A Phase II Study of Split-Dose R-CHOP in Older Adults with Diffuse Large B-cell Lymphoma

7/21/23

NCT03943901

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Short Title: Split-Dose R-CHOP for Older Adults with DLBCL

A Phase II Study of Split-Dose R-CHOP in Older Adults with Diffuse Large B-cell Lymphoma

Version 6 Date: 7/21/23

Principal Investigator
Christopher D. Fletcher, MD
Assistant Professor of Medicine
University of Wisconsin Carbone Cancer Center
Phone: 608-263-5006
E-mail: cdfletcher@medicine.wisc.edu

Study Chair
Nirav Shah, MD MS
Associate Professor of Medicine
Department of Medicine, Division of Hematology and Oncology
Medical College of Wisconsin
Clinical Cancer Center
9200 W. Wisconsin Ave
Phone: 414-805-4600/Fax: 414-806-6815
Email address: nishah@mcw.edu

Biostatistician
Aniko Szabo, PhD
Associate Professor
Division of Biostatistics
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI, 53226
Phone: 414-955-4096/Fax: 414-955-0176
E-mail: aszabo@mcw.edu

WON Contact
Wisconsin Oncology Network

multisite_research@cancer.wisc.edu

Protocol No.: *UW18131*
Study Phase: *Phase II*

Study Summary

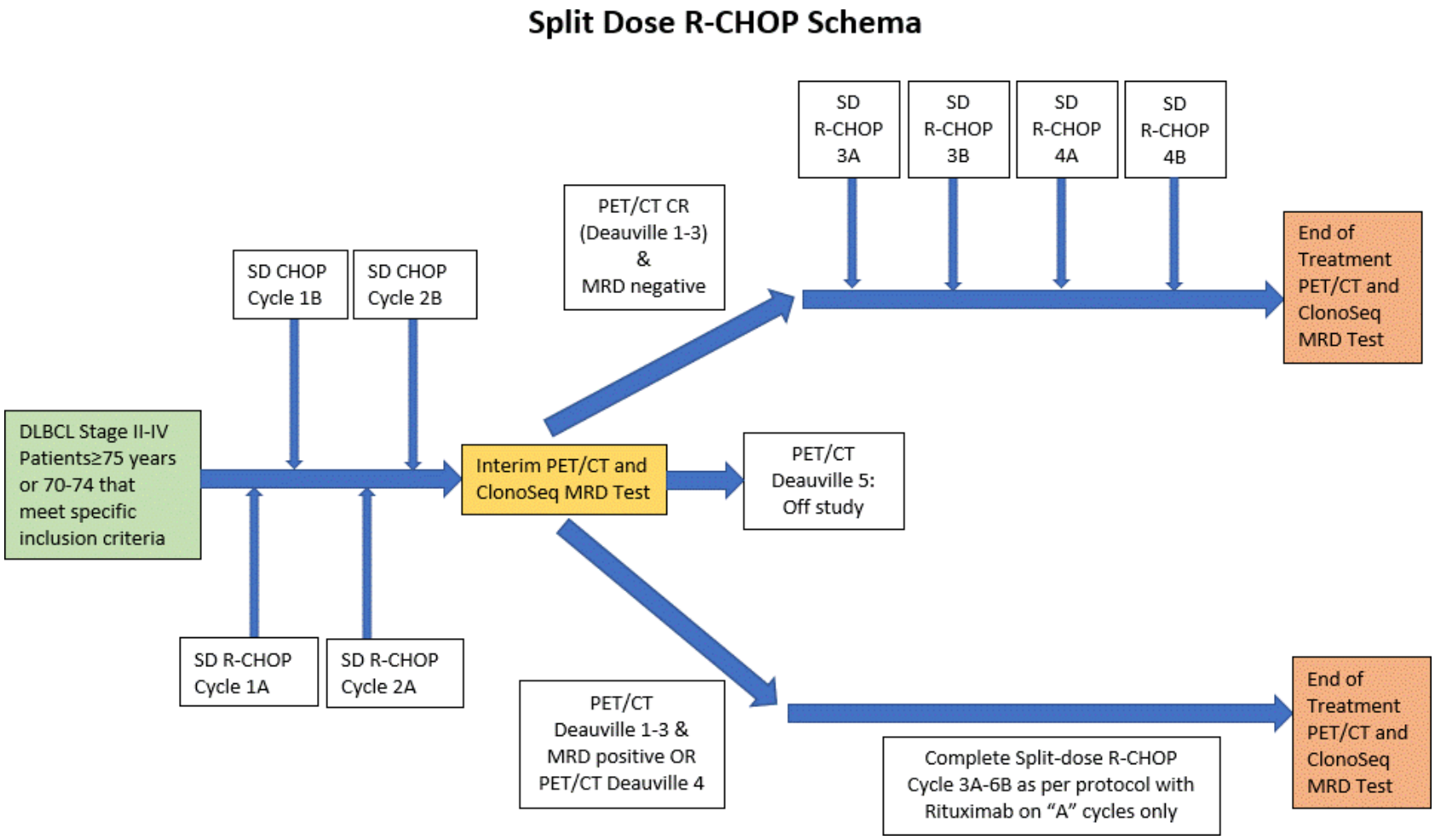
Title	*A Phase II study of Split-Dose R-CHOP in Older Adults with Diffuse Large B-cell Lymphoma*
Protocol Number	*UW18131*
Principal Investigator	**Principal Investigator** Christopher D. Fletcher, MD Assistant Professor, Department of Medicine University of Wisconsin Carbone Cancer Center **Study Chair** Nirav Shah, MD MSHP Associate Professor, Department of Medicine Medical College of Wisconsin
Study Sites	Froedtert Hospital, Medical College of Wisconsin, University of Wisconsin Hospital and Clinics, and the Wisconsin Oncology Network
Clinical Trial Phase	Phase 2 study
Study Disease	Diffuse Large B-Cell Lymphoma (DLBCL)
Inclusion Criteria	1) Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial. 2) All patients age ≥75 years and patients aged 70-74 years who are determined to be unfit or frail by Cumulative Illness Rating scale for Geriatrics (CIRS-G scale) (Appendix D). *a. For 70-74 years aged patients: CIRS-G score with 5-8 comorbid conditions scored 2 or ≥1 comorbidity scored 3-4. CIRS-G score is to be reviewed by the study PI prior to enrollment.* 3) Newly diagnosed, untreated, biopsy proven CD20 positive DLBCL (including high grade B-cell lymphoma & T-cell/histiocytic rich large B-cell lymphoma). Patients with discordant bone marrow involvement (i.e. involved with low-grade/indolent non-Hodgkin lymphoma (NHL)) are eligible. Patients with transformed DLBCL from underlying low-grade disease are eligible. Patients with composite DLBCL and concurrent low-grade lymphoma are eligible. *a. Copy of pathology report must be sent to coordinating site to confirm diagnosis for eligibility.* *b. Patients with prior treatment for low grade NHL with non-anthracycline based regimens are eligible.* 4) Measurable disease by positron emission tomography (PET)/computed tomography (CT) or bone marrow (BM) biopsy prior to enrollment 5) Left ventricular ejection fraction ≥50% by resting echocardiography or resting multi-gated acquisition (MUGA) scan. 6) Karnofsky Performance Score ≥50 (Appendix A).

	8) Minimum life expectancy greater than 3 months. 9) Negative HIV test. 10) For patients with hepatitis B virus antigen (HbsAg) or core antibody (HbcAb) seropositivity, patients must have a negative Hep B viral load and an appropriate prophylaxis plan must be in place during chemotherapy therapy treatment. For all patients that have Hep B core antibody positive, they should take entecavir prophylaxis (0.5 mg PO daily) until 1 year from completion of chemotherapy. Hep B viral load should be checked on these patients prior to starting chemotherapy and every 3 months thereafter if initial Hep B viral load is negative (+/- 1 week if chemotherapy cycle is delayed). If Hep B viral load is positive, Hepatology or ID referral is recommended, and HBV viral load should be checked monthly. 11) For patients with hepatitis C Ab (HbcAb) positivity, a viral load must be checked and be negative for enrollment. 12) Intrathecal chemotherapy for central nervous system prophylaxis only can be given at the discretion of the primary oncologist.
Exclusion Criteria	1) History of previous anthracycline exposure. 2) CNS or meningeal involvement at diagnosis. 3) Creatinine Clearance less than or equal to 25 mL/min by Cockroft-Gault. 4) Poor hepatic function, defined as total bilirubin concentration greater than 3.0 mg/dL or transaminases over 4 times the maximum normal concentration, unless these abnormalities are felt to be related to the lymphoma. 5) Pulmonary dysfunction defined as >2L of oxygen required by nasal cannula to maintain peripheral capillary oxygen saturation (SpO2) ≥90% unless felt to be related to underlying lymphoma. 6) Myocardial Infarction within 6 months of enrollment. 7) Active, uncontrolled infectious disease. 8) Known concurrent bone marrow malignancies (e.g. myelodysplastic syndrome) or poor bone-marrow reserve, defined as neutrophil count less than 1.5×10^9/L or platelet count less than 100×10^9/L, unless caused by bone-marrow infiltration with lymphoma. 9) History of a second concurrent active malignancy or prior malignancy which required chemotherapy treatment within the preceding 2 years. 10) Treatment with any investigational drug within 30 days before the planned first cycle of chemotherapy. 11) Unable or unwilling to sign consent.
Primary Objectives	To determine the complete response rate of split-dose R-CHOP in older adults with treatment naïve de novo or transformed DLBCL.

Secondary Objectives	1) To determine the progression free survival of patients treated with split-dose R-CHOP. 2) To determine overall survival of patients treated with split-dose R-CHOP. 3) To evaluate the significance of interim minimal residual disease (MRD) and PET/CT negativity on clinical outcomes. 4) To evaluate frequency and degree of adverse events with split-dose R-CHOP. 5) To perform a cancer-specific geriatric assessment prior to, during, and after completion of chemotherapy treatments and to evaluate for changes in physical function, mental health, cognition, and other relevant geriatric specific outcomes.
Exploratory Objective	To evaluate minimal residual disease (MRD) testing in whole blood vs plasma.
Study Design	Single arm, interventional phase 2 study.
Study Agent Description	*Split-dose R-CHOP is administered as follows:* Each cycle is 28 days and consists of one "A" treatment on Day 1 and one "B" treatment on Day 15 for 6 cycles **Day 1 ("A" part of cycle)** Rituximab 375 mg/m2 IV (or biosimilars Ruxience or Truxima) Cyclophosphamide 375 mg/m2 IV Doxorubicin 25 mg/m2 IV Vincristine 1 mg IV Prednisone 50 mg (Days 1-5) PO Pegfilgrastim 6 mg on Day 2 (24 hours after completion of chemotherapy) or filgrastim daily as indicated (starting 24 hours post completion of chemotherapy), or institutional standard granulocyte stimulating factor. **Day 15 ("B" part of cycle)** Cyclophosphamide 375 mg/m2 IV Doxorubicin 25 mg/m2 IV Vincristine 1 mg IV Prednisone 50 mg (Days 15-19) PO Pegfilgrastim 6 mg on Day 16 (24 hours after completion of chemotherapy) or filgrastim daily as indicated (starting 24 hours post completion of chemotherapy), or institutional standard granulocyte stimulating factor.
Number of Subjects	26
Subject Participation Duration	6 months for treatment, 2-year long-term follow-up after completion of treatment
Duration of Follow up	2 years after completion of treatment
Estimated Time to Complete Enrollment:	2.5 years

Statistical Methodology:	For this phase II study the original study design utilized a Simon 2-stage design with complete response (CR) rate at the end of treatment as our primary outcome. Based on previously published studies, we will use 40% as our unacceptable boundary for complete response rate and 60% as the acceptable complete response rate. We will set the power at 80% and Type I error at 5% which will require a maximum sample size of 46 patients. In the first stage 16 patients are recruited and the trial will only proceed to the second stage if more than 7 patients achieve a complete response. If the true CR rate is 40% or lower, this stopping rule would have a 71.6% probability of stopping the study after the first stage. Based on an unplanned sample size recalculation when 14 patients have been enrolled, the study design was modified using the method of Müller and Schäfer, maintaining the original type I error of 5% and conditional power of at least 80%. With this redesign a total of 26 patients will be enrolled.
Safety Assessments	We expect up to a 30% risk of grade 3 and 4 **non-hematologic adverse events** to be considered acceptable. Toxicity monitoring will start from the 4th patient and every 3rd patient afterwards. Details of stopping rules are detailed below in Section 7.2, "Toxicity Monitoring".
Unique Aspects of this Study	This study is investigating a new administration schedule of R-CHOP chemotherapy and focuses on an underserved elderly population that is often excluded from clinical trials.

