation therapy of the abdomen, and a low performance status.

Embryo-Fetal Toxicity

Cyclophosphamide can cause fetal harm when administered to a pregnant woman. Exposure to cyclophosphamide during pregnancy may cause birth defects, miscarriage, fetal growth retardation, and fetotoxic effects in the newborn. Cyclophosphamide is teratogenic and embryo-fetal toxic in mice, rats, rabbits and monkeys.

Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception during treatment and for up to 1 year after completion of therapy.

Reproductive System Toxicity

Male and female reproductive function and fertility may be impaired in patients being treated with cyclophosphamide. Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Development of sterility appears to depend on the dose of cyclophosphamide, duration of therapy, and the state of gonadal function at the time of treatment. Cyclophosphamide-induced sterility may be irreversible in some patients. Advise patients on the potential risks for infertility.

Impaired Wound Healing

Cyclophosphamide may interfere with normal wound healing.

Hyponatremia

Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone), which may be fatal, has been reported.

Common Adverse Reactions

Hematopoietic system:

Neutropenia occurs in patients treated with cyclophosphamide. The degree of neutropenia is particularly important because it correlates with a reduction in resistance to infections. Fever without documented infection has been reported in neutropenic patients.

Gastrointestinal system:

Nausea and vomiting occur with cyclophosphamide therapy. Anorexia and, less frequently, abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy.

Skin and its structures:

Alopecia occurs in patients treated with cyclophosphamide. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur.

Postmarketing Experience

The following adverse reactions have been identified from clinical trials or post-marketing surveillance. Because they are reported from a population from unknown size, precise estimates of frequency cannot be made.

Cardiac: cardiac arrest, ventricular fibrillation, ventricular tachycardia, cardiogenic shock, pericardial effusion (progressing to cardiac tamponade), myocardial hemorrhage, myocardial infarction, cardiac failure (including fatal outcomes), cardiomyopathy, myocarditis, pericarditis, carditis, atrial fibrillation, supraventricular arrhythmia, ventricular arrhythmia, bradycardia, tachycardia, palpitations, QT prolongation.

Congenital, Familial and Genetic: intra-uterine death, fetal malformation, fetal growth retardation, fetal toxicity (including myelosuppression, gastroenteritis).

Ear and Labyrinth: deafness, hearing impaired, tinnitus.

Endocrine: water intoxication.

Eye: visual impairment, conjunctivitis, lacrimation.

Gastrointestinal: gastrointestinal hemorrhage, acute pancreatitis, colitis, enteritis, cecitis, stomatitis, constipation, parotid gland inflammation.

General Disorders and Administrative Site Conditions: multiorgan failure, general physical deterioration, influenza-like illness, injection/infusion site reactions (thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema), pyrexia, edema, chest pain, mucosal inflammation, asthenia, pain, chills, fatigue, malaise, headache.

Hematologic: myelosuppression, bone marrow failure, disseminated intravascular coagulation and hemolytic uremic syndrome (with thrombotic microangiopathy).

Hepatic: veno-occlusive liver disease, cholestatic hepatitis, cytolytic hepatitis, hepatitis, cholestasis; hepatotoxicity with hepatic failure, hepatic encephalopathy, ascites, hepatomegaly, blood bilirubin increased, hepatic function abnormal, hepatic enzymes increased.

Immune: immunosuppression, anaphylactic shock and hypersensitivity reaction.

Infections: The following manifestations have been associated with myelosuppression and immunosuppression caused by cyclophosphamide: increased risk for and severity of pneumonias (including fatal outcomes), other bacterial, fungal, viral, protozoal and, parasitic infections; reactivation of latent infections, (including viral hepatitis, tuberculosis), *Pneumocystis jiroveci*, herpes zoster, *Strongyloides*, sepsis and septic shock.

Investigations: blood lactate dehydrogenase increased, C-reactive protein increased.

Metabolism and Nutrition: hyponatremia, fluid retention, blood glucose increased, blood glucose decreased.

Musculoskeletal and Connective Tissue: rhabdomyolysis, scleroderma, muscle spasms, myalgia, arthralgia.

Neoplasms: acute leukemia, myelodysplastic syndrome, lymphoma, sarcomas, renal cell carcinoma, renal pelvis cancer, bladder cancer, ureteric cancer, thyroid cancer.

Nervous System: encephalopathy, convulsion, dizziness, neurotoxicity has been reported and manifested as reversible posterior leukoencephalopathy syndrome, myelopathy, peripheral neuropathy, polyneuropathy, neuralgia, dysesthesia, hypoesthesia, paresthesia, tremor, dysgeusia, hypogeusia, parosmia.

Pregnancy: premature labor.

Psychiatric: confusional state.

Renal and Urinary: renal failure, renal tubular disorder, renal impairment, nephropathy toxic, hemorrhagic cystitis, bladder necrosis, cystitis ulcerative, bladder contracture, hematuria, nephrogenic diabetes insipidus, atypical urinary bladder epithelial cells.

Reproductive System: infertility, ovarian failure, ovarian disorder, amenorrhea, oligomenorrhea, testicular atrophy, azoospermia, oligospermia.

Respiratory: pulmonary veno-occlusive disease, acute respiratory distress syndrome, interstitial lung disease as manifested by respiratory failure (including fatal outcomes), obliterative bronchiolitis, organizing pneumonia, alveolitis allergic, pneumonitis, pulmonary hemorrhage; respiratory distress, pulmonary hypertension, pulmonary edema, pleural effusion, bronchospasm, dyspnea, hypoxia, cough, nasal congestion, nasal discomfort, oropharyngeal pain, rhinorrhea.

Skin and Subcutaneous Tissue: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, palmar-plantar erythrodysesthesia syndrome, radiation recall dermatitis, toxic skin eruption, urticaria, dermatitis, blister, pruritus, erythema, nail disorder, facial swelling, hyperhidrosis.

Tumor lysis syndrome: like other cytotoxic drugs, cyclophosphamide may induce tumor-lysis syndrome and hyperuricemia in patients with rapidly growing tumors.

Vascular: pulmonary embolism, venous thrombosis, vasculitis, peripheral ischemia, hypertension, hypotension, flushing, hot flush.

9.6 Adverse Events List for Filgrastim

Serious Adverse Reactions

- Splenic Rupture
- Acute Respiratory Distress Syndrome
- Serious Allergic Reactions
- Sickle Cell Disorders
- Glomerulonephritis
- Alveolar Hemorrhage and Hemoptysis
- Capillary Leak Syndrome
- Thrombocytopenia
- Leukocytosis
- Cutaneous Vasculitis

Cardiovascular

Common (1% to 10%): Hypotension

Uncommon (0.1% to 1%): Veno-occlusive disease, fluid volume disturbances, capillary leak syndrome

Dermatologic

Very common (10% or more): Rash, alopecia

Uncommon (0.1% to 1%): Sweets syndrome, cutaneous vasculitis

Gastrointestinal

Very common (10% or more): Diarrhea, vomiting, constipation, nausea, mucosal inflammation

Genitourinary

Common (1% to 10%): Dysuria

Uncommon (0.1% to 1%): Urine abnormality, proteinuria, hematuria

Hematologic

Very common (10% or more): Thrombocytopenia, leukocytosis, anemia, splenomegaly

Common (1% to 10%): Splenic rupture

Uncommon (0.1% to 1%): Sickle cell crisis

Hepatic

Very common (10% or more): Gamma-glutamyltransferase increased, blood alkaline phosphatase increased, hepatomegaly