Protocol Schema



* Subjects who present with an interim PET/CT Deauville 5 score must have a pattern consistent with progressive disease. Progression per Lugano 2014 response criteria (Appendix F) is defined by the following: increased uptake from baseline and/or change in size and/or new lesions. Subjects who present with a Deauville 5 score that do not have a pattern consistent with progressive disease per the Lugano response criteria will continue protocol therapy and complete cycles 3A through 6B.

Schedule of Activities

Table 1. Study Schedule

1 Cycle=28 days	Day -28 to start oftreatment	SD R-CHOP **Cycle 1A	SD CHOP Cycle 1B	SD R-CHOP Cycle 2A	SD CHOP Cycle 2B	SD R-CHOP $	SD (R?)-CHOP *Cycle 3B	SD R-CHOP *Cycle 4A	SD (R?)-CHOP *Cycle 4B	SD R-CHOP #Cycle 5A	SD R-CHOP #Cycle 5B	SD R-CHOP #Cycle 6A	SD R-CHOP #Cycle 6B	EOT evaluation 4-6 weeks post-tx	Long-term Follow-up Q6 months up to 2 years+
Visit Window	Screening/ Enrollment		+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 30 days
Day	Day -28	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 183-Day 197	6 months post-end of treatment Q6 months
Signed Inform Consent	X														
Pathological Diagnosis of de novo or transformed DLBCL (CD20 positive)[1]	X														
International Prognostic Index (Appendix C)	X														
Recent History and Physical Examination [2]	X	X**	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky Performance Score	X	X**		X		X		X		X		X		X	X
Vitals [3]	X	X**	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication & Evaluation of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prednisone Pill Diary Assessment (Appendix E)			X	X	X	X	X	X	X	X	X	X	X	X	
Tumor Measurements by PET/CT[4]	X[4]					X[4]								X[4]	
ECHO/MUGA[11]	X[11]														
Bone Marrow Biopsy & Aspirate [5]	X													X	
CBC and Differential	X	X**	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic Panel [6]	X	X**	X	X	X	X	X	X	X	X	X	X	X	X	X
LDH	X	X**	X	X	X	X	X	X	X	X	X	X	X	X	X
Uric Acid	X	X**	X												
HIV and Hepatitis screening[10]	X														

1 Cycle=28 days	Day -28 to start of treatment	SD R-CHOP **Cycle 1A	SD CHOP Cycle 1B	SD R-CHOP Cycle 2A	SD CHOP Cycle 2B	SD R-CHOP $	SD (R?)-CHOP *Cycle 3B	SD R-CHOP *Cycle 4A	SD (R?)-CHOP *Cycle 4B	SD R-CHOP #Cycle 5A	SD R-CHOP #Cycle 5B	SD R-CHOP #Cycle 6A	SD R-CHOP #Cycle 6B	EOT evaluation 4-6 weeks post-tx	Long-term Follow-up Q6 months up to 2 years+
Visit Window	Screening/ Enrollment		+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 30 days
Day	Day -28	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 183-Day 197	6 months post-end of treatment Q6 months
CT neck/chest/abdomen/pelvis OR PET/CT[7]															X
Research Assessments															
Geriatric Assessments[8]	X					X								X	
Clonoseq MRD Testing[9]	X					X								X	

FOOTNOTES for Schedule of Events

* For patients who are MRD negative and have interim PET/CT with Deauville Score 1-3, will be assigned to abbreviated chemotherapy course and receive R-CHOP every 14 days through Cycle 4B.

** Screening labs completed within 24 hours of cycle 1, day 1 do not need to be repeated. History, physical exam, karnofsky performance score, and weight completed within 7 days of cycle 1, day 1 do not need to be repeated.

$ All patients regardless of arm will receive Cycle 3A R-CHOP. MRD status and PET/CT results will determine treatment for Cycle 3B and beyond.

For patients who are MRD positive or have interim PET/CT positivity, they will be assigned to complete split-dose R-CHOP for a full 6 cycles. Additionally, subjects who do not have an identifiable clone at baseline and patients with an indeterminate/unclassifiable result at the interim endpoint will not be eligible for the abbreviated arm and will complete split-dose R-CHOP for a full 6 cycles.

\+ Long-term follow-up. Patient will be seen every 6 months by treating physician after end of treatment evaluation and CT neck/chest/abdomen/pelvis and/or PET/CT for disease assessment should be performed at minimum 6 months, 1 year and 2 years post-end of treatment evaluation. Patients will be followed for progression, survival, and initiation of new lymphoma directed treatments at these specified time points.

1- Pathological report must be sent to coordinating site for review prior to enrollment.
2- History and height only required at screening, physical exam at all other time points
3- Vitals should include Weight, Blood Pressure, Temperature, Pulse & Pulse Ox.
4- PET/CT

a. Baseline PET/CT should be done within 6 weeks of 1st treatment.
b. Interim PET/CT should be done within 7 days prior to Cycle 3A of split-dose R-CHOP.
c. End of Treatment PET/CT should be performed 4-6 weeks after last dose of chemotherapy.

5- Bone Marrow Biopsy + Aspirate prior to treatment is strongly recommended for all subjects; however, BmBx is only required at screening if a subject presents with a PET scan abnormality and/or any lineage cytopenias (platelets<100 K/uL or absolute neutrophil count <1.0 K/μL) suggesting BM involvement. If pre-treatment BM biopsy is positive for lymphomatous involvement then BM biopsy is required to be repeated at end of treatment.

6- Comprehensive Metabolic Panel: Albumin, Alkaline Phosphatase, AST, Bicarb, Bili T, Calcium (total), Chloride, Creatinine, Glucose, Potassium (K), Sodium (Na), Protein Total, BUN, ALT.

7- Patients will obtain either CT Neck/Chest/Abdomen/Pelvis or PET/CT at 6 months, 1 year, and 2 years post-end of treatment evaluation for surveillance.

8- Geriatric Assessment will be performed at baseline prior to treatment, with or within 7 days prior to Cycle 3A, and at end of treatment evaluation. Full GA questionnaire can be found in Appendix H.

9- Minimal Residual Disease Testing
a. Baseline: Biopsy sent to Adaptive Technology for Identification test. See section 6.7 for baseline MRD sample collection details.
b. Peripheral Blood Sample: Cycle 3A (drawn within one week of Cycle 3A and blood will be drawn only in patients with successful ID test) Two samples will be drawn: **Sample 1 –** 10 ml of peripheral blood in EDTA tube and **Sample 2** – 10 ml of fresh peripheral blood in EDTA tube. Sample 1 is to be processed into plasma per Appendix I and shipped to Adaptive within 7 days of collection. Sample 2 is to be stored as PB locally and batch shipped to Adaptive every 12-18 months from the first patient enrolled into this trial (for collected plasma and PB samples, instructions for separating plasma and sending Plasma and PB are listed in Appendix I). Adaptive orders should only be placed within the Adaptive Diagnostic Portal for Plasma samples and are not required for stored PB samples. .
c. End of Treatment Blood Sample: 4-6 weeks after last treatment (blood to be drawn pre-treatment only in patients with successful ID test) Two samples will be drawn: **Sample 1 –** 10 ml of peripheral blood in EDTA tube and **Sample 2** – 10 ml of fresh peripheral blood in EDTA tube. Sample 1 is to be processed into plasma per Appendix I and shipped to Adaptive within 7 days of collection. Sample 2 is to be stored as PB locally and batch shipped to Adaptive every 12-18 months from the first patient enrolled into this trial. (for plasma and PB samples, instructions for separating plasma and sending Plasma and PB are listed in Appendix I). Adaptive orders should only be placed within the Adaptive Diagnostic Portal for Plasma samples and are not required for stored PB samples

10- HIV and hepatitis screening to include: HIV antibody, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody and hepatitis C antibody.

11. Baseline ECHO/MUGA must be done within 90 days of first treatment provided no cardiac diagnoses in that time interval (arrhythmia, angina, syncope). If patient has cardiac diagnosis within the previous 90 days, an ECHO/MUGA must be done within 28 days prior to treatment.

Table of Contents

1 List of Abbreviations and Definitions

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANC	Absolute neutrophil count
BCR	B-cell receptor
BM	Bone marrow
BR	Bendamustine-rituximab
BSA	Body surface area
CBC	Complete blood count
CDR3	Complimentary determining region 3
CIRS-G	Cumulative Illness Rating Score-Geriatrics
CMP	Complete metabolic profile
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CT	Computed tomography
cfDNA	Cell-free DNA
ctDNA	Circulating tumor DNA
DLBCL	Diffuse Large B-cell Lymphoma
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event-free survival
EOT	End of Treatment
FDG	Fludeoxyglucose
GA	Geriatric assessments
G-CSF	Granulocyte-colony stimulating factor
HbsAg	Hepatitis B virus antigen
HbcAb	Hepatitis B virus core antibody
HCT	Hematocrit
HGB	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
IADLs	Instrumental Activities of Daily Living
ID	Identification
IPI	International Prognostic Index
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
MCW/FH	Medical College of Wisconsin/Froedtert Hospital
MRD	Minimal Residual Disease
MUGA	Multi-gated acquisition
NHL	Non-Hodgkin Lymphoma
OS	Overall survival
PCR	Polymerase chain reaction

PET	Positron emission tomography
PFS	Progression-free survival
PO	Per os
PPI	Proton pump inhibitor
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
SAE	Serious Adverse Event
SD	Split-Dose
SEER	Surveillance, Epidemiology, and End Results
SpO2	Peripheral capillary oxygen saturation
UP	Unanticipated problem
WBC	White blood cell
WON	Wisconsin Oncology Network

Biosimilar A **biosimilar** is a biological product. FDA-approved **biosimilars** have been comparedto an FDA-approved biologic, known as the reference product. Rituxan (rituximab) is the reference product for Ruxience (Rituximab-PVVR; Pfizer) and Truxima (Rituximab-abbs;Cephelon).

2 Introduction

2.1 Background

Diffuse large B-cell lymphoma (DLBCL) is a form of high-grade non-Hodgkin lymphoma (NHL) with a high mortality rate if untreated. It is the most common form of NHL and its incidence increases with age with a median age of presentation of 70 years.[1, 2] As a result of improved medical care, the population aged ≥70 years old is growing and consequently, there has been an increase in the number of cases of NHL in this specific age group.[3] However, despite this shifting demographic, the standard treatment approach for most patients with DLBCL remains immunotherapy with the anti-CD20 monoclonal antibody rituximab in combination with cytotoxic chemotherapy that includes cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP 21) given in 21 day cycles.[4-6] While this regimen has been established as the standard of care for most patients, maintaining dose density and intensity in geriatric patients may be difficult due to age-related changes in metabolism and comorbid conditions.[4, 7] Given that 85% of patients over the age of 80 years will present with comorbidity, many of these patients do not receive curative intent chemotherapy.[8] Many providers are hesitant to prescribe multi-agent anthracycline based chemotherapeutic regimens to this age group due to concerns for excessive therapy-related toxicity and poor hematologic reserve.[7, 8] This is best exemplified by a Surveillance, Epidemiology, and End Results (SEER)-Medicare database review that demonstrated only 42% of approximately 9400 patients over the age of 65 with DLBCL received doxorubicin-based therapy.[9]

Although there is limited data to guide the treatment of geriatric patients diagnosed with DLBCL, the importance of offering treatment is clear as the main cause of death in this population is progressive lymphoma.[8, 10] Despite this, patients in the most vulnerable age group, age ≥80, often do not receive combination therapy with curative intent.[10] A study comparing outcomes in the pre/post rituximab era in DLBCL patients ≥80 years found that curative intent chemotherapy was offered to only 21/40 (53%) patients in the post-rituximab era.[11] However, elderly patients who are offered R-CHOP 21 often experience more toxicity than their younger counterparts.[12] While R-CHOP 21 is offered to all patients felt to be candidates for this regimen, many centers have developed alternative schedules and regimens due to concern with toxicity with standard cytotoxic chemotherapeutic regimens. One group studied a novel regimen termed “R-miniCHOP” prospectively in the treatment of DLBCL, specifically in patients ≥80 years of age. This was an attenuated regimen with approximately 50% dose reductions in all the drugs in R-CHOP 21 except for rituximab. In the single-arm study of R-miniCHOP the median progression-free survival (PFS) was 21 months and median overall survival (OS) was 29 months. The complete response rate at the end of treatment was 63%. [13]

In addition to R-miniCHOP, several other groups have described institutional modifications to R-CHOP chemotherapy for the treatment of elderly patients with DLBCL. One such regimen, R-split-CHOP, divided the administration of cyclophosphamide and doxorubicin over 2 days to decrease toxicity. In a retrospective review of 30 patients, the 3-year OS was 61% with no treatment-related deaths in their cohort.[14] Another group reported their results with dose modifications of R-CHOP by age. Patients aged ≥70 received 70% of chemotherapy dose while patients age ≥80 received 50% of the dose, similar to R-miniCHOP. Based on toxicity, dose escalations could be made as tolerated. In this cohort, patients in the 70-79 age group had a 2-year OS of 75% while patients in the age ≥80 group had a 2-year OS of 65%.[15] All the mentioned regimens represent variations on the administration and dosing of R-CHOP chemotherapy. Alternative regimens explored for the very elderly include non-anthracycline based therapies such as bendamustine-rituximab (BR). In a Phase II study incorporating 14 patients ≥80 years with aggressive lymphomas felt not to be eligible for R-CHOP chemotherapy, the median OS with BR chemotherapy was 7.7 months with no treatment related mortality.[16] Although this represents a reasonable option in select patients, anthracycline therapy has historically been a mainstay in the

treatment of aggressive lymphomas with an overall survival benefit seen even in an elderly population.[17, 18] However, without prospective clinical trials, the optimal regimen for older adults with DLBCL remains an unanswered question.