Uncommon (0.1% to 1%): Aspartate aminotransferase increased

Hypersensitivity

Common (1% to 10%): Hypersensitivity

Uncommon (0.1% to 1%): Graft versus host disease, anaphylactic reaction

Local

Common (1% to 10%): Injection site reaction

Metabolic

Very common (10% or more): Blood uric acid increased, blood lactate dehydrogenase increased, decreased appetite, hyperuricemia, blood glucose decreased

Uncommon (0.1% to 1%): Pseudogout

Musculoskeletal

Very common (10% or more): Bone pain, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, neck pain

Common (1% to 10%): Osteoporosis

Uncommon (0.1% to 1%): Exacerbation of rheumatoid arthritis

Nervous system

Very common (10% or more): Headache

Other

Very common (10% or more): Asthenia, fatigue, pain

Renal

Common (1% to 10%): Glomerulonephritis

Respiratory

Very common (10% or more): Oropharyngeal pain, cough, dyspnea, epistaxis

Common (1% to 10%): Hemoptysis

Uncommon (0.1% to 1%): Acute respiratory distress syndrome, respiratory failure, pulmonary edema, interstitial lung disease, lung infiltration, pulmonary hemorrhage

9.7 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).
- **‘Expectedness’:** AEs can be ‘Unexpected’ or ‘Expected’ (see [Section 9.0](#) above) for expedited reporting purposes only.
- **Attribution** of the AE:
 - Definite – The AE **is clearly related** to the study treatment.
 - Probable – The AE **is likely related** to the study treatment.
 - Possible – The AE **may be related** to the study treatment.
 - Unlikely – The AE **is doubtfully related** to the study treatment.
 - Unrelated – The AE **is clearly NOT related** to the study treatment.

9.8 DSMC SAE Reporting Requirements

The Safety and Toxicity Reporting Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in [Appendix D](#). DSMC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All WFBCCC Clinical Protocol Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

9.9 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are

not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

10.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in [Section 9.0](#).

10.1 Pharmaceutical Accountability

The components of R-CHOP are commercially available.

10.2 Rituximab

Product description: Rituxan[®] (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG₁ kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Water for Injection. The pH is 6.5.

Solution preparation: Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use vial if particulates or discoloration is present. Withdraw the necessary amount of Rituxan and dilute to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

Storage requirements:

Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Rituxan solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or polyethylene bags have been observed.

Stability: Rituxan vials [100 mg (NDC 50242-051-21) and 500 mg (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

Route of administration: Intravenous.

Disposal: Dispose of any unused portions as indicated through the Wake Forest waste stream.

10.3 Prednisone

Product description: Prednisone Tablets contain prednisone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Prednisone is a white to practically white, odorless, crystalline powder. It is very slightly soluble in water; slightly soluble in alcohol, chloroform, dioxane, and methanol

Tablets are round, white, biconvex with a score on one side.

Storage requirements: Store at 20° to 25°C (68° to 77°F).

Stability: Prednisone is stable under normal conditions.

Route of administration: Oral. Pill taken by mouth.

Disposal: Dispose of any unused pills as indicated through the Wake Forest waste stream.

10.4 Vincristine

Product description:

Vincristine Sulfate Injection, USP is the salt of an alkaloid obtained from a common flowering herb, the periwinkle plant (*Vinca rosea* Linn). Originally known as leurocristine, it has also been referred to as LCR and VCR. The molecular formula for Vincristine Sulfate, USP is $C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$. It has a molecular weight of 923.04.

Solution preparation: TO REDUCE THE POTENTIAL FOR FATAL MEDICATION ERRORS DUE TO INCORRECT ROUTE OF ADMINISTRATION, VINCRIStINE SULFATE INJECTION SHOULD BE DILUTED IN A FLEXIBLE PLASTIC CONTAINER AND PROMINENTLY LABELED FOR INTRAVENOUS USE ONLY (See WARNINGS in Label).

The concentration of Vincristine Sulfate Injection, USP is 1 mg/mL. Do not add extra fluid to the vial prior to removal of the dose. Withdraw the solution of Vincristine Sulfate Injection, USP into an accurate dry syringe, measuring the dose carefully. Do not add extra fluid to the vial in an attempt to empty it completely.

Preparation for flexible plastic container

Vincristine Sulfate Injection, USP when diluted with 0.9% Sodium Chloride Injection in concentrations from 0.0015 mg/mL to 0.08 mg/mL is stable for up to 24 hours when protected from light or 8 hours under normal light at 25°C.

Preparation for syringe

Special Dispensing Information: when dispensing Vincristine Sulfate Injection, USP in a syringe, it is imperative that it be packaged in the provided overwrap which bears the following statement: ***“DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES”*** (see **WARNINGS** in label). A syringe containing a specific dose must be labeled, using the auxiliary sticker provided, to state: ***“FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES.”***

Caution: It is extremely important that the intravenous needle or catheter be properly positioned before any vincristine is injected. Leakage into surrounding tissue during intravenous administration of Vincristine Sulfate Injection, USP may cause considerable irritation.

Storage requirements: Store and transport refrigerated (2-8°C). Keep vial in the outer carton in order to protect from light.

Stability: Vial before opening 24 months After dilution, chemical and physical in-use stability of the solution prepared for injection or infusion has been demonstrated for 48 hours at 2-8° C or 24 hours at 15 to 25°C when diluted to a concentration range of 0.01 mg/ml to 0.1 mg/ml in 9 mg/ml (0.9%) sodium chloride solution for infusion or in 50 mg/ml (5%) glucose solution for infusion. From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Route of administration: Intravenous infusion. Neurotoxicity appears to be dose related. Extreme care must be used in calculating and administering the dose of **Vincristine Sulfate Injection, USP** since overdosage may have a very serious or fatal outcome. See [section 6.2](#) for dose calculation.

If extravasation occurs, the injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage will help disperse the drug and may minimize discomfort and the possibility of cellulitis.

Vincristine Sulfate Injection, USP must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken that there is no leakage or swelling occurring during administration.

Disposal: Dispose of any unused pills as indicated through the Wake Forest waste stream.

10.5 Cyclophosphamide

Product description: Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate.

Cyclophosphamide has a molecular formula of $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$ and a molecular weight of 279.1. Cyclophosphamide is soluble in water, saline, or ethanol.

Cyclophosphamide for Injection, USP is a sterile white cake available as 500 mg, 1 g, and 2 g strength vials.

- 500 mg vial contains 534.5 mg cyclophosphamide monohydrate equivalent to 500 mg cyclophosphamide and 375 mg mannitol

- 1 g vial contains 1069.0 mg cyclophosphamide monohydrate equivalent to 1 g cyclophosphamide and 750 mg mannitol
- 2 g vial contains 2138.0 mg cyclophosphamide monohydrate equivalent to 2 g cyclophosphamide and 1500 mg mannitol.

Solution preparation: *Preparation, Handling and Administration*

Handle and dispose of cyclophosphamide in a manner consistent with other cytotoxic drugs.¹ Caution should be exercised when handling and preparing Cyclophosphamide for Injection, USP (lyophilized powder), or bottles containing cyclophosphamide tablets. To minimize the risk of dermal exposure, always wear gloves when handling vials containing Cyclophosphamide for Injection, USP (lyophilized powder), or bottles containing cyclophosphamide tablets. The coating of the cyclophosphamide tablets prevents direct contact of persons handling the tablets with the active substance. However, to prevent inadvertent exposure to the active substance, the cyclophosphamide tablets should not be cut, chewed, or crushed. Personnel should avoid exposure to broken tablets. If contact with broken tablets occurs, wash hands immediately and thoroughly.

Cyclophosphamide for Injection, USP

Intravenous Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use cyclophosphamide vials if there are signs of melting. Melted cyclophosphamide is a clear or yellowish viscous liquid usually found as a connected phase or in droplets in the affected vials.

Cyclophosphamide does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions. Use aseptic technique.

For Intravenous Infusion

Reconstitution of Cyclophosphamide: Reconstitute Cyclophosphamide using 0.9% Sodium Chloride Injection, USP or Sterile Water for Injection, USP with the volume of diluent listed below in the Table below. Add the diluent to the vial and gently swirl to dissolve the drug completely.

Reconstitution in preparation for Intravenous Infusion Strength	Volume of Diluent	Cyclophosphamide Concentration
500 mg	25 mL	20 mg per mL
1 g	50 mL	
2 g	100 mL	

Dilution of Reconstituted Cyclophosphamide: Further dilute the reconstituted Cyclophosphamide solution to a minimum concentration of 2 mg per mL with any of the following diluents:

- 5% Dextrose Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- 0.45% Sodium Chloride Injection, USP

To reduce the likelihood of adverse reactions that appear to be administration rate-dependent (e.g., facial swelling, headache, nasal congestion, scalp burning), cyclophosphamide should be injected or infused very slowly. Duration of the infusion also should be appropriate for the volume and type of carrier fluid to be infused.

Storage requirements: Store vials at or below 25°C (77°F). During transport or storage of cyclophosphamide vials, temperature influences can lead to melting of the active ingredient, cyclophosphamide.

Storage of Cyclophosphamide Solutions Diluent	Storage	
	Room Temperature	Refrigerated
Reconstituted Solution (Without Further Dilution)		
0.9% Sodium Chloride Injection, USP	up to 24 hrs	Up to 6 days
Sterile Water for Injection, USP	Do not store; use immediately	
Diluted Solutions		
0.45% Sodium Chloride Injection, USP	up to 24 hrs	up to 6 days
5% Dextrose Injection, USP	up to 24 hrs	up to 36 hrs
5% Dextrose and 0.9% Sodium Chloride Injection, USP	up to 24 hrs	up to 36 hrs

Stability: See storage requirements above

Route of administration: IV infusion

Disposal: Dispose of any unused portions through the Wake Forest Waste Stream.

10.6 Doxorubicin

Product description:

Doxorubicin Hydrochloride Injection, USP is a clear, red, sterile, isotonic aqueous solution provided in vials containing 10 mg/5 mL, 20 mg/10 mL, 50 mg/25 mL, 150 mg/75 mL, or 200 mg/100 mL of doxorubicin HCl. The drug product has demonstrated inherent antimicrobial activity suitable for a multiple dose presentation. Each milliliter of solution contains 2 mg of doxorubicin HCl. Inactive ingredients include sodium chloride 0.9%, USP, and water for injection, USP,

quantity sufficient. The pH of the solution is adjusted to 3.0 with hydrochloric acid, USP.

Doxorubicin Hydrochloride for Injection, USP is a sterile red-orange lyophilized powder, provided in vials containing 10 mg, 20 mg, 50 mg, or 150 mg doxorubicin HCl. The drug product has demonstrated inherent antimicrobial activity suitable for a multiple dose presentation. For each 10 mg doxorubicin HCl, each vial contains 50 mg lactose and 1 mg methylparaben.

Doxorubicin Hydrochloride Injection, USP is a sterile parenteral, isotonic solution, available in polypropylene (CYTOSAFE)® vials in single vial packs as:

SINGLE-DOSE VIALS:

10 mg/5 mL (2 mg/mL) NDC 0069-3030-20
20 mg/10 mL (2 mg/mL) NDC 0069-3031-20
50 mg/25 mL (2 mg/mL) NDC 0069-3032-20

Retain in carton until time of use. Discard unused portion.

MULTIPLE-DOSE VIALS:

150 mg/75 mL (2 mg/mL) NDC 0069-3033-20
200 mg/100 mL (2 mg/mL) NDC 0069-3034-20

Retain in carton until contents are used.

Solution preparation: *Preparation of Doxorubicin HCl for injection*

Reconstitute doxorubicin hydrochloride for injection with 0.9% Sodium Chloride Injection, USP to obtain a final concentration of 2 mg per mL as follows:

- 5 mL 0.9% Sodium Chloride Injection, USP to reconstitute 10 mg doxorubicin HCl vial
- 10 mL 0.9% Sodium Chloride Injection, USP to reconstitute 20 mg doxorubicin HCl vial
- 25 mL 0.9% Sodium Chloride Injection, USP to reconstitute 50 mg doxorubicin HCl vial
- 75 mL 0.9% Sodium Chloride Injection, USP to reconstitute 150 mg doxorubicin HCl vial

Gently shake vial until the contents have dissolved.

Protect reconstituted solution from light.

Preparation for Continuous Intravenous Infusion

Dilute doxorubicin HCl solution or reconstituted solution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Protect from light following preparation until completion of infusion.

Administration

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if the solution is discolored, cloudy, or contains particulate matter.

Storage of vials of Doxorubicin HCl Injection or Doxorubicin HCl for Injection following reconstitution under refrigerated conditions can result in the formation of a gelled product. Place gelled product at room temperature [15° to 30°C (59° to 86°F)] for 2 to 4 hours to return the product to a slightly viscous, mobile solution.

Administration by Intravenous Injection:

- Administer doxorubicin HCl as an intravenous injection through a central intravenous line or a secure and free-flowing peripheral venous line containing 0.9% Sodium Chloride Injection, USP, 0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.
- Administer doxorubicin HCl intravenously over 3 to 10 minutes. Decrease the rate of doxorubicin HCl administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur.

Administration by Continuous Intravenous Infusion:

- Infuse only through a central catheter. Decrease the rate of doxorubicin HCl administration if erythematous streaking along the vein proximal to the site of infusion or facial flushing occur.
- Protect from light from preparation for infusion until completion of infusion.

Management of Suspected Extravasation

Discontinue doxorubicin HCl for burning or stinging sensation or other evidence indicating peri-venous infiltration or extravasation. Manage confirmed or suspected extravasation as follows:

- Do not remove the needle until attempts are made to aspirate extravasated fluid.
- Do not flush the line.
- Avoid applying pressure to the site.
- Apply ice to the site intermittently for 15 min 4 times a day for 3 days.
- If the extravasation is in an extremity, elevate the extremity.
- In adults, consider administration of dexrazoxane [see *Warnings and Precautions (5.3) of package insert*].

Incompatibility with Other Drugs

Do not admix doxorubicin HCl with other drugs. If doxorubicin HCl is mixed with heparin or fluorouracil a precipitate may form. Avoid contact with alkaline solutions which can lead to hydrolysis of doxorubicin HCl.

Storage requirements: Store all vials at 2° to 8°C (36° to 46°F). Protect from light.

Storage of Doxorubicin Hydrochloride Injection under refrigerated conditions can result in the formation of a gelled product. Place gelled product at room temperature [15° to 30°C (59° to 86°F)] for 2 to 4 hours to return the product to a slightly viscous, mobile solution.

Stability: See storage requirements.

Route of administration: Intravenous

Disposal: Dispose of remaining portions as indicated through the Wake Forest waste stream.