An alternative strategy to deliver equivalent dosages of curative intent therapy to the older adult population is to administer R-CHOP in split doses. This strategy was first developed at the University of Pennsylvania Abramson Cancer center and is termed split-dose R-CHOP [19]. This regimen is reserved for the very elderly or the elderly with comorbid conditions who are felt to not be candidates for standard approach R-CHOP 21 chemotherapy. Patients receive CHOP at a 50% dose reduction on day 1 ("A" cycle) and day 15 ("B" cycle) of each 28-day cycle. Rituximab is given at full dose on day 1 of each cycle. The total amount of chemotherapy delivered during each 28-day cycle of SD R-CHOP is equivalent to the total doses in R-CHOP 21. All patients are supported with granulocyte-colony stimulating factor (G-CSF) after each half cycle. This regimen is given for 6 months for a combined total of 12 "A" and "B" cycles. A retrospective analysis of patients with large cell lymphoma treated with this regimen at the University of Pennsylvania demonstrated a median OS of 47 months in a group of patients with a median age of 81.[20]

2.2 Interim PET/CT and MRD Testing in DLBCL

There is increasing data that both imaging and blood testing for minimal residual disease (MRD) can help predict outcomes in patients with DLBCL. Interim PET/CT testing is considered a standard in patients with DLBCL and interim negativity has been shown to be predictive of disease outcomes. In one study of 161 patients with DLBCL treated with R-CHOP chemotherapy, an interim negative PET/CT correlated with a 3-year OS of 93.8% vs 53.3% among patients who had a positive interim PET/CT. This finding was statistically significant and suggests that interim PET/CT imaging may be a strong predictor of response.[21] In a prospective study evaluating the role of interim PET/CT imaging with R-CHOP 14, while there was no difference in OS at 2 years, the primary outcome, event-free survival (EFS) was significantly improved among the PET/CT negative patients (2 year EFS 48% for PET positive versus 74% for PET negative).[22] Furthermore, the use of interim PET/CT to drive clinical trial decision making has been established with other studies utilizing such results to drive treatment choice. [23] In addition to PET/CT there has been increasing interest in the utility of peripheral blood-based MRD testing to drive clinical care and decision making. In one analysis of patients with DLBCL, interim circulating tumor DNA (ctDNA) analysis had a negative predictive value of 79.8%. Follow-up surveillance analysis had a negative predictive value of 97.8%. These studies suggest that both interim and end of treatment blood samples for ctDNA may have prognostic value.[24]

For this study we intend to use a combination of PET/CT and ctDNA MRD testing after 2 cycles of treatment to identify who can receive an abbreviated course of chemotherapy. Only in those patients who are both MRD negative and interim PET/CT negative will an abbreviated course of therapy be offered. For an older population where the toxicity associated with chemotherapy may be high, minimizing potentially unnecessary therapy may have significant clinical benefit. For patients who are either MRD positive or interim PET/CT positive, the full course of therapy will be administered.

2.2.1 Adaptive Technology MRD Test

For the purpose of this study we will utilize Adaptive Biotechnologies' clonoSEQ assay. The clonoSEQ assay is a multiplex polymerase chain reaction (PCR)-based method that amplifies rearranged B-cell receptors (BCR) complimentary determining region 3 (CDR3) sequences and exploits the capacity of high throughput sequencing technology, characterizes tens of thousands of IGH or IHK/L CDR3 chains and BCL1/2 translocations simultaneously. The primary obstacle to

addressing amplification bias in repertoire analysis has been the lack of any gold standard in which the exact concentration of each target is known prior to amplification. To address this problem, Adaptive Biotechnologies developed a rigorous PCR amplification bias-control process, ensuring a quantitative read-out of the adaptive immune repertoire. Additionally, because the technology utilizes genomic DNA, the frequency of sequenced CDR3 chains is highly representative of the relative frequency of each CDR3 sequence in the sample population of B cells. Thus, the assay captures the full BCR repertoire including individual clones and provides a novel method to identify and track the presence and frequency of common and rare clones in the context of the total adaptive immune system. The test is a two-step process. First, an identification (ID) sample is required to identify the clonal population of B-cells associated with the malignancy, then the clones can be tracked through the duration of treatment to detect MRD. The ID test will be performed using the diagnostic biopsy. Subsequent MRD assessments will occur prior to Cycle 3A and at the end of treatment.

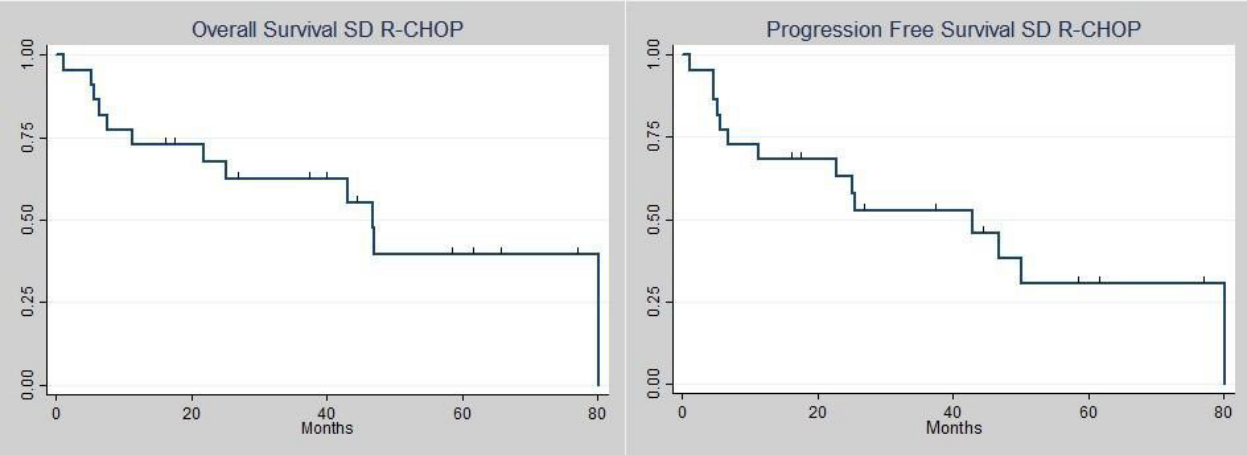
2.3 Rationale and Hypothesis

By 2030, nearly 20% of the US population will be over the age of 65 years, and the most rapidly growing population is people age ≥ 85 years.[25] As a result of improved medical care and resulting increasing longevity, there has been an increase in the number of cases of NHL in patients ≥80 years.[3] Despite this fact, the elderly remain an underrepresented group in cancer research resulting in a lack of guidelines for a standard treatment approach in this patient population.[26] Specifically in NHL, one systematic review found that in Phase II/III studies published between 2005 and 2011, only 10% focused exclusively in patients age >65 years and another 80% either directly or indirectly made it difficult for patients >65 years to enroll.[27] As a result of this report and others like it, the American Society of Clinical Oncology published a call to action in 2015 to increase the number of clinical studies for older patients.[28] In this proposed study, we aim to evaluate a new treatment regimen for an underserved older adult population with DLBLCL.[1, 2]

The optimal regimen for elderly patients with DLBCL remains unknown. R-miniCHOP, R-split-CHOP, DA-POCH-R and others have all been studied as alternative treatment schedules for older patients who were felt not to be candidates for full intensity R-CHOP 21.[13, 14, 29] However, R-CHOP 21 for 6 cycles has been well established through a series of large phase 3 randomized control trials to be the optimal regimen for patients with DLBCL. Split-dose R-CHOP is an alternative approach to treat patients with the same cumulative dose as R-CHOP 21, albeit in a prolonged, de-escalated fashion. The goal of split-dosing with growth factor support is to maintain intensity of treatment and decrease the toxicity of the regimen by exposing patients to lower levels of chemotherapy over a longer period of time. In effect, this is a similar dosing schedule as what patients receive for another type of lymphoma, Hodgkin's disease, which utilizes a Q2week dosing schedule for 6 months.[30]

The efficacy of split-dose R-CHOP was studied in a retrospective review of 22 patients with a median age of 81 years. 68% of patients had advanced stage disease and the majority had an International Prognostic Index (IPI)≥3 (64%). Almost half of patients had a Charlson comorbidity index ≥2 which correlates with a poor survival in lymphoma patients.[31] The overall response rate for all patients was 73% with 12 patients (55%) achieving a complete response (CR) at the end of therapy. There was toxicity with 2 deaths attributed to treatment. The OS for all patients was 47 months with a PFS of 43 months (Figure 1). Together these data support the investigation of this regimen in a Phase 2 study and will be an important clinical trial opportunity for older patients who may otherwise not be offered curative intent chemotherapy.

Figure 1: OS and PFS for Split-dose R-CHOP



In this study, we plan to test the efficacy of split-dose R-CHOP for the treatment of elderly patients with de novo diagnosis of DLBCL or transformed DLBCL. Split-dose R-CHOP involves giving CHOP chemotherapy at 14 days' interval with Rituximab given once/month. The safety for every 14-day CHOP administration was studied in a large prospective randomized control trial of patients up to the age of 80 years. In this study, R-CHOP given every 14 days for up to 6 cycles was felt to be the best method of delivery of chemotherapy. Receiving greater than 6 cycles of R-CHOP chemotherapy was not found to be beneficial compared to patients receiving 6 cycles of R-CHOP. [32] Additionally, we will use an interim response adapted approach by combining imaging and MRD testing to identify patients who will receive an abbreviated chemotherapy course if they are both PET/CT and MRD negative.

In our proposed study, subjects will receive a 50% dose reduction of CHOP chemotherapy on Day 1 and Day 15 of each cycle with full dose Rituximab on Day 1 for up to a total of 6 months of chemotherapy. Subjects who are MRD and PET/CT negative after 2 months will be placed on an abbreviated regimen with R-CHOP x 4 additional doses with full dose Rituximab and a 50% dose reduction in CHOP chemotherapy. We hypothesize that this method of administration of R-CHOP will be a safe and effective form of chemotherapy for older patients with DLBCL and will allow older patients to receive curative intent treatment.

3 Objectives

3.1 Primary Outcome/Endpoint(s)

The primary goal of this study is to determine the efficacy of split-dose R-CHOP in the treatment of older patients with DLBCL. The primary outcome will be the end of treatment rate of complete remission as assessed using the Lugano classification criteria.[33] We hypothesize that split-dose R-CHOP is an effective regimen and well tolerated method of delivering chemotherapy to older patients with DLBCL. We will utilize a two-stage Simon design to test the efficacy of this regimen.

Primary Objective

- To determine the complete response rate of split-dose R-CHOP in older adult patients with treatment naïve de novo or transformed DLBCL.

3.2 Secondary Outcome/Endpoint(s)

Secondary objectives include the following:

1) To determine the PFS of subjects treated with split-dose R-CHOP.
2) To determine OS of subjects treated with split-dose R-CHOP.
3) To describe clinical outcomes among subjects with interim MRD and PET/CT negativity.
4) To evaluate frequency and degree of adverse events with split-dose R-CHOP.
5) To perform a cancer-specific geriatric assessment prior to, during, and after completion of chemotherapy to evaluate for changes in physical function, mental health, cognition, and other relevant geriatric specific outcomes.3.3 Exploratory Outcome/Endpoint

3.3 Exploratory objective - To evaluate minimal residual disease (MRD) testing in whole blood vs plasma.

4 Study Design

4.1 Overall Study Design and Plan

This is an open-label, prospective, phase II, multi-center, single arm study of split-dose R-CHOP chemotherapy in older adults with DLBCL. Subjects aged 70 years or older (specific inclusion criteria for subjects aged 70-74 years) with a diagnosis of advanced stage (II bulky, III, or IV) de novo or transformed DLBCL will be included in this study. Subjects will be treated with split dose R-CHOP chemotherapy for 6 cycles and followed for up to 2 years for response and survival post-treatment. Subjects will receive interim PET/CT and MRD testing after 2 cycles of split dose R-CHOP. Both MRD testing and PET/CT testing will be repeated at the end of treatment. The primary outcome will be the CR rate at the end of treatment as assessed on a PET/CT. For subjects with a positive bone marrow (BM) biopsy at diagnosis, one will be repeated at the end of therapy. After therapy completion, subjects will be followed every 6 months for up to 2 years post-final chemotherapy treatment. Repeat PET/CT imaging will be requested at 6 months, 1 year, and at 2 years post-end of treatment scan.

4.2 Treatment Plan

Subjects age ≥70 years will be enrolled on to the study if they have a diagnosis of previously untreated de novo or transformed DLBCL. For subjects who are aged 70-74 years as the standard of care is R-CHOP 21 chemotherapy, they will only be eligible if they are determined to be unfit or frail as per the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) score.[34] The CIRS-G score is a tool to measure comorbid conditions that has been used to stratify patients for cancer clinical trials in hematological malignancies.[35, 36] We will use this tool to identify younger subjects who would be at higher risk for complications when receiving standard R-CHOP chemotherapy but would be candidates for an attenuated regimen as prescribed in this protocol. Subjects will need to have advanced stage IIB, III, or IV disease at baseline. All subjects who meet eligibility criteria in Section 5 will receive the experimental arm with split-dose R-CHOP chemotherapy (Figure 2). Subjects will have required study visits every 2 weeks for each dose of chemotherapy and will be monitored for toxicity and adverse events during the 6 months of treatment. Intrathecal chemotherapy given as central nervous system prophylaxis

and consolidative radiation treatment at the end of therapy can be given at the discretion of the treating physician.

5 Study Population

Study: UW18131
Patient Name:
Subject ID:
Date:

5.1 Eligibility Criteria

Subjects must meet all the below inclusion and exclusion criteria prior to enrollment on this clinical trial.

5.2 Inclusion Criteria

1) Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial.
2) All patients age ≥75 years and patients aged 70-74 years who are determined to be unfit or frail by CIRS-G scale (Appendix D).
    a. For patients aged 70-74 years: CIRS-G score with 5-8 comorbid conditions scored 2 or ≥1 comorbidity scored 3-4. CIRS-G score is to be reviewed by the study PI prior to enrollment.
3) Newly diagnosed, untreated, biopsy proven CD20 positive DLBCL (including high grade B-cell lymphoma & T-cell/histiocytic rich large B-cell lymphoma). Patients with discordant bone marrow (i.e. involved by low-grade/indolent NHL) are eligible. Patients with transformed DLBCL from underlying low-grade disease are eligible. Patients with composite DLBCL and concurrent low-grade lymphoma are eligible.
    a. Copy of pathology report must be sent to coordinating site to confirm diagnosis for eligibility.
    b. Patients with prior treatment for low grade NHL with non-anthracycline based regimens are eligible.
4) Measurable disease by PET/CT or BM biopsy prior to enrollment.
5) Left ventricular ejection fraction ≥50% by resting echocardiography or resting MUGA scan.
6) Karnofsky Performance Score ≥50 (Appendix A).
7) Ann Arbor Stage II bulky, III, or IV disease (Appendix B).
8) Minimum life expectancy greater than 3 months.
9) Negative HIV test.
10) For patients with hepatitis B virus antigen (HbsAg) or core antibody (HbcAb) seropositivity, patients must have a negative Hep B viral load and an appropriate prophylaxis plan must be in place during chemotherapy therapy treatment. For all patients that have Hep B core antibody positive, they should take entecavir prophylaxis (0.5 mg PO daily) until 1 year from completion of chemotherapy. Hep B viral load should be checked on these patients prior to starting chemotherapy and every 3 months thereafter if initial Hep B viral load is negative (+/- 1 week if chemotherapy cycle is delayed). If Hep B viral load is positive, Hepatology or ID referral is recommended, and HBV viral load should be checked monthly.
11) For patients with hepatitis C Ab (HbcAb) positivity, a viral load must be checked and be negative for enrollment.
12) Intrathecal chemotherapy for central nervous system prophylaxis only can be given at the discretion of the primary oncologist.

5.3 Exclusion criteria

1) History of previous anthracycline exposure.
2) CNS or meningeal involvement at diagnosis.

3) Creatinine Clearance ≤25 mL/min by Cockroft-Gault. See Appendix J for Cockroft-Gault calculation.
4) Poor hepatic function, defined as total bilirubin concentration greater than 3.0 mg/dL or transaminases over 4 times the maximum normal concentration, unless these abnormalities are felt to be related to the lymphoma.
5) Pulmonary dysfunction defined as >2L of oxygen required by nasal cannula to maintain peripheral capillary oxygen saturation (SpO2) ≥90% unless felt to be related to underlying lymphoma.
6) Myocardial Infarction within 6 months of enrollment.
7) Active, uncontrolled infectious disease.
8) Known concurrent bone marrow malignancies (e.g. myelodysplastic syndrome) or poor bone-marrow reserve, defined as neutrophil count less than 1.5×10^9/L or platelet count less than 100×10^9/L, unless caused by bone-marrow infiltration with lymphoma.
9) History of a second concurrent active malignancy or prior malignancy which required chemotherapy treatment within the preceding 2 years.
10) Treatment with any investigational drug within 30 days before the planned first cycle of chemotherapy.
11) Unable or unwilling to sign consent.

Treating Investigator Signature and Date:_____

6 Study Interventions and Procedures

6.1 Enrollment

A written, signed informed consent form (ICF) and Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

For enrollment, the following documents are required:

Each subject enrolled in the study is to be registered into the UWCCC OnCore Database prior to starting protocol treatment. Research personnel at WON sites who enter data into OnCore must have completed human subjects protection training and HIPAA training. WON site research personnel receive training from the UWCCC OnCore Support Team on how to enter subject data into OnCore.

At the time of registration, the following will be required and verified by (UWCCC):
- Subject eligibility
- Signed informed consent form
- Signed HIPAA authorization

In the event that a potential subject presents who has limited English proficiency, we will use a short form consent process that follows the requirements in HRP-090 and HRP-091 (the SOPs for informed consent process and documentation) and in the Investigator Manual. Consenting of subjects with limited English proficiency will only be done in person in order to ensure we can follow the guidelines set forth in HRP-090 and HRP-091. Any required research communication will occur with a Certified Interpreter, where allowed, per institutional policies. If you have a potential subject who has limited English proficiency, please contact the study team.

6.2 Study Entry Procedures

The study-specific assessments are detailed in this section and outlined in Table 1. Screening assessments must be performed within 28 days prior to treatment initiation. Any results falling outside of the reference ranges may be repeated at the investigator's discretion within the 28 day window. All on-study visit procedures are allowed a window as noted in the study calendar. Subjects who meet all eligibility criteria and sign the informed consent document will receive therapy as per the study schema.

6.3 Pretreatment Period

Screening Assessments

The following screening procedures and assessments, unless noted otherwise, must be completed within ≤28 days of initiation of split-dose R-CHOP chemotherapy.

- History including height, and physical examination including weight, Performance Status Assessment (Karnofsky), concomitant medications, and review of adverse events.
- Vitals: Blood Pressure, Temperature, Pulse & Pulse Ox.
- Complete Blood Count and differential.
- Comprehensive Metabolic Panel: Albumin, Alkaline Phosphatase, AST, Bicarb, Bilirubin (total), Calcium (total), Chloride, Creatinine, Glucose, Potassium (K), Sodium (Na), Protein Total, BUN, and ALT.
- Uric Acid
- LDH
- HIV antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C antibody.
- Bone marrow and aspirate evaluation within 4 weeks of study treatment initiation.
- Cardiac Echocardiogram or multi-gate acquisition (MUGA) scan for evaluation of ejection fraction.
- IPI, see Appendix C for details of scoring.

6.4 Study Visits

Subjects will have a study visit prior to each dose of split-dose R-CHOP chemotherapy (~every 2 weeks). At this visit, a physical examination and laboratory tests including a complete blood count, complete metabolic profile, and other tests as per the study schedule (Table 1) will be performed to ensure adequate blood counts and intact organ function prior to administration of chemotherapy. Anti-emetic therapy and infusion reaction prophylaxis will be left to the discretion of the treating physician and be given per institutional standard of care protocols. Subjects are recommended to have placement of a central venous catheter for administration of chemotherapy. Split-dose R-CHOP will be given after the study visit in the following fashion:

SD R-CHOP Regimen

Each cycle is 28 days and consists of one "A" treatment on Day 1 and one "B" treatment on Day 15 for 6 cycles.

Day 1 ("A" part of cycle)	**Day 15 ("B" part of cycle)**
[1]Rituximab 375 mg/m2 IV*	
Cyclophosphamide 375 mg/m2 IV	Cyclophosphamide 375 mg/m2 IV
Doxorubicin 25 mg/m2 IV	Doxorubicin 25 mg/m2 IV
Vincristine 1 mg IV	Vincristine 1 mg IV
Prednisone 50 mg (Days 1-5) PO**	Prednisone 50 mg (Days 15-19) PO**
Pegfilgrastim (supportive care) 6 mg on Day 2***	Pegfilgrastim (supportive care) 6 mg on Day 16***

[1]Rituximab or its biosimilars Ruxience or Truxima

*In subjects at high risk for cytokine release syndrome, tumor lysis syndrome, or other defined safety and tolerability concerns, rituximab may be delayed during cycle 1 and administered at any time prior to cycle 2. Cycle 1 rituximab may also be omitted entirely at the discretion of the treating investigator (this alternative dosing of rituximab applies to cycle 1 of induction therapy only). In these circumstances, delaying rituximab dosing is acceptable to reduce additional complications. Given the long half-life of rituximab (median half-life of 32 days), this flexibility in dosing of rituximab during cycle 1 only will not have a clinically significant impact on the response to induction chemoimmunotherapy. Rapid Rituximab can be given after Cycle 1 as per institutional standards.

**Subjects provided a Pill Diary to record prednisone intake on Days 1-5 and Days 15-19 (see Appendix E).
*** Pegfilgrastim (administered as supportive care) 6 mg on Day 2 and Day 16 (24 hours after completion of chemotherapy) or filgrastim daily as institutionally indicated (starting 24 hours post completion of chemotherapy), or institutional standard granulocyte stimulating factor. For patients with residual leukocytosis on Day 15, growth factor treatment can be withheld at investigator discretion with "B" cycle.

There will be no dose adjustment in the event of hematological toxicity. However, the next cycle of R-CHOP chemotherapy should be postponed until the neutrophil count reached is 1.0 K/μL and the platelet count is 50 K/μL with a maximum of 28 days between two consecutive A and B cycles (transfusions and growth factor are permitted). If these counts were not reached within 28 days, treatment will be stopped. In the event of grade 2 or greater neurological vincristine-related toxicity (sensory or motor polyneuritis, constipation, or visual or auditory changes) vincristine can be dose reduced per investigator decision or discontinued from future cycles.

After completion of the first two months of split-dose R-CHOP chemotherapy, subjects will undergo interim response assessment with PET/CT and MRD testing supported by Adaptive Technologies prior to Cycle 3A. Subjects who have a PET/CT Deauville Score of 1-3 and are MRD negative will be placed on an abbreviated chemotherapy regimen. In this abbreviated chemotherapy arm, subjects will receive full dose Rituximab with both A & B cycles. For subjects on this abbreviated arm, treatment regimen will be as follows:

Abbreviated Chemotherapy Arm of Split-Dose R-CHOP (Cycle 3 and 4 only)
(Only for subjects who are Deauville 1-3 and MRD negative by clonoSEQ assay)

Day 1 ("A" part of cycle)	**Day 15 ("B" part of cycle)**
[1]Rituximab 375 mg/m2 IV*	Rituximab 375 mg/m2 IV*
Cyclophosphamide 375 mg/m2 IV	Cyclophosphamide 375 mg/m2 IV
Doxorubicin 25 mg/m2 IV	Doxorubicin 25 mg/m2 IV
Vincristine 1 mg IV	Vincristine 1 mg IV
Prednisone 50 mg (Days 1-5) PO**	Prednisone 50 mg (Days 15-19) PO**
Pegfilgrastim (supportive care) 6 mg on Day 2***	Pegfilgrastim (supportive care) 6 mg on Day 16***

[1]Rituximab or its biosimilars Ruxience or Truxima
* Rapid Rituximab can be given after Cycle 1 as per institutional standards.
** Subjects provided a Pill Diary to record prednisone intake on Days 1-5 and Days 15-19 (see Appendix E).
*** Pegfilgrastim (administered as supportive care) 6 mg on Day 2 and Day 16 (24 hours after completion of chemotherapy) or filgrastim daily as institutionally indicated (starting 24 hours post completion of chemotherapy), or institutional standard granulocyte stimulating factor. For patients with residual leukocytosis on Day 15, growth factor treatment can be withheld at investigator discretion with "B" cycle.