11.0 Correlative/Special Studies

PROMIS

The Patient-Reported Outcomes Measurement Information System (PROMIS®) is a product of a multi-year cooperative agreement between the NIH and several research institutions and academic medical centers.

PROMIS® is a health *domain*-focused, rather than a *disease*-focused measurement system. To ensure comparable data and the accumulation of knowledge across patient subgroups and therapies, PROMIS® refers to aspects of functioning and well-being that are relevant across most chronic conditions (e.g., cognitive functioning or fatigue). Thus, PROMIS® is designed to provide a valid assessment of this broad definition of health (historically referred to as “health-related quality of life”). We will assess the following profile instruments using PROMIS-29 v 2.0

PROMIS SF v1.0	Anxiety 4a
PROMIS SF v1.0	Depression 4a
PROMIS SF v1.0	Fatigue 4a
PROMIS SF v1.0	Pain Interference 4a
PROMIS SF v1.0	Physical Function 4a
PROMIS SF v1.0	Sleep Disturbance 4a
PROMIS SF v1.0	Ability to Participate in Social Roles and Activities 4a
	PROMIS Pain Intensity item (Global 07)

Functional Assessment of Cancer Therapy (FACT)

The Functional Assessment of Cancer Therapy – General (FACT-G), was developed and validated over a quarter of a century ago and has been used in hundreds of studies worldwide. Since the publication of the first FACT-G validation paper in 1993, now there are more than 90 questionnaires and translated and linguistically validated them into over 70 languages for use in over 100 countries. The FACT-Lym is a specific instrument for lymphoma which includes the FACT-G questionnaire and fifteen additional items referring to specific concerns of the disease. FACT-Lym has been tested successfully for reliability and validity in patients with NHL.²⁴ The FACT-GOG Ntx-4, V4 will target peripheral symptoms of the hands and feet.

PRO-CTCAE

The PRO-CTCAE is a patient reported outcome, modifiable instrument to capture adverse events during clinical trials. The PRO-CTCAE in this study is targeted toward capturing adverse events related to prednisone.

11.1 Laboratory Correlative Studies

11.1.1 Samples for hyperglycemia testing and storage for future research

Blood for fasting blood glucose, fructosamine, fasting insulin and hemoglobin A1c will be collected at visits baseline, post- cycle 3 (day 1 cycle 4) and cycle 6, and 6 months post treatment completion. The following blood draw tubes would be collected by the research nurse in the cancer center and transported to the Main CRU Lab for processing. * Please note collection schedule provided in the study calendar in [section 6.1](#).

Vacutainer tubes for collections:

Fasting blood glucose: 1 x 10 mL red top,

Fructosamine: 1 x 10 mL red top

HbA1c: 1 x 4 mL K2 EDTA

Fasting Insulin: 1 x 8.5mL SST

Fasting Blood Glucose and Fructosamine Processing:

1. Allow the 10 mL red top tube to clot vertically for 45 minutes at room temperature from the time of collection.
2. Centrifuge the 10 mL red top tube at 3000 rpm, 15 minutes at 4°C.
3. Transfer the serum from the 10 mL red top tube to (1) 15mL tube.
4. Gently invert the tube 5 times
5. From the serum tube, transfer 2 mL serum to (1) LabCorp serum transport vial and route to LabCorp for fasting glucose, test 001032, \$1.50 per sample or fructosamine, test 100800, \$5.00 per sample.
6. From the remaining serum, prepare 2 x 2 mL and 2 x .5 mL aliquots (any remaining serum volume should be further divided into .5 mL aliquots) for long-term storage at -70°C in CRU freezers.
7. Route the 4 mL whole blood collection tube to LabCorp for HbA1c, test 001453, \$3.00 per sample.
8. The Fasting Insulin will also be sent to LabCorp for testing.

The CRU will provide CRU Lab Requisitions, freezer boxes, freezer vials, freezer vial labels, transport bags, blood collection tubes (10 mL red and 4 mL K2 EDTA), LabCorp requisitioning and LabCorp serum transport tubes and will setup a LabCorp account.

12.0 Data Management

Informed consent document	EPIC
Protocol registration form	OnCore
Lymphoma Response Form (Appendix F)	OnCore
FACT-Lym (Version 4) (Appendix G)	REDCap
FACT/GOG-NTX (Version 4)—Additional concerns (Appendix H)	REDCap
PROMIS-29 Profile v2.0 (Appendix I)	REDCap
Adverse Events Log (Appendix E)	OnCore
Baseline Form (Appendix J)	OnCore
Hyperglycemia Outcomes Form (Appendix K)	OnCore
R-CHOP Cycle Form (Appendix L)	OnCore
Off Study Form (Appendix O)	OnCore
PRO-CTCAE (Appendix Q)	REDCap
30-day Treatment Follow-up (Appendix R)	OnCore

13.0 Statistical Considerations

13.1 Analysis of Primary Objective

13.1.1 To analyze the primary objective 2.1.1 we will use the Kaplan Meier method to estimate the cumulative incidence of hyperglycemia, and the log-rank test to compare hyperglycemia incidence by arm after 3 cycles of R-CHOP chemotherapy.

13.2 Analysis of Secondary Objective

13.2.1 To analyze objective 2.2.1 we will use the Kaplan Meier method to estimate the cumulative incidence of hyperglycemia, and the log-rank test to compare hyperglycemia incidence by arm after 6 cycles and after 6 months of R-CHOP chemotherapy.

13.2.2 We will use a Fisher's exact test to compare response rates after 6 cycles of R-CHOP by arm (Objective 2.2.2).

13.2.3 We will compare the rates of the incidence of grade III and higher events by arm of R-CHOP for each cycle using Fisher's exact tests (Objective 2.2.3).

13.2.4 We will compare the scoring of PRO-CTCAE assessments by arm of R-CHOP using two group t-tests at each time point of interest (Objective 2.2.4).

13.2.5 We will compare the HRQOL measures between arms receiving R-CHOP chemotherapy using two group t-tests at each time point of interest (Objective 2.2.5).

13.3 Analysis of Exploratory Analysis

- 13.3.1 To compare the use of RBG to alternative measures, we will characterize participants as hyperglycemic or diabetic per fasting blood glucose measurements. Using area under the receiver operating characteristic curve (ROC) analysis, we will characterize the sensitivity and specificity of the RBG test. Because we will have repeated measures of the test, we will use a generalized linear mixed model with a logit link to account for the correlation among measures on the same individual. We will also examine glucose variability over time in RBG, FBG, HbA1c, fasting insulin and fructosamine using linear mixed effects models to model between and with-person variation in glucose.
- 13.3.2 We will compare quality of life between the those who are hyperglycemic and those that are not at cycle 3, cycle 6, and 12 months using a mixed model ANCOVA with adjustment for baseline quality of life (Objective 2.3.2).
- 13.3.3 To compare glycemic variability between the arms, we will model variability using mixed effect models of FBG and RBG over time, allowing for differing within-person variance by arm as well as fitting a model with pooled variance and any characteristics that differ between the groups. We will use likelihood ratio tests to compare if there is greater variability in the tailored versus standard arms by comparing the pooled variance model to the model that allows the within-person variation to vary by arm (Objective 2.3.3).
- 13.3.4 To analyze objective 2.3.4 we will compare the proportion of participants who complete 6 cycles of chemotherapy by arm using Fisher's exact test (Objective 2.3.4).
- 13.3.5 To analyze overall survival, we will use the Kapan-Meier method to estimate median survival in each group, and a log-rank test to compare the two arms.

Table 1: Definitions

	Hyperglycemia	Diabetes Mellitus
Fasting blood glucose (FBG)	100-125mg/dL	$\geq 126\text{mg/dL}$
Random blood glucose (RBG)	$\geq 200\text{ mg/dL}$	$\geq 200\text{ mg/dL}$ with typical symptoms

13.4 Power and Sample Size

- 13.4.1 Because the goal of a Phase II trial is to screen interventions for future study, and not to provide evidence of superior efficacy, the alpha level is set to be one-sided at a level higher than standard of 0.05 used for an efficacy trial; Rubinstein et al. suggest values of one-sided alpha ranging

from 0.10 to 0.20 and power from 80% to 90%²⁵. Power is based on the primary endpoint of the incidence of hyperglycemia in the R-CHOP strata. With 37 participants per arm in the R-CHOP strata, we have 85% power to detect a difference of 23% in the cumulative incidence of hyperglycemia post cycle 1 (e.g., reduced from 46% to 23%) at a one-sided $\alpha = 0.15$. To allow for dropout, we will enroll 40 participants per arm in the R-CHOP strata.

13.5 Estimated Accrual Rate:

13.5.1 We estimate accrual will be 2-3 patients per month

13.6 Estimated Study Length

13.6.1 3 - 4 years

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA: a cancer journal for clinicians*. 2015;65(1):5-29.
2. Ng AK, LaCasce A, Travis LB. Long-term complications of lymphoma and its treatment. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(14):1885-1892.
3. Migdady Y, Salhab M, Dang NH, Markham MJ, Olszewski AJ. Disparities in conditional net survival among non-Hodgkin lymphoma survivors: a population-based analysis. *Leukemia & lymphoma*. 2016;57(3):676-684.
4. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*. 2009;15(5):469-474.
5. Liu XX, Zhu XM, Miao Q, Ye HY, Zhang ZY, Li YM. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. *Annals of nutrition & metabolism*. 2014;65(4):324-332.
6. Kwon S, Hermayer KL, Hermayer K. Glucocorticoid-Induced Hyperglycemia. *The American Journal of the Medical Sciences*. 2013;345(4):274-277.
7. Moreno A, Colon-Otero G, Solberg LA, Jr. The prednisone dosage in the CHOP chemotherapy regimen for non-Hodgkin's lymphomas (NHL): is there a standard? *The oncologist*. 2000;5(3):238-249.
8. Fisher RI, Gaynor ER, Dahlborg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *The New England journal of medicine*. 1993;328(14):1002-1006.
9. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(19):3121-3127.
10. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *The Lancet Oncology*. 2006;7(5):379-391.
11. Lee SY, Kurita N, Yokoyama Y, et al. Glucocorticoid-induced diabetes mellitus in patients with lymphoma treated with CHOP chemotherapy. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. 2014;22(5):1385-1390.
12. Janssen-Heijnen ML, van Spronsen DJ, Lemmens VE, Houterman S, Verheij KD, Coebergh JW. A population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. *British journal of haematology*. 2005;129(5):597-606.
13. Wieringa A, Boslooper K, Hoogendoorn M, et al. Comorbidity is an independent prognostic factor in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP: a population-based cohort study. *British journal of haematology*. 2014;165(4):489-496.
14. Hassan S, Karpova Y, Baiz D, et al. Behavioral stress accelerates prostate cancer development in mice. *The Journal of clinical investigation*. 2013;123(2):874-886.
15. CDC. Data Source: Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Health Interview Statistics, data from the National Health Interview Survey. Statistical analysis by the Centers for Disease Control and Prevention,

- National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. 2015.
16. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *The New England journal of medicine*. 2001;344(18):1343-1350.
 17. Lindstrom J, Ilanne-Parikka P, Peltonen M, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet (London, England)*. 2006;368(9548):1673-1679.
 18. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *The Lancet Oncology*. 2011;12(5):460-468.
 19. Aoki K, Takahashi T, Tabata S, et al. Efficacy and tolerability of reduced-dose 21-day cycle rituximab and cyclophosphamide, doxorubicin, vincristine and prednisolone therapy for elderly patients with diffuse large B-cell lymphoma. *Leukemia & lymphoma*. 2013;54(11):2441-2447.
 20. Healy SJ, Dungan KM. Hyperglycemia in patients with hematologic malignancies. *Current diabetes reports*. 2015;15(3):8.
 21. Juraschek SP, Steffes MW, Selvin E. Associations of alternative markers of glycemia with hemoglobin A(1c) and fasting glucose. *Clinical chemistry*. 2012;58(12):1648-1655.
 22. Danese E, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. *Journal of diabetes science and technology*. 2015;9(2):169-176.
 23. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014;32(27):3059-3068.
 24. David Cella KW, John Cashy, Lucie Kutikova, Michael F. Burgess, Boris K. Lin, Lee Bowman, Astra M. Liepa, Janine E. Gauthier, Stephanie A. Gregory, Stephen A. Johnson and Bruce D. Cheson. Development of a Measure of Health-Related Quality of Life for Non-Hodgkin's Lymphoma Clinical Research: The Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym). *Blood reviews*. 2005;106(11):750.
 25. Rubinstein L, Crowley J, Ivy P, Leblanc M, Sargent D. Randomized phase II designs. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2009;15(6):1883-1890.

Appendix A – Eligibility Checklist

IRB Protocol No. <u>00050108</u>	WFBCCC Protocol No. <u>98317</u>
Study Title: A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia during R-CHOP chemotherapy	
Principal Investigator: <u>Rakhee Vaidya, M.D.</u>	

Inclusion Criteria (as outlined in study protocol)	Criteria is met	Criteria is NOT met	Source Used to Confirm * (Please document dates and lab results)
Diagnosis of B cell non-Hodgkin lymphoma confirmed by WHO criteria	☐	☐	
Planned treatment with R-CHOP chemotherapy	☐	☐	
18 years of age or older	☐	☐	
ECOG performance status of 0-3	☐	☐	
Life expectancy of greater than 3 months with chemotherapy	☐	☐	
The effects of R-CHOP on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately	☐	☐	
Ability to understand and the willingness to sign an IRB-approved informed consent document	☐	☐	
Exclusion Criteria (as outlined in study protocol)	Criteria NOT present	Criteria is present	Source Used to Confirm * (Please document dates and lab results)
Uncontrolled HIV, CD4 count < 50	☐	☐	
Diagnosis of Primary CNS lymphoma	☐	☐	
Unable to receive R-CHOP chemotherapy	☐	☐	

A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia
during R-CHOP chemotherapy
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC # 98317

History of severe (i.e. anaphylactic) allergic reactions attributed to compounds of similar chemical or biologic composition to glucocorticoids and other components of R-CHOP	☐	☐	
Uncontrolled intercurrent illness including, but not limited to ongoing or active infection not controlled with antibiotics, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia that cannot be rate controlled with medications, or psychiatric illness/social situations that would limit compliance with study requirements.	☐	☐	
Pregnant women are excluded from this study because R-CHOP includes D Class agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with R-CHOP, breastfeeding should be discontinued if the mother is treated with these agents.	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

OnCore Assigned PID: _____

Signature of research professional confirming eligibility: _____

Date (mm/dd/yy): ____ / ____ / ____

Signature of Treating Physician: _____

Date(mm/dd/yy): ____ / ____ / ____

Signature of Principal Investigator**: _____

Date(mm/dd/yy): ____ / ____ / ____

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: "Pathology report, 01/01/14" or "Clinic note, 01/01/14"

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: _____ DOB (mm/dd/yy): ____ / ____ / ____

ZIPCODE: _____

SEX: ☐ Male ☐ Female

Ethnicity (choose one): ☐ Hispanic
☐ Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐ BLACK ☐ ASIAN
☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: _____.____ inches Weight: _____.____ lbs.(actual)

Surface Area: _____.____ m²

Primary Diagnosis: _____

Date of Diagnosis: ____ / ____ / ____

Performance Status: ____ ECOG

Study Arms

☐ Standard (prednisone) ☐ Tailored (prednisone)

PROTOCOL INFORMATION

Date of Registration: ____ / ____ / ____

MD Name (last): _____

Date protocol treatment started(mm/dd/yy): ____ / ____ / ____

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed(mm/dd/yy): ____ / ____ / ____

PID # (to be assigned by OnCore): _____ - _____

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix C - Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:

- ☐ Hispanic or Latino/a
☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.