6.5 PET/CT Disease Assessment

Subjects will undergo PET/CT as part of interim assessment after 2 months of split-dose R-CHOP chemotherapy and end of treatment assessment 4-6 weeks after completion of therapy. PET/CT assessment will be per the Lugano classification and will utilize Deauville Score for response assessment.[33] PET/CT assessment guidelines and Deauville Score are listed in Appendix F and Appendix G, respectively. A copy of the PET/CT report will be forwarded to the coordinating center for review prior to determination for candidacy for the abbreviated arm of this protocol.

6.6 Blood Sample Collection

Blood will be requested for routine laboratory testing. The MRD test will be the only research blood sample performed in this study.

6.7 Minimal Residual Disease Testing

Minimal residual disease (MRD) testing will be performed by Adaptive Biotechnology. The test is a two-step process. First, an ID sample is required to identify the clonal population of B-cells associated with the malignancy, then the clones can be tracked through the duration of treatment to detect MRD. For the ID sample, a high-disease burden sample is required. For interrogating samples from subjects with NHL, these samples include BM, blood or lymph node biopsy. In DLBCL, the highest disease burden may be in the lymph node so this source would be preferred. To successfully ID a clone, greater than 1μg of genomic DNA is required or 15ng/μL. For BM greater than 200μL is required, if sending slides, 3-5 unstained slides without coverslips are preferred but stained are acceptable. For the MRD portion of the assay, cell-free DNA (cfDNA) we will be performing MRD analysis in two methods: one with whole blood and one sample utilizing plasma. Either 10mL of whole blood or 2mL of plasma is required to identify cfDNA associated with the clonal population. Clinical decision making for the purpose of this study will be based on the results of the plasma sample.

To be eligible for MRD evaluation subjects will have a sample of baseline biopsy sent to Adaptive Technology to determine if there is a tumor-associated DNA sequence (or "clone") that can be followed. This identification (ID) test will be sent off during screening and is not a requirement for eligibility. Subjects who have an identifiable sequence will have serologic MRD testing within one week prior to Cycle 3 of chemotherapy and during the end of treatment assessment 4-6 weeks after completion of treatment. Subjects who do not have an identifiable clone will not be eligible for the abbreviated chemotherapy arm.

6.8 Geriatric Assessments

The cancer-specific geriatric assessment that will be used in this study includes valid and reliable measures of geriatric domains regarding instrumental activities of daily living (IADLs), physical function, medications/polypharmacy, medical co-morbidities, nutritional status, mental health, social support, and cognitive function. This geriatric assessment has been proven feasible in academic [37], community [38], and cooperative group settings [39]. This geriatric assessment includes two parts: 1. Patient-reported section and 2. Healthcare provider administered section. The details of the geriatric assessment questionnaire can be found in Appendix H. In the cooperative group setting, the median time to completion was 22 minutes. Nearly all subjects were able to complete the patient-reported section without assistance (87%) and 100% of the healthcare provider section was completed. Patient satisfaction was high; 92% of subjects were satisfied with the length, 95% reported it was easy to comprehend, and 96% reported that the assessment was not upsetting.[39] By including the geriatric assessment into this clinical trial, important additional information will be obtained about subjects enrolled on this trial beyond standard performance status measures.[40, 41] In addition, various measures within the geriatric assessment have shown to be predictive for treatment related toxicity in older adults with solid tumors. Lastly, by including the geriatric assessment in this clinical trial we will be able to understand the effect of treatment on relevant geriatric outcomes such as cognition, function, and independence, which are important to older adults when weighing the risks and benefits to treatment.

All subjects will undergo geriatric assessment testing at baseline prior to or on Cycle 1 Day 1, on the day of or within 7 days prior to Cycle 3A and at the end of treatment evaluation visit. The subject and healthcare provider will complete the assessment that is listed in Appendix H.

6.9 Long-Term Follow-up

At the end of treatment, subjects will undergo an end of treatment MRD testing and PET/CT 4-6 weeks after administration after the last dose of chemotherapy. This PET/CT will be measured for complete response, partial response, or progressive disease. Subjects with a partial or complete response will enter the surveillance phase of the study. Standard CT imaging or PET/CT imaging will be performed at 6 months, 1 year, and 2 years post end of treatment evaluation. Additional imaging can be done per the treating physician and data from those reports will be collected for the 2 years of the study time period. Subjects who develop progressive disease will be taken off study and followed only for survival at every 6 month intervals as per study schedule. At follow-up visits, standard blood work with complete blood count with differential, complete metabolic profile, and lactate dehydrogenase (LDH) will be collected. Subjects will be assessed at each visit for long-term toxicities of chemotherapy including secondary malignancies, cardiac toxicities, or other adverse events felt to be related to treatment drugs.

6.10 Concomitant Medications

1) **Corticosteroids**: The use of corticosteroids to treat conditions other than DLBCL is permitted per institutional standard. Systemic corticosteroids may be used to keep DLBCL-related symptoms under control prior to Cycle 1 Day 1 as long as the duration of steroid use is no longer than 14 days.

2) **Transfusions**: The use of transfusions, platelet and/or red blood cells will be deferred to the treating oncologist.

3) **Intrathecal *prophylactic* chemotherapy treatment** (cytarabine and/or methotrexate): Can be administered for prevention of cerebral/meningeal disease at the discretion of the treating physician.

4) **Consolidative radiotherapy**: May be given at the treating physicians' discretion after end of treatment procedures are completed.

5) **Proton pump inhibitors or H2 blockers:** Either daily PPI or H2 blocker are required for the prevention of ulcers in the setting of high dose Prednisone during the duration of the treatment period.

6) **Allopurinol 300 mg daily with adjustment to creatinine clearance (CrCl):** Is required forall subjects for 14 days for prevention of tumor lysis.

6.11 Prohibited Concomitant Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy from Day 1 through end of treatment (the treatment phase of the study).

6.12 Management of Infusion Reactions

Infusion reactions related to rituximab, cyclophosphamide, doxorubicin, and vincristine should be managed per the package insert and/or institutional standard of care.

6.13 Subject Withdrawals

In accordance with the Declaration of Helsinki and applicable regulations, a subject has the right to discontinue treatment or withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Any subject may be discontinued from the study for any of the following reasons:

- Subject withdrawal of consent
- Study termination by Sponsor, UWCCC, UWCCC Data and Safety Monitoring Committee (DSMC), PI
- Progressive disease
- Lost to follow-up
- Severe adverse event
- Death
- Early termination of the protocol
- Other

Patients who die during study treatment before the primary outcome assessment can be made and the cause of death is unrelated to study treatment OR disease progression (e.g. car crash, unrelated procedural complication),that patient will not count towards the study accrual for statistical purposes and will be replaced.

6.14 Stopping Rules

Please see Section 7.2 for toxicity monitoring and stopping rules for adverse events.

By Data Safety and Monitoring Committee
The DSMC may request enrollment be suspended due to safety concerns. For a complete description of the role and duties of the DSMC, please refer to Section 9 “Trial Safety Monitoring”.

7 Data Analysis and Statistical Considerations

7.1 Study Statistics

Original study design
For this phase II study we will utilize a Simon 2-stage optimal design with CR rate at the end of treatment as our primary outcome. Based on previously published studies (see Table 2, Kreher et al [14]), we will use 40% as our unacceptable boundary for complete response rate and 60% as the acceptable complete response rate. We will set the power at 80% and Type I error at a one-sided 5% which will require a maximum sample size of 46 subjects. In the first stage 16 subjects are recruited and the trial will only proceed to the second stage if more than 7 subjects achieve a complete response. If the true CR rate is as low as 40%, the study will be stopped at the first stage with 71.6% probability. If the true CR rate is 60%, the study has an 80% chance of declaring it promising and 14.2% probability of stopping early. If >7 subjects meet the predefined endpoint, then the study would accrue an additional 30 subjects and the treatment will be declared as promising if more than 23 complete responses at the EOT are observed.

Unplanned sample size recalculation
Due to lower-than-expected rate of enrollment, an unplanned redesign using the method of Müller and Schäfer [Müller HH, Schäfer H. A general statistical principle for changing a design any time during the course of a trial. Stat Med. 2004 Aug 30;23(16):2497-508.] was performed after 14 patients were treated. This approach allows modification of the pre-planned sample size and success criteria while controlling the type I error, as long as the conditional probability of rejection under the null hypothesis does not increase. The total sample size and

success cutoff were selected to maintain the original study power at the alternative hypothesis.

Conditioning criterion
When the decision to modify the study design was made, 10 complete responses have been observed in the first 14 patients. Conditioning on this information, the original Simon's two-stage design would continue to the second stage, and the conditional probability of achieving the originally targeted 24 or more complete responses out of the originally planned 46 patients under the null hypothesis (EoT CR rate is 40%) equals 34%.

Modified design
In the modified design a total of 26 subjects (ie 12 subjects in addition to the 14 subjects whose information was used in the redesign) will be recruited. The null hypothesis of CR rate of 40% will be rejected if 16 or more complete responses are observed among the 26 subjects (ie 6 or more among the 12 additional subjects). Under the null hypothesis the conditional probability of this event is 33.4%, which is lower than 34% under the original design. With this sample size, under the alternative hypothesis of CR rate of 60%, the conditional power is 84%.

Table 2: Adapted from Kreher et al.

Study	Regimen	Median age	# of Pts	CR Rate	Infectious Complications Grade≥3	Cardiac Toxicity Grade≥3	Treatment related death
Pfreundschuh et al. [32]	R-CHOP-14 x 6 cycles	69 (61 -80)	306	78%	28%	7%	6%

Study	Regimen	Median age	# of Pts	CR Rate	Infectious Complications Grade≥3	Cardiac Toxicity Grade≥3	Treatment related death
Habermann et al.[42]	R-CHOP	69 (60-92)	267	N/A	17%	9%	5%
Coiffier et al.[5]	R-CHOP	70 (60-80)	202	75%	12%	8%	5.8%
Delarue et al. [43]	R-CHOP-21	70 (59-80)	298	74%	17%	3.7%	4.7%
Musolino et al. [29]	DA-POCH-R	77 (70-90)	23	52%	13%	0%	0%
Peyrade et al. [13]	R-miniCHOP	83 (80-95)	149	62%	16%	7%	8%
Kreher et al. [14]	R-split-CHOP	77 (60-89)	30	60%	30%	3%	0%
Shah et al. [44]	Split-Dose R-CHOP	81 years (60-90)	22	55%	N/A	9%	9%

7.2 Toxicity Monitoring

Based on literature review, we expect up to a 30% risk of grade 3 and 4 **non-hematologic adverse events** to be considered acceptable. Toxicity monitoring oversight will be the responsibility of the Principal Investigator and the Study Chair and will start from the 4th subject and every 3rd subject afterwards. Stopping rules for study therapy related toxicity is defined in Table 3 below both for the original design, and for the redesign, which was built to have the same boundary for the first 10 patients and achieve the same Type I error as the boundary for the original design :

Table 3. Stopping Rules for Toxicities

Number of Patients Accrued	Number of Patients with Grade 3-4 Toxicities related to study treatment resulting in Stoppage of Trial [Original design]	Number of Patients with Grade 3-4 Toxicities related to study treatment resulting in Stoppage of Trial [Redesign]
4	3+	3+
7	5+	5+
10	6+	6+
13	8+	7+
16	9+	8+
19	10+	10+
22	11+	11+
25	12+	12+
28	14+	
31	15+	
34	16+	
37	17+	
40	18+	
43	19+	
46	20+	

The following table shows the probability of crossing this boundary as a function of the underlying probability of toxicity:

Table 4. Probability of Crossing the Boundary as a Function of Toxicity Probability

Probability of toxicity	crossing the Boundary [Original design]	Probability of crossing the Boundary [Redesign]
30%	16%	16%
40%	55%	48%
50%	91%	77%
55%	98%	88%

7.3 Analysis of Primary Outcome

The primary outcome, the proportion of subjects achieving CR at the end of treatment, will be estimated as the observed proportion and presented with a 95% Wilson confidence interval. The formal decision about the success of the regimen will be made based on the modified design cutoffs described in Section 7.1.

7.4 Secondary Outcomes:

7.4.1 To determine the PFS of subjects treated with SD R-CHOP

PFS measures survival without relapse/progression or death starting from study enrollment. Relapse or progression of disease and death will be considered as events; subjects who survive without recurrence or progression will be censored at last contact. PFS will be estimated using the Kaplan-Meier estimate and presented with graphically with pointwise 95% confidence intervals.

7.4.2 To determine the OS of subjects treated with SD R-CHOP

OS measures time to death starting from study enrollment. Death from any cause will be considered an event; surviving subjects will be censored at time of last follow-up. OS will be estimated using the Kaplan-Meier estimate and presented with graphically with pointwise 95% confidence intervals. Exploratory Cox proportional hazards regression will be used to evaluate the effect of baseline covariates on PFS and OS.

7.4.3 To describe clinical outcomes among subjects with interim MRD and PET/CT negativity

We will describe outcomes in the varying treatment groups (MRD- PET/CT- vs MRD- PET/CT+ and MRD+ PET/CT-)

7.4.4 To evaluate frequency and degree of adverse events with split-dose R-CHOP.

The incidence of serious adverse events will be reported for all subjects who received at least one dose of the study treatment. The proportion of subjects experiencing an SAE will be reported with 95% confidence intervals overall, as well as classified by grade and organ system. Toxicity will be monitored using the formal boundary described in Section 7.2.

7.4.5 To perform a cancer-specific geriatric assessment prior to, during, and after completion of chemotherapy treatments to evaluate for changes in physical function, mental health, cognition, and other relevant geriatric specific outcomes.

The geriatric assessment measures will be summarized descriptively at each measurement time-point using appropriate descriptive statistics such as frequencies and percentages with standard errors for categorical variables, mean with standard error or median with quartiles for continuous variables. Repeated measures analysis will be used to evaluate any changes between the time-points.

7.5 Exploratory Outcome: To evaluate minimal residual disease (MRD) testing in whole blood vs plasma

A contingency table of the results of the MRD testing using whole blood vs plasma from the same subject will be computed with counts, and row and column percentages. These percentages can be interpreted as sensitivity or specificity while treating one of the methods compared to the other. The agreement will be quantified as the overall proportion of patients with the same result and presented with a 95% Cloppe-Pearson confidence interval. Cohen's kappa, which adjusts the overall agreement for chance, will also be computed.

8 Adverse Events and Unanticipated Problems

8.1 Adverse Event Definitions

Adverse Event (AE)
An adverse event is defined as any untoward or unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Include the type and duration of the follow-up of subjects after adverse events.

Serious Adverse Event (SAE)
A serious adverse event is defined as any adverse event that meets one of the following criteria:

- Results in death; OR
- Is life-threatening; OR
- Requires hospitalization or prolongs existing hospitalization; OR
- Results in significant or persistent disability or incapacity; OR
- Results in a congenital anomaly/birth defect; OR
- An important medical event, based on appropriate medical judgment, that is believed to jeopardize the patient and/or requires medical or surgical intervention to prevent one of the outcomes defining a SAE. For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that may not result in hospitalization.

However, as applies specifically to this study, we additionally define the following event as constituting an SAE:

- New cardiomyopathy

Unanticipated Problem (UP)

An unanticipated problem is defined as an event that meets all of the following criteria:

1) Unexpected in severity, nature, or frequency given the research procedures and the characteristics of the subject population (i.e., problems that are not described in this protocol or other study documents); AND
2) Related or possibly related to participation in the research; AND
3) Suggests that research places subjects or others at a greater risk of harm related to the research than was previously known or recognized.

8.2 Causality Assessment

The Investigator will determine the relationship of adverse events to the research intervention using the following scale:

- Definite = AE is clearly related to the study procedures
- Probable = AE is likely related to the study procedures
- Possible = AE is possibly related to the study procedures
- Unlikely = AE is doubtfully related to the study procedures
- Unrelated = AE is clearly not related to the study procedures

8.3 Procedures for Recording and Reporting Adverse Events

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events.

Adverse events will be recorded from the beginning of informed consent until 2 weeks after completion of the last cycle of chemotherapy. For this study, all AEs (Grade 1-5) will be recorded and evaluated for attribution to the treatment therapy.

Dose modifications or treatment delays for related AND non-related adverse events must be documented within the study subject's electronic medical record, including the respective reason. If a treatment-related or non-treatment-related AE/SAE requires a treatment delay of more than 28 days, the subject will be removed from protocol therapy.

Delayed doses should be managed as follows:

- If a dose was missed, the schedule of that week should be altered to accommodate the dose within the protocol-defined 7-day dosing window, if possible. If a dose is delayed due to an adverse event or serious adverse event, the next scheduled A or B cycle should be given with a maximum of 28 days between consecutive A and B cycles (transfusions and growth factor are permitted). If AE/SAE requiring dose delay is not clinically resolved/stabilized within 28 days, treatment will be stopped.

AEs will be reported into OnCore reporting system.

8.4 Reporting by Study Sites to Local IRB

Study sites will follow their local IRBs guidance for reporting all events to the local IRBs. The UWCCC Affiliate Coordinator will assist the sites with study-wide event data that is required to be reported.

9 Trial Safety Monitoring

9.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.

- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC DSMC acts as an oversight body.
- Reviews all reports generated through the UWCCC Data and Safety Monitoring System elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports).
- Notifies the protocol Principal Investigator of DSMC decisions, recommendations, and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCCC monitoring requirements for this trial are as follows:

9.1.1 Intermediate Monitoring

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled Disease Oriented Team (DOT) meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes, as appropriate, the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted every six months by the study team for review by the DSMC.

9.2 Reporting and Oversight Requirements

a) Serious Adverse Event – Reported within 24 Hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the DSMC Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available subsequent SAE documentation must be submitted electronically along with a 24 hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC OnCore database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators

b) Serious Adverse Event – Reported within 10 Days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the DSMC Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (FDA Medwatch Form #3500 and/or any other documentation available at the time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC OnCore database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

c) Study Progress Review

Protocol Summary Reports (PSRs) are required to be submitted by the UWCCC study team to the UWCCC DSMC in the timeframe determined by the risk level of the study (annually). The PSR provides a cumulative report of SAEs, as well as instances of noncompliance protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol at all participating sites in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at UWCCC DSMC meetings.

PSRs enable UWCCC DSMC members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the UWCCC DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews) occurring since the prior review of the protocol by the UWCCC DSMC. Additionally, the UWCCC DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

Documentation of these reviews and the resulting UWCCC DSMC recommendation (e.g., protocol continuation, protocol continuation with modifications, protocol suspension, or discontinue protocol or treatment arm) will be provided to the UWCCC study team and the WON Affiliate Coordinator. Issues of immediate concern will be brought to the attention of the UWCCC PI and other regulatory bodies as appropriate. The UWCCC PI will work with the Study Chair to address these concerns.

In the event that there is significant risk warranting study suspension or closure, the UWCCC DSMC will notify the PI of the findings and ensure the appropriate action is taken for the protocol. The UWCCC DSMC ensures that the UWCCC PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

e) Expedited Reporting of Serious Adverse Events

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both per Table below. All serious adverse events must also be reported to the UWCCC Data and Safety Monitoring Committee Chair, or designee. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list. **FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)**

NOTE: Investigators MUST immediately report to the *UWCCC* and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).
An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria* MUST be immediately reported to the UWCCC within the timeframes detailed in the table below:

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

*** New cardiomyopathy of any grade is to be expeditiously reported.**

Expedited AE reporting timelines are defined as in the table:

- **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

- Grade 3 events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Then refer to sections (i) and (ii) below if the SAE occurred at the UWCCC or sections (iii) and (iv) if the SAE occurred at 1 South Park, Johnson Creek, or a WON Site:

(i) SAE Requiring [24] Hour Reporting Occurs at UWCCC:

1. Report to the UWCCC: Reference the SAE SOP (Standard Operating Procedure) and the SAE Reporting Workflow for DOTs on the UWCCC website (https://kb.wisc.edu/uwccc/internal/) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial [24] hour report.**

For this protocol, the following UWCCC entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) UWCCC PI
c) UWCCC Clinical Team Manager
d) UWCCC POD Manager
e Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

2. Report to the IRB: Consult the UW Health Sciences IRBs website for reporting guidelines.

(ii) SAE Requiring [10] Day Reporting Occurs at UWCCC:

1. Report to the UWCCC: Reference the SAE SOP and the SAE Reporting Workflow for DOTs on the UWCCC website (https://kb.wisc.edu/uwccc/internal/) for specific instructions on how and what to report to the UWCCC for [10] day reports. For this protocol, the following entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Any appropriate parties listed on SAE Routing Form

2. Report to the IRB: Consult the UW Health Sciences IRBs website for reporting guidelines.

(iii) SAE Requiring [24] hour reporting Occurs at 1 South Park (1SP), Johnson Creek (JC), or a WON Site:

1. Report to the UWCCC: Reference the SAE SOP and the SAE Reporting Workflow for 1SP, JC, and Affiliate Sites on the UWCCC website (https://kb.wisc.edu/uwccc/internal/ and https://kb.wisc.edu/uwccc) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports. A follow-up report is required to be submitted within 10 days of the initial [24] hour report. Send the OnCore SAE details report and any supporting, applicable documentation to: saenotify@uwcarbone.wisc.edu.

NOTE: After 1SP, JC, or a WON site has submitted the [24] hour SAE follow-up report, the report is triaged initially to the UW Principal Investigator or Study Chair, the DOT Program Manager, the Affiliate Coordinator, and the DSMC Chair for review. **The Principal Investigator**

or Study Chair is then responsible for ensuring the SAE is reported to the FDA, the UW IRB, and any other entity requiring notification, in accordance each entities' reporting requirements.

2. Report to the IRB: WON sites should follow their local IRB reporting guidelines for SAE submission. The UW PI/Study Chair is responsible for the submission of the SAE to the UW Health Sciences IRBs for any sites for which the UW serves as the IRB of record.

(iv) SAE Requiring [10] Day Reporting Occurs at 1 South Park (1SP), Johnson Creek (JC), or a WON Site:

1. Report to the UWCCC: Reference the SAE SOP and the SAE Reporting Workflow for 1SP, JC, and Affiliate Sites on the UWCCC website (https://kb.wisc.edu/uwccc/internal/ and https://kb.wisc.edu/uwccc) for specific instructions on how and what to report to the UWCCC for [10] day reports. Send the OnCore SAE details report and any supporting, applicable documentation to: saenotify@uwcarbone.wisc.edu.

NOTE: After 1SP, JC, or a WON site has submitted the [24] hour SAE follow-up report, the report is triaged initially to the UW Principal Investigator or Study Chair, the DOT Program Manager, the Affiliate Coordinator, and the DSMC Chair for review. **The Principal Investigator or Study Chair is then responsible for ensuring the SAE is reported to the FDA, the global sponsor (if applicable), the UW IRB, and any other entity requiring notification, and in accordance each entities' reporting requirements.**

2. Report to the IRB: The UW PI/Study Chair is responsible for the submission of the SAE to the UW Health Sciences IRBs. WON sites should follow their local IRB reporting guidelines for SAE submission.

9.3 Other Reporting Requirements

Reporting to the FDA

Serious Adverse Events occurring on studies on which a UW PI is acting as sponsor investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website:
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm.

9.4 Administrative Requirements

a. Ethical Consideration

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent form, written information given to the patients, safety updates, annual progress reports and any revisions to these documents will be provided to the IRB by the investigator.

b. Investigator Compliance

The investigator will conduct the trial in compliance with the protocol approved by the IRB. Changes to the protocol will require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects.

9.5 WON Site Oversight

The UWCCC Affiliate Office serves as the coordinating center for WON. Coordinating center responsibilities are shared between the Affiliate Coordinator and UWCCC Lymphoma/Myeloma DOT. A detailed description of coordinating center responsibilities, as well as other WON processes and procedures, is provided in the WON Manual available on the UWCCC website (https://kb.wisc.edu/uwccc/41040).

Regular communication (e.g., email updates and conference calls) between the UWCCC Affiliate Office and WON sites ensures that all participating parties are notified of protocol changes, informed consent document revisions, action letters, study status changes, reportable events/Serious Adverse Events (as necessary), and any other applicable information.