- ☐ White or Caucasian
☐ Black or African American
☐ American Indian or Alaskan Native
☐ Asian
☐ Native Hawaiian or Other Pacific Islander
☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?

☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** ☐ **No** ☐

If yes, please provide what is currently indicated in the EMR:

Ethnicity: _____ Race: _____

Additional comments: _____

Appendix D – Mandatory DSMC SAE Reporting Guidelines

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	Date: 02/11/2021
---	-------------------------

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC)**. A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

- 1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
- 2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
- 3) The trial is designated as “Interventional” using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation.
(<https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4>)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

- 1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites**. These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
- 2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.
There are three types of trials that are included in this category:
 - a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
 - b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
 - c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either

1) unexpected grade 4, 2) unplanned inpatient hospitalization $\geq$ 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event

Narrative field in the SAE console of the particular subject.

4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

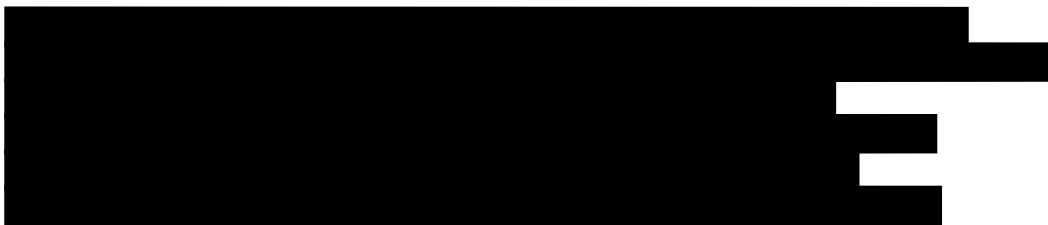
Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
 - i. DSMC clinician name, date/time contacted and comments
 - ii. Date of last dose before the event
 - iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
 - a. Course start date
 - b. Category
 - c. AE Detail
 - d. Comments
 - e. Grade/Severity
 - f. Unexpected Y/N
 - g. DLT Y/N
 - h. Attributions
 - i. Action
 - j. Therapy
 - k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not

been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars



Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment should be considered.

A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia during R-CHOP chemotherapy
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC # 98317

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email “reply to all”. Entitle this new email “**Amendment** for (list date of event and patient ID)” this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

Acronyms

AE – Adverse Event

DSMC-Data and Safety Monitoring Committee

SAE-Serious Adverse Event

WFBCCC – Wake Forest Baptist Comprehensive Cancer Center

NCI-National Cancer Institute

WISER –Wake Integrated Solution for Enterprise Research

Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

Screen Shot 1:

The screenshot shows the 'Subject Console' interface. On the left sidebar, the 'SAEs' tab is selected and circled in red. The main content area displays the following sections:

- Subject Demographics:** Includes fields for MRN, Last Name, First Name, Middle Name, Suffix, Birth Date, Gender (F), Race (White), Ethnicity (Non-Hispanic), and Last Date Known Alive.
- Additional Subject Identifiers:** Includes fields for Identifier Type, Identifier, and Identifier Owner. A note states 'No information entered'.
- Contact Information:** Includes fields for Name, Primary, Address, City, State, ZIP, County, Country, Phone No, and Email Address.
- Emergency Contacts:** Includes fields for Name, Primary, Address, City, State, ZIP, County, Country, Phone No, and Email Address. A note states 'No information entered'.

At the bottom right of the main content area, there is an 'Update' button. The footer of the page reads 'Copyright © 2001-2018 Forta Research Systems. All rights reserved.'

Screen Shot 2:

The screenshot shows the 'Subject Console' interface. On the left sidebar, the 'SAEs' tab is selected and circled in red. The main content area displays a message: 'No Records Found'. At the bottom right of the main content area, there is a 'New' button circled in red. The footer of the page reads 'Copyright © 2001-2018 Forta Research Systems. All rights reserved.'

A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia during R-CHOP chemotherapy
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC # 98317

Screen Shot 3:

Subject Console
Protocol No: CCMW00000000
Subject Name: SAC-00888
Subject Status: OPEN TO ACCRUAL
Sequence No: 1

Event Data
Event Date: 10/22/2018
Event Type: Respiratory, thoracic and mediastinal disorders
Event Description: STAC (Statin-Associated Thrombocytopenia) - Patient had a fall on 10/22/18 @ 3:00 PM. She was found unresponsive and unresponsive. Patient admitted through ED with respiratory distress.

Adverse Event Details
Course Start: 10/22/2018
Course End: 10/22/2018
Category: Respiratory, thoracic and mediastinal disorders
Action: Unreviewed
Status: Unreviewed
Comments: 200 characters remaining

Treatment Details
Action: Unreviewed
Comments: 200 characters remaining

Supporting Documents
No Records Found

Screen Shot 4:

Subject Console
Protocol No: CCMW00000000
Subject Name: SAC-00888
Subject Status: OPEN TO ACCRUAL
Sequence No: 1

Event Data
Event Date: 10/22/2018
Event Type: Respiratory, thoracic and mediastinal disorders
Event Description: STAC (Statin-Associated Thrombocytopenia) - Patient had a fall on 10/22/18 @ 3:00 PM. She was found unresponsive and unresponsive. Patient admitted through ED with respiratory distress.

Adverse Event Details
Course Start: 10/22/2018
Course End: 10/22/2018
Category: Respiratory, thoracic and mediastinal disorders
Action: Unreviewed
Status: Unreviewed
Comments: 200 characters remaining

Treatment Details
Action: Unreviewed
Comments: 200 characters remaining

Supporting Documents
No Records Found

Appendix E – Adverse Event Log

WFBCCC Adverse Event (AE) Log														
PI: _____					Subject PID: _____					MRN: _____				
Cycle #: _____		Cycle Start Date (mm/dd/yyyy): ____/____/____			Cycle Start Time: ____:____			Cycle End Date (mm/dd/yyyy): ____/____/____			Cycle End Time: ____:____			
Adverse Event CTC Term	Lab Value	Grade (1-5) per CTC	Start Date	Attribution DEF=Definite PROB=Probable POSS=Possible UNLK=Unlikely UNRL=Unrelated	Treating MD Initials/Date	End Date	Expected N=No Y=Yes	Serious Adverse Event Detail NO=No LT=Life Threatening DTH=Death DIS=Disability HOS=Hospitalization CA=Caused congenital anomaly RI=Required intervention to prevent impairment	Dose Limiting Toxicity (DLT) N=No Y=Yes	Action Taken NO=None DR=Dose Reduced RI=Regimen Interrupted TD=Therapy discontinued INTR=Interrupted then reduced	Therapy Given NO=None SYM=Symptomatic SUP=Supportive VSUP=Vigorous supportive	Reportable ? IRB-IRB STRC-STRC FDA-FDA SPON-Sponsor (Mark all that apply)	Adverse Event Report (AER) Filed N=No Y=Yes	Outcome R=Recovered TX=Still under treatment/observation A=Alive with sequelae D=Died
Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.														
CTCAE Version 4 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf														
STRC- Safety and Toxicity Review Committee												Version 10/30/17		

Appendix F - Lymphoma Response Form

Study Number: 98317 PID: _____
Investigator: Rakhee Vaidya, M.D. Date (mm/dd/yy): ____/____/____

Instructions: Use this form to record response.

Time point of assessment: ☐ post-Cycle 3
☐ post-Cycle 6

Please check the response that applies to this patient. Refer to response definitions below.

- ☐ Complete Remission (**CR**)
☐ Partial Response (**PR**)
☐ No response/Stable Disease
☐ Progressive Disease

Deauville Score: ☐ 0-2 ☐ 3 ☐ 4-5

Treating Physician Signature: _____
Date(mm/dd/yy): ____/____/____

PI Signature: _____
Date(mm/dd/yy): ____/____/____

Cheson et al., 2014 Response Definitions:

Response	Site	PET-CT-Based Response	CT-Based Response
Complete Response		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 5PS [‡]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
		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	No extralymphatic sites of disease
	Nonmeasured 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

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the

A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia
during R-CHOP chemotherapy
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC # 98317

requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Partial Response		Partial metabolic response	Partial remission (all of the following):
Lymph nodes and extralymphatic sites		Score 4 or 5 [†] with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
		At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
		At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
Nonmeasured lesions		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 interval scan	Not applicable

† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma

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
Nonmeasured 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

A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia
during R-CHOP chemotherapy
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC # 98317

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: LDi > 1.5 cm and Increase by $\geq 50\%$ from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm 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
	Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured 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

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

Appendix G – FACT-Lym

Study Number: <u>98317</u>	PID: _____
Investigator: <u>Rakhee Vaidya, M.D.</u>	Date(mm/dd/yy): _____ / _____ / _____

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

<u>SOCIAL/FAMILY WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>EMOTIONAL WELL-BEING</u>		Not at all	A little bit	Some -what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>		Not at all	A little bit	Some -what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4

GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	<u>ADDITIONAL CONCERNS</u>	Not at all	A little bit	Some -what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4

A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia
during R-CHOP chemotherapy
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC # 98317

HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

Appendix H – FACT - GOG/NTX-4, v4

Study Number: _____ PID: _____

Investigator: Rakhee Vaidya, M.D. Date(mm/dd/yy): ____ / ____ / ____

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some -what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4

Appendix I – PROMIS 29

PROMIS-29

Study Number: 98317

PID: _____

Investigator: Rakhee Vaidya, M.D.

Date(mm/dd/yy): ____/____/____

26 June 2016 © 2008-2016 PROMIS Health Organization and PROMIS Cooperative Group Page 1 of 3

Please respond to each question or statement by marking one box per row.

	<u>Physical Function</u>	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	<u>Anxiety</u> In the past 7 days...	Never	Rarely	Sometimes	Often	Always
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	<u>Depression</u> In the past 7 days...	Never	Rarely	Sometimes	Often	Always
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	<u>Fatigue</u> During the past 7 days...	Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	<u>Fatigue</u> In the past 7 days...	Not at all	A little bit	Somewhat	Quite a bit	Very much

A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia
during R-CHOP chemotherapy
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC # 98317

FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5						
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5						
	<u>Sleep Disturbance</u> In the past 7 days...	Very poor	Poor	Fair	Good	Very good						
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1						
	In the past 7 days...	Not at all	A little bit	Somewhat	Quite a bit	Very much						
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1						
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5						
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5						
	<u>Ability to Participate in Social Roles and Activities</u>	Never	Rarely	Sometimes	Usually	Always						
SRPPER11_ CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1						
SRPPER18_ CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1						
SRPPER23_ CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1						
SRPPER46_ CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1						
	<u>Pain Interference</u> In the past 7 days...	Not at all	A little bit	Somewhat	Quite a bit	Very much						
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5						
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5						
PAININ31	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5						
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5						
	<u>Pain Intensity</u> In the past 7 days...											
Global07	How would you rate your pain on average?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	No pain										Worst imaginable pain	

Appendix J – Baseline (Pre-Treatment) Data Collection Form

OnCore PID: _____	PI: <u>Rakhee Vaidya, M.D.</u>
Study Number: 98317	Date(mm/dd/yy): ____/____/____

International Prognostic Index (IPI) Score

☐0-1 ☐2 ☐3 ☐4-5

☐Y/☐N Double or Triple Hit Lymphoma, ☐ unknown

ECOG PS:

☐0 ☐1 ☐2 ☐3 ☐4 ☐5

Pre-PET fasting glucose

____.____ mg/dL

Appendix K- Hyperglycemia Outcomes

OnCore PID: _____ PI: Rakhee Vaidya, M.D.

Study Number: 98317 Date(mm/dd/yy): _____ / _____ / _____

Instructions: To be filled out at baseline, beginning of each cycle with the exception of cycle 3 and 6 in which case this form should also be completed at the end of the cycle.

CYCLE INFORMATION

☐ Baseline

☐ Cycle _____

Cycle start date (mm/dd/yy): _____ / _____ / _____

Cycle End Date (mm/dd/yy): _____ / _____ / _____

If Cycle 6, end of washout date (mm/dd/yy): _____ / _____ / _____

☐ 6 months post treatment completion

PREVIOUS MEAL

Time of last meal eaten (HH:MM): _____ : _____ ☐ am ☐ pm

What was eaten:

HYPERGLYCEMIA RELATED INFORMATION

1. Measures

Random blood Glucose (day 1, each cycle):

Levels prior to chemotherapy administration _____ mg/dL

Levels after chemotherapy administration _____ mg/dL

2. Any symptoms of Diabetes Mellitus? ☐ Yes ☐ No

To be measured for baseline, end of cycles 3 and 6 and 6 months post therapy completion

FBG: _____ mg/dL ☐ NA

HbA1C: _____ % ☐ NA

Fructosamine: _____ umol/L ☐ NA

Fasting Insulin: _____ pmol/L ☐ NA

Date of Blood Draw: _____ / _____ / _____

Time of Blood Draw: _____ : _____ ☐ am ☐ pm

Person filling out form: _____

Date(mm/dd/yy): _____ / _____ / _____

Appendix L - R-CHOP Cycle Form

OnCore PID: _____	PI: <u>Rakhee Vaidya, M.D.</u>
Study Number: 98317	Date(mm/dd/yy): ____/____/____

INSTRUCTIONS: To be filled out at the beginning of each cycle

PREDNISONE DOSE DURING THERAPY

1. Current Cycle: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐
2. Dose of Prednisone for Cycle: ____ mg (determined by previous cycle RBG)

CHEMOTHERAPY

Chemotherapy	Dose	Standard?	If reduced, new dose	Reason for reduction
Rituximab	375 mg/m ²	☐ Yes ☐ No		
Rituximab Hycela				
Cytosan	750mg/m ²	☐ Yes ☐ No		
Hydroxorubicin (Adriamycin)	50mg/m ²	☐ Yes ☐ No		
Ocovin (Vincristine)	2 mg/m ²	☐ Yes ☐ No		
Prednisone	100 mg	☐ Yes ☐ No		

If Cycle 6, count 30 days post end of cycle(mm/dd/yy): ____/____/____

3. Was the cycle delayed 7 days or more? ☐Yes ☐No

If yes, why?