10 References

1. Morton, L.M., et al., *Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001.* Blood, 2006. **107**(1): p. 265-76.
2. Smith, A., et al., *Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network.* Br J Cancer, 2011. **105**(11): p. 1684-92.
3. Nabhan, C., et al., *Analysis of very elderly (>/=80 years) non-hodgkin lymphoma: impact of functional status and co-morbidities on outcome.* Br J Haematol, 2012. **156**(2): p. 196-204.
4. Feugier, P., et al., *Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte.* J Clin Oncol, 2005. **23**(18): p. 4117-26.
5. Coiffier, B., et al., *CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma.* New England Journal of Medicine, 2002. **346**(4): p. 235-242.
6. Habermann, T.M., et al., *Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma.* J Clin Oncol, 2006. **24**(19): p. 3121-7.
7. Pfreundschuh, M., *How I treat elderly patients with diffuse large B-cell lymphoma.* Blood, 2010. **116**(24): p. 5103-10.
8. Sarkozy, C. and B. Coiffier, *Diffuse large B-cell lymphoma in the elderly: a review of potential difficulties.* Clin Cancer Res, 2013. **19**(7): p. 1660-9.
9. Hershman, D.L., et al., *Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma.* J Clin Oncol, 2008. **26**(19): p. 3159-65.
10. Thieblemont, C., et al., *Non-Hodgkin's lymphoma in very elderly patients over 80 years. A descriptive analysis of clinical presentation and outcome.* Ann Oncol, 2008. **19**(4): p. 774-9.
11. Hasselblom, S., et al., *Improved outcome for very elderly patients with diffuse large B-cell lymphoma in the immunochemotherapy era.* Leuk Lymphoma, 2012. **53**(3): p. 394-9.
12. Huntington, S.F., et al., *Toxicities and outcomes among septuagenarians and octogenarians with diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone therapy.* Leuk Lymphoma, 2012. **53**(8): p. 1461-8.
13. Peyrade, F., 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.* Lancet Oncol, 2011. **12**(5): p. 460-8.
14. Kreher, S., et al., *R-split-CHOP chemotherapy for elderly patients with diffuse large B-cell lymphoma.* European Journal of Haematology, 2014. **93**(1): p. 70-76.
15. Aoki, K., 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.* Leuk Lymphoma, 2013. **54**(11): p. 2441-7.
16. Weidmann, E., et al., *Phase II study of bendamustine in combination with rituximab as first-line treatment in patients 80 years or older with aggressive B-cell lymphomas.* Ann Oncol, 2011. **22**(8): p. 1839-44.

17. Smith, S.D., et al., *Diffuse large B-cell lymphoma in adults aged 75 years and older: a single institution analysis of cause-specific survival and prognostic factors.* Ther Adv Hematol, 2013. **4**(6): p. 349-53.
18. Bastion, Y., et al., *Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation, response to treatment, and survival--a Groupe d'Etude des Lymphomes de l'Adulte study on 453 patients older than 69 years.* Journal of Clinical Oncology, 1997. **15**(8): p. 2945-53.
19. Mato, A.R., et al., *Primary cardiac lymphoma: utility of multimodality imaging in diagnosis and management.* Cancer Biol Ther, 2007. **6**(12): p. 1867-70.
20. Shah, N.N., et al., *Split-dose R-CHOP: A novel approach to administer cytotoxic chemotherapy to geriatric patients with DLBCL.* American Association of Cancer Research Annual Meeting. **Abstract**(3427).
21. Yang, D.H., et al., *Prognostic significance of interim (1)(8)F-FDG PET/CT after three or four cycles of R-CHOP chemotherapy in the treatment of diffuse large B-cell lymphoma.* Eur J Cancer, 2011. **47**(9): p. 1312-8.
22. Mamot, C., et al., *Final Results of a Prospective Evaluation of the Predictive Value of Interim Positron Emission Tomography in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP-14 (SAKK 38/07).* J Clin Oncol, 2015. **33**(23): p. 2523-9.
23. Casasnovas, R.O., et al., *FDG-PET-driven consolidation strategy in diffuse large B-cell lymphoma: final results of a randomized phase 2 study.* Blood, 2017. **130**(11): p. 1315-1326.
24. Roschewski, M., et al., *Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study.* Lancet Oncol, 2015. **16**(5): p. 541-9.
25. Vincent, G.K. and V.A. Velkoff. *The Next Four Decades: The Older Population in the United States—2010 to 2050: Population Estimates and Projections.* 2015 [cited 2015 July 2015]; Available from: http://www.census.gov/prod/2010pubs/p25-1138.pdf.
26. Scher, K.S. and A. Hurria, *Under-representation of older adults in cancer registration trials: known problem, little progress.* J Clin Oncol, 2012. **30**(17): p. 2036-8.
27. Bellera, C., et al., *Barriers to inclusion of older adults in randomised controlled clinical trials on Non-Hodgkin's lymphoma: a systematic review.* Cancer Treat Rev, 2013. **39**(7): p. 812-7.
28. Hurria, A., et al., *Improving the Evidence Base for Treating Older Adults With Cancer: American Society of Clinical Oncology Statement.* Journal of Clinical Oncology, 2015.
29. Musolino, A., et al., *Activity and safety of dose-adjusted infusional cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy with rituximab in very elderly patients with poor-prognostic untreated diffuse large B-cell non-Hodgkin lymphoma.* Cancer, 2011. **117**(5): p. 964-73.
30. Gordon, L.I., et al., *Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496).* J Clin Oncol, 2013. **31**(6): p. 684-91.
31. Kobayashi, Y., et al., *Charlson Comorbidity Index is an independent prognostic factor among elderly patients with diffuse large B-cell lymphoma.* Journal of Cancer Research and Clinical Oncology, 2011. **137**(7): p. 1079-1084.

32. Pfreundschuh, M., et al., *Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60).* Lancet Oncol, 2008. **9**(2): p. 105-16.
33. Cheson, B.D., et al., *Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification.* J Clin Oncol, 2014. **32**(27): p. 3059-68.
34. Miller, M.D., et al., *Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale.* Psychiatry Res, 1992. **41**(3): p. 237-48.
35. Tucci, A., et al., *Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: a prospective multicenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL).* Leuk Lymphoma, 2015. **56**(4): p. 921-6.
36. Goede, V., et al., *Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions.* New England Journal of Medicine, 2014. **370**(12): p. 1101-1110.
37. Hurria, A., et al., *Developing a cancer-specific geriatric assessment: a feasibility study.* Cancer, 2005. **104**(9): p. 1998-2005.
38. Williams, G.R., et al., *Feasibility of geriatric assessment in community oncology clinics.* J Geriatr Oncol, 2014. **5**(3): p. 245-51.
39. Hurria, A., et al., *Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401.* J Clin Oncol, 2011. **29**(10): p. 1290-6.
40. Repetto, L., et al., *Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study.* J Clin Oncol, 2002. **20**(2): p. 494-502.
41. Jolly, T.A., et al., *Geriatric assessment-identified deficits in older cancer patients with normal performance status.* Oncologist, 2015. **20**(4): p. 379-85.
42. Habermann, T.M., et al., *Rituximab-CHOP Versus CHOP Alone or With Maintenance Rituximab in Older Patients With Diffuse Large B-Cell Lymphoma.* Journal of Clinical Oncology, 2006. **24**(19): p. 3121-3127.
43. Delarue, R., et al., *Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial.* Lancet Oncol, 2013. **14**(6): p. 525-33.
44. Shah, N.N., et al., *Split-dose R-CHOP: A new approach to administer cytotoxic chemo-immunotherapy to elderly patients with DLBCL.* The Journal of Community and Supportive Oncology, 2016. **14**(11): p. 450-456.

Appendix A: Karnofsky Performance Status

Karnofsky Status	Karnofsky Grade		
Normal, no complaints	100		
Able to carry on normal activities. Minor signs or symptoms of disease	90		
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70		
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50		
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death non-imminent	30		
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0		

Appendix B: Ann Arbor Staging

Modified Ann Arbor Staging System

Stage I - Involvement of a single lymph node region.
Stage II - Involvement of 2 or more lymph node regions on the same side of the diaphragm.
- Stage II bulky disease is defined as a single lymph node, extranodal lesion, or a conglomerate of contiguous lymph nodes measuring >/= to 7.5cm. Patients with disease measuring <7.5cm are considered ineligible.
Stage III - Involvement of lymph node regions on both sides of the diaphragm.
Stage IV - Diffuse or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.

The subscript E (e.g., II_E or III_E) is used to denote involvement of an extra lymphatic site primarily or by direct extension, rather than hematogenous spread, as in the case of a mediastinal mass extending to involve the lung.

The presence of (B) or absence of (A) fever, night sweats, and/or unexplained loss of 10% or more body weight in the 6 months prior to admission are denoted by the corresponding suffix letters B and A.

Appendix C: International Prognostic Index

One point is assigned to each of the following risk factors:

- Age greater than 60 years
- Stage III or IV disease
- Elevated serum LDH
- ECOG performance status of 2, 3, or 4
- More than 1 extranodal site

Appendix D: CIRS-G Scale[34]

Study: UW18131 Patient Name:
Subject ID: Timepoint/Date:

Cumulative Illness Rating Scale for Geriatrics (CIRS-G): Please score each organ system on a graded scale of 0-4 (use highest score within organ system for scoring calculation). For 70-74 years aged patients: CIRS-G score with 5-8 comorbid conditions scored 2 or ≥1 comorbidity scored 3-4. CIRS-G score is to be reviewed by the study PI prior to enrollment. Calculator: https://eforms.moffitt.org/cirsgScore.aspx

Rating Strategy

0 – No problem
1 - Current mild problem or past significant problem
2 - Moderate disability or morbidity/requires "first line" therapy
3 - Severe/constant significant disability/ “uncontrollable” chronic problems
4 - Extremely severe/immediate treatment required/end organ failure/severe impairment function

Please insert the appropriate grade of illness/impairment		
Organ system	If illness/impairment present, please specify:	Score
Heart		
Vascular		
Respiratory		
Ear/nose/throat		
Upper gastrointestinal		
Lower gastrointestinal		
Liver		
Renal		
Genitourinary		
Musculoskeletal		
Endocrine/metabolic		
Neurological		
Psychiatric		
Hematopoietic		
	Total Score:	
	Numbers of categories at level-3 or above:	

Treating Investigator Signtature:_____ Date:_____

Appendix E: Prednisone Pill Diary

Study: UW18131 Patient Name:

Subject ID: Cycle:

Day	Date prednisone was taken	Time prednisone was taken	Dose taken
1		: am/pm	50 mg
2		: am/pm	50 mg
3		: am/pm	50 mg
4		: am/pm	50 mg
5		: am/pm	50 mg
6			
7			
8			
9			
10			
11			
12			
13			
14			
15		: am/pm	50 mg
16		: am/pm	50 mg
17		: am/pm	50 mg
18		: am/pm	50 mg
19		: am/pm	50 mg
20			
21			
22			
23			
24			
25			
26			
27			
28			

**Please make a note of any doses missed.*

_____

Subject Signature and date

Appendix F: PET/CT Based Response Assessment [33]

Response and Site	PET-CT–Based Response
Complete	Complete metabolic response
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†
	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
Nonmeasured lesion	Not applicable
Organ enlargement	Not applicable
New lesions	None
Bone marrow	No evidence of FDG-avid disease in marrow
Partial	Partial metabolic response
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size
	At interim, these findings suggest responding disease
	At end of treatment, these findings indicate residual disease
Nonmeasured lesions	Not applicable
Organ enlargement	Not applicable
New lesions	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
No response or stable disease	No metabolic response
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
Nonmeasured lesions	Not applicable
Organ enlargement	Not applicable
New lesions	None
Bone marrow	No change from baseline
Progressive disease	Progressive metabolic disease
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment
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
Bone marrow	New or recurrent FDG-avid foci

Appendix G: Deauville Scoring System

Score	FDG Uptake
1	No uptake at disease sites
2	Uptake in disease site ≤ uptake in mediastinum
3	Uptake in disease site > uptake in mediastinum but ≤ uptake in liver
4	Uptake in disease site > uptake in liver
5	Uptake in disease site markedly increased at any site or new disease sites

FDG=fludeoxyglucose

* Subjects who present with an interim PET/CT Deauville 5 score must have a pattern consistent with progressive disease. Progression per Lugano 2014 response criteria (Appendix F) is defined by the following: increased uptake from baseline and/or change in size and/or new lesions. Subjects who present with a Deauville 5 score that do not have a pattern consistent with progressive disease per the Lugano response criteria will continue protocol therapy and complete cycles 3A through 6B.

Appendix H: Geriatric Assessments

Study: UW18131
Patient Name:
Subject ID:
Time point:
Date:

SUB- APPENDIX I: GERIATRIC ASSESSMENT PATIENT QUESTIONNAIRE

A. BACKGROUND INFORMATION

1. What is the highest grade you finished in school? *(Mark one with an X).*

- ☐ 8th grade or less
- ☐ 9-11th grade
- ☐ High school graduate/GED
- ☐ Associate degree/some college
- ☐ Vocational/technical school
- ☐ Bachelor's degree
- ☐ Advanced degree
- ☐ I prefer not to answer

2. What is your marital status? *(Mark one with an X.)*

- ☐ Married
- ☐ Domestic partnership
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Never married
- ☐ I prefer not to answer

3. With whom do you live? *(Mark all that apply with an X.)*

- ☐ Spouse / partner
- ☐ Girlfriend / boyfriend
- ☐ Children aged 18 years or younger
- ☐ Children aged 19 years or older
- ☐ Parent(s)/ parent(s)-in-law
- ☐ Live alone
- ☐ Other specify _____
- ☐ Other relative specify _____

4. What is your current employment status? *(Mark one with an X.)*

- ☐ Employed 32 hours or more per week
- ☐ Employed less than 32 hours per week
- ☐ Homemaker
- ☐ Disabled
- ☐ On medical leave
- ☐ Unemployed
- ☐ Retired
- ☐ Full-time student
- ☐ Part-time student
- ☐ Other specify _____

PATIENT QUESTIONNAIRE

Subject ID:
Time point:
Date:

B. DAILY ACTIVITIES*

PATIENT INSTRUCTIONS: Indicate your response by marking an X in one box per question.