4. Was the patient hospitalized during this cycle? ☐Yes ☐No

- If yes, cause of hospitalization:

5. Was growth factor administered during this cycle? ☐Yes ☐No
6. Were there adverse events expected to be attributable to Prednisone during the last cycle?

☐Yes, If Yes please check all those that are applicable below. ☐No

- ☐ Dry mouth
- ☐ Nausea
- ☐ Vomiting
- ☐ Heartburn

A randomized phase II pilot of tailored prednisone reduction versus usual care for the treatment of hyperglycemia
during R-CHOP chemotherapy
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC # 98317

☐ Constipation

☐ Diarrhea

☐ Urinary Frequency: ☐Increase or ☐Decrease

☐ Other: _____

Person filling out form: _____

Date(mm/dd/yy): ____/____/____

Appendix M - CRU Processing Laboratory Requisition

OnCore PID: _____ PI: Rakhee Vaidya, M.D.

Study Number: 98317 Date(mm/dd/yy): ____/____/____

CLINICAL BARCODE LABEL HERE

If label is not available, please complete the following

Last name: _____

First name: _____

MRN: _____

Participant Study ID #: _____

Participant Study Acrostic: _____

Circle Visit: Baseline End of Cycle 3 End of Cycle 6 6 mos. post-treatment

Date Collected (mm/dd/yy): ____/____/____

Time Collected (HH:MM): ____:____ ☐am ☐pm

Draw the following tubes and deliver to the Main CRU Lab within 45 minutes of collection:

- 2 x 10mL Red for Fructosamine, test 100800; serum Glucose, test 001032 and serum storage.
- 1 x 4mL K2 EDTA for HbA1c, Lab Corp test 001453
- 1 x 8.5 ml SST for Fasting Insulin

Time Delivered (HH:MM): ____:____ ☐am ☐pm

Person filling out form: _____

Date(mm/dd/yy): ____/____/____

Appendix N – Prednisone Diary

OnCore PID: _____ PI: Rakhee Vaidya, M.D.

Study Number: 98317 Date(mm/dd/yy): ____/____/____

Instructions: Record that you have taken your prescribed prednisone. Please bring back your prednisone blister pack at your next visit. Please comment when needed.

Day 1

Did you take your prednisone?

☐ Yes

☐ No

Comment, If no why:

Day 2

Did you take your prednisone?

☐ Yes

☐ No

Comment:

Day 3

Did you take your prednisone?

☐ Yes

☐ No

Comment:

Day 4

Did you take your prednisone?

☐ Yes

☐ No

Comment:

Day 5

Did you take your prednisone?

☐ Yes

☐ No

Comment:

To be filled out by research staff

Blister pack received? ☐ Yes

☐ No

All pills taken? ☐ Yes

☐ No

Research Staff Member: _____

Date(mm/dd/yy): ____/____/____

Appendix O – Off-Study Form

Study Number: 98317

PID: _____

Investigator: Rakhee Vaidya, M.D.

Date(mm/dd/yy): ____/____/____

Instructions: Complete this form if the patient either withdraws consent or is removed from the study.

Name of Person Completing form _____

Did the subject meet eligibility criteria for study enrollment? Yes ☐ No ☐

Was the subject removed from the study per physician decision? Yes ☐ No ☐
(if yes, move to #5)

Did the patient withdraw consent to participate in the study? Yes ☐ No ☐
(if yes move to #1)

Reason for patient withdrawal:

1. ☐ Unacceptable toxicity from
 - a. ☐ Prednisone
 - b. ☐ Rituximab
 - c. ☐ Cyclophosphamide
 - d. ☐ Vincristine
 - e. ☐ Doxorubicin

2. ☐ Did not want to participate anymore. Reason:

3. ☐ Other: _____

4. Please specify what portion of the study the subject wishes to withdraw from:

- ☐ For just the Prednisone administration only
☐ For all components of the research study (including follow up in the medical record)

Reason(s) for Removal:

5. ☐ Patient exhibited progression of disease

6. ☐ Unacceptable toxicity from
 - a. ☐ Prednisone
 - b. ☐ Rituximab
 - c. ☐ Cyclophosphamide
 - d. ☐ Vincristine
 - e. ☐ Doxorubicin

7. ☐ Investigator's discretion to withdraw patient from the study because continued participation in the study is not in the patient's best interest (*Describe below)
8. ☐ Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible (*Describe below)
9. ☐ General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment (*Describe below)
10. ☐ Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits (*Describe below)
11. ☐ Termination of the clinical trial by the clinical sponsor
12. ☐ Patient Died: Date of death (mm/dd/yy): ____/____/____

Comment:

If reason for withdrawal includes #7, 8, 9, or 10 then please add comments clarifying this information)_____

Appendix P– Drug Inserts

The FDA Labels and drug inserts that are referenced in this protocol can be found at the following links.

Prednisone

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202020s000lbl.pdf

Cyclophosphamide

https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf

Vincristine

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/071484s042lbl.pdf

Rituximab

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf

Doxorubicin

https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/050467s068lbl.pdf

Appendix Q – PRO-CTCAE

Study Number: 98317

PID: _____

Investigator: Rakhee Vaidya, M.D. _____

Date(mm/dd/yy): ____/____/____

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
	☐ None	☐ Moderate	☐ Mild	☐ Severe	☐ Very severe
2.	In the last 7 days, how OFTEN did you have NAUSEA?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
3.	In the last 7 days, how OFTEN did you have VOMITING?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
4.	In the last 7 days, how OFTEN did you have HEARTBURN?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
5.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
6.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly
7.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much
8.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH				

	CONCENTRATION at their WORST?
	☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe
	In the last 7 days, how much did PROBLEMS WITH CONCENTRATION INTERFERE with your usual or daily activities?
	☐ Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much
9.	In the last 7 days, what was the SEVERITY of your PROBLEMS WITH MEMORY at their WORST?
	☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe
	In the last 7 days, how much did PROBLEMS WITH MEMORY INTERFERE with your usual or daily activities?
	☐ Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much
10.	In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?
	☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe
	In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?
	☐ Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much
11.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?
	☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?
	☐ Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much
12.	In the last 7 days, were there times when you had to URINATE FREQUENTLY?
	☐ Never ☐ Rarely ☐ Occasionally ☐ Frequently ☐ Almost constantly
	In the last 7 days, how much did FREQUENT URINATION INTERFERE with your usual or daily activities?
	☐ Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much
	Do you have any other symptoms that you wish to report?
	☐ Yes ☐ No

If “Yes”, please fill out the section on the next page.

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?
	☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?

	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

Appendix R – 30-day Treatment Follow-up Form

Study Number: 98317

PID: _____

Investigator: Rakhee Vaidya, M.D.

Date: ____/____/____

Instructions: Complete this form to follow-up with patients for adverse events.

Name of Person Completing form _____

Did the subject have any adverse events in the last 30 days? Yes ☐ No ☐

If yes, please describe nature and grade of AE (Note*: If an SAE occurs in this period, report the event as required in [Appendix D](#)):

Was the subject removed from the study by the PI? Yes ☐ No ☐

Did the subject withdraw from the study? Yes ☐ No ☐

Did the subject complete the study? Yes ☐ No ☐