1. Can you use the telephone…
   - ☐ without help, including looking up and dialing;
   - ☐ with some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing); or
   - ☐ are you completely unable to use the telephone?
2. Can you get to places out of walking distance…
   - ☐ without help (can travel alone on buses, taxis, or drive your own car);
   - ☐ with some help (need someone to help you or go with you when traveling); or
   - ☐ are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?
3. Can you go shopping for groceries or clothes (assuming you have transportation) …
   - ☐ without help (taking care of all shopping needs yourself, assuming you have transportation);
   - ☐ with some help (need someone to go with you on all shopping trips); or
   - ☐ are you completely unable to do any shopping?
4. Can you prepare your own meals…
   - ☐ without help (plan and cook full meals yourself);
   - ☐ with some help (can prepare some things but unable to cook full meals yourself); or
   - ☐ are you completely unable to prepare any meals?
5. Can you do your housework…
   - ☐ without help (can clean floors, etc.);
   - ☐ with some help (can do light housework but need help with heavy work); or
   - ☐ are you completely unable to do any housework?
6. Can you take your own medicines…
   - ☐ without help (in the right doses at the right time);
   - ☐ with some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or
   - ☐ are you completely unable to take your medicines?
7. Can you handle your own money…
   - ☐ without help (write checks, pay bills, etc.);
   - ☐ with some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or
   - ☐ are you completely unable to handle money?

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

PATIENT QUESTIONNAIRE

Subject ID:
Time point:
Date:

C. PHYSICAL ACTIVITIES*

1. The following items are activities you might do during a typical day. Does your health limit you in these activities? **(*Mark an X in the box on each line that best reflects your situation.*)**

Activities	Limited a lot	Limited a little	Not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
c. Lifting or carrying groceries	☐	☐	☐
d. Climbing several flights of stairs	☐	☐	☐
e. Climbing one flight of stairs	☐	☐	☐
f. Bending, kneeling, or stooping	☐	☐	☐
g. Walking more than a mile	☐	☐	☐
h. Walking several blocks	☐	☐	☐
i. Walking one block	☐	☐	☐
j. Bathing or dressing yourself	☐	☐	☐

* MOS, Physical Functioning Scale – Stewart, A.L. and Ware, J.E.,1992

PATIENT QUESTIONNAIRE

Subject ID:
Time point:
Date:

D. CURRENT HEALTH RATING*

Which one of the following phrases best describes you at this time? *(Mark one with an X.)*

- ☐ Normal, no complaints, no symptoms of disease
- ☐ Able to carry on normal activity, minor symptoms of disease
- ☐ Normal activity with effort, some symptoms of disease
- ☐ Care for self, unable to carry on normal activity or do active work
- ☐ Require occasional assistance but able to care for most of personal needs
- ☐ Require considerable assistance for personal care
- ☐ Disabled, require special care and assistance
- ☐ Severely disabled, require continuous nursing care

* Patient KPS – Loprinzi, C.L., et al., 1994

E. FALLS

How many times have you fallen in the last 6 months? _____

PATIENT QUESTIONNAIRE

Subject ID:
Time point:
Date:

F. YOUR HEALTH

1. Your General Health*

Patient Instructions: Do you have any of the following illnesses at the present time, and if so, how much does it interfere with your activities: **Not at All, A Little or A Great Deal?** *(Mark an X in the box that best reflects your answer.)*

				If you have this illness: How much does it interfere with your activities?		
Illness	**No**	**Yes**		**Not at all**	**A little**	**A great deal**
a. Other cancers or leukemia	☐	☐	→	☐	☐	☐
b. Arthritis or rheumatism	☐	☐	→	☐	☐	☐
c. Glaucoma	☐	☐	→	☐	☐	☐
d. Emphysema or chronic bronchitis	☐	☐	→	☐	☐	☐
e. High blood pressure	☐	☐	→	☐	☐	☐
f. Heart trouble	☐	☐	→	☐	☐	☐
g. Circulation trouble in arms or legs	☐	☐	→	☐	☐	☐
h. Diabetes	☐	☐	→	☐	☐	☐
i. Stomach or intestinal disorders	☐	☐	→	☐	☐	☐
j. Osteoporosis	☐	☐	→	☐	☐	☐
k. Liver disease	☐	☐	→	☐	☐	☐
l. Kidney disease	☐	☐	→	☐	☐	☐
m. Stroke	☐	☐	→	☐	☐	☐
n. Depression	☐	☐	→	☐	☐	☐

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

PATIENT QUESTIONNAIRE

Subject ID:
Time point:
Date:

2. How is your eyesight (with glasses or contacts)? *(Mark one with an X.)*

- ☐ Excellent
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Totally blind

3. How is your hearing (with a hearing aid, if needed)? *(Mark one with an X.)*

- ☐ Excellent
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Totally deaf

4. Do you have any other physical problems or illnesses *(other than listed in questions 1-4)* at the present time that seriously affect your health?

- ☐ No
- ☐ Yes *(If yes),* specify _____

(If yes), how much does this interfere with your activities? *(Mark one with an X.)*

☐ Not at all ☐ Somewhat ☐ A great deal

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

PATIENT QUESTIONNAIRE

Subject ID:
Time point:
Date:

G. MENTAL HEALTH QUESTIONNAIRE*

INSTRUCTIONS: These questions are about how you have been feeling within the past month. Please mark an "X" in the box on each line that best reflects your situation.

How much of the time during the past month:	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
1. has your daily life been full of things that were interesting to you?	☐	☐	☐	☐	☐	☐
2. did you feel depressed?	☐	☐	☐	☐	☐	☐
3. have you felt loved and wanted?	☐	☐	☐	☐	☐	☐
4. have you been a very nervous person?	☐	☐	☐	☐	☐	☐
5. have you been in firm control of your behavior, thoughts, emotions, feelings?	☐	☐	☐	☐	☐	☐
6. have you felt tense or "high-strung"?	☐	☐	☐	☐	☐	☐
7. have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
8. have you felt emotionally stable?	☐	☐	☐	☐	☐	☐
9. have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
10. have you felt restless, fidgety, or impatient?	☐	☐	☐	☐	☐	☐
11. have you been moody, or brooded about things?	☐	☐	☐	☐	☐	☐
12. have you felt cheerful, lighthearted?	☐	☐	☐	☐	☐	☐
13. have you been in low or very low spirits?	☐	☐	☐	☐	☐	☐
14. have you been a happy person?	☐	☐	☐	☐	☐	☐
15. did you feel you had nothing to look forward to?	☐	☐	☐	☐	☐	☐
16. have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐

17. have you been anxious or worried?	☐	☐	☐	☐	☐	☐

* MHI-17 – Stewart, A.L. and Ware, J.E., 1992

Subject ID:
Time point:
Date:

PATIENT QUESTIONNAIRE

Subject ID:
Time point:
Date:

H. SOCIAL ACTIVITIES*

1. During the past 4 weeks, how much time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
   (Mark one with an X.)

   ☐ All of the time
   ☐ Most of the time
   ☐ Some of the time
   ☐ A little of the time
   ☐ None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition? *(Mark one with an X.)*

   ☐ Much less socially active than before
   ☐ Somewhat less socially active than before
   ☐ About as socially active as before
   ☐ Somewhat more socially active as before
   ☐ Much more socially active than before

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems? *(Mark one with an X.)*

   ☐ Much more limited than others
   ☐ Somewhat more limited than others
   ☐ About the same as others
   ☐ Somewhat less limited than others
   ☐ Much less limited than others

* MOS, Social Activities – Stewart, A.L. and Ware, J.E., 1992

PATIENT QUESTIONNAIRE

Subject ID:
Time point:
Date:

I. SOCIAL SUPPORT*

INSTRUCTIONS: People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kinds of support available to you if you need it? (*Mark an X in the box on each line that best reflects your situation.*)

	None of the Time	A Little of the Time	Some of the Time	Most of the Time	All of the Time
1. Someone to help you if you were confined to bed.	☐	☐	☐	☐	☐
2. Someone you can count on to listen to you when you need to talk.	☐	☐	☐	☐	☐
3. Someone to give you good advice about a crisis.	☐	☐	☐	☐	☐
4. Someone to take you to the doctor if you needed it.	☐	☐	☐	☐	☐
5. Someone to give you information to help you understand a situation.	☐	☐	☐	☐	☐
6. Someone to confide in or talk to about yourself or your problem.	☐	☐	☐	☐	☐
7. Someone to prepare your meals if you were unable to do it yourself.	☐	☐	☐	☐	☐
8. Someone whose advice you really want.	☐	☐	☐	☐	☐
9. Someone to help you with daily chores if you were sick.	☐	☐	☐	☐	☐
10. Someone to share your most private worries and fears with.	☐	☐	☐	☐	☐
11. Someone to turn to for suggestions about how to deal with a personal problem.	☐	☐	☐	☐	☐
12. Someone who understands your problems.	☐	☐	☐	☐	☐

MOS Social Support Survey – Sherbourne, C.D. and Stewart, A.L., 1991

SUB-APPENDIX II: GERIATRIC ASSESSMENT
HEALTHCARE PROFESSIONAL QUESTIONNAIRE

Subject ID:
Time point:
Date:

II. Functional Status

A. Karnofsky Performance Status *(Healthcare professional rated)**

INSTRUCTIONS: Please rate your assessment of patient's Karnofsky Performance Status as of date this form is completed. (Scale is listed below.)

_____%

%	CRITERIA
100	Normal: no complaints; no evidence of disease.
90	Able to carry on normal activity; only minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, but unable to carry on normal activity or do active work.
60	Requires occasional assistance, but is able to care for most personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated although death not imminent.
20	Very sick; hospitalization necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

* Physician KPS – Karnofsky, D.A. and Burchenal, J.H., 1949

B. Timed "Up and Go"**

INSTRUCTIONS: The timed "Up and Go" measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given. The subject starts with his back against the chair, his arm resting on the chair's arm, and his walking aid in hand. He is instructed that on the word "go", he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters (approximately 10 feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stop-watch can be used to time the performance.

Time to perform "Up and Go"_____. seconds

** Timed "Up and Go" – Podsiadio, D. and Richardson, S., 1991

HEALTHCARE PROFESSIONAL QUESTIONNAIRE

III. Cognition

Subject ID:
Time point: Date:

BLESSED ORIENTATION-MEMORY-CONCENTRATION TEST*				
	Patient's Response	**Maximum errors**	**Score Weight**	**Final score**
1. What year is it now? [without looking at a calendar]	_____	1	_____ x 4 =	_____
2. What month is it now? [without looking at a calendar]	_____	1	_____ x 3 =	_____
Memory Phrase: Repeat this phrase after me: 'John Brown, 42 Market Street, Chicago'				
3. About what time is it? [within 1 hour]	_____: _____ (24-hour clock)	1	_____ x 3 =	_____
4. Count backwards 20 to 1.		2	_____ x 2 =	_____
5. Say the months in reverse order.		2	_____ x 2 =	_____
6. Repeat the Memory Phrase.		5	_____ x 2 =	_____
			TOTAL SCORE:	_____

Scoring: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, add one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in "Final Score" column. Data from participants found to have gross cognitive impairment as determined by the Orientation-Memory-Concentration Score ≥11 will be excluded from the analysis. Maximum score = 28.

* Blessed OMC – Katzman, R., et al., 1983; Kawas, C., et al., 1995

IV. Scoring

This question is only applicable to the BOMC-Test in Section III.

1. Did the patient score greater than or equal to 11 on the Blessed Orientation-Memory-Concentration Test?
   ☐ No
   ☐ Yes **(If yes, notify the patient's treating physician.)**

This question is only applicable to question #1 in "Section K. Your Feelings" from the Patient Questionnaire.

2. How did the patient answer the question "Do you often feel sad or depressed?" in the Patient Questionnaire *(Section K)*?
   ☐ No
   ☐ Yes **(If yes, notify the patient's treating physician.)**

HEALTHCARE PROFESSIONAL QUESTIONNAIRE

V. Nutrition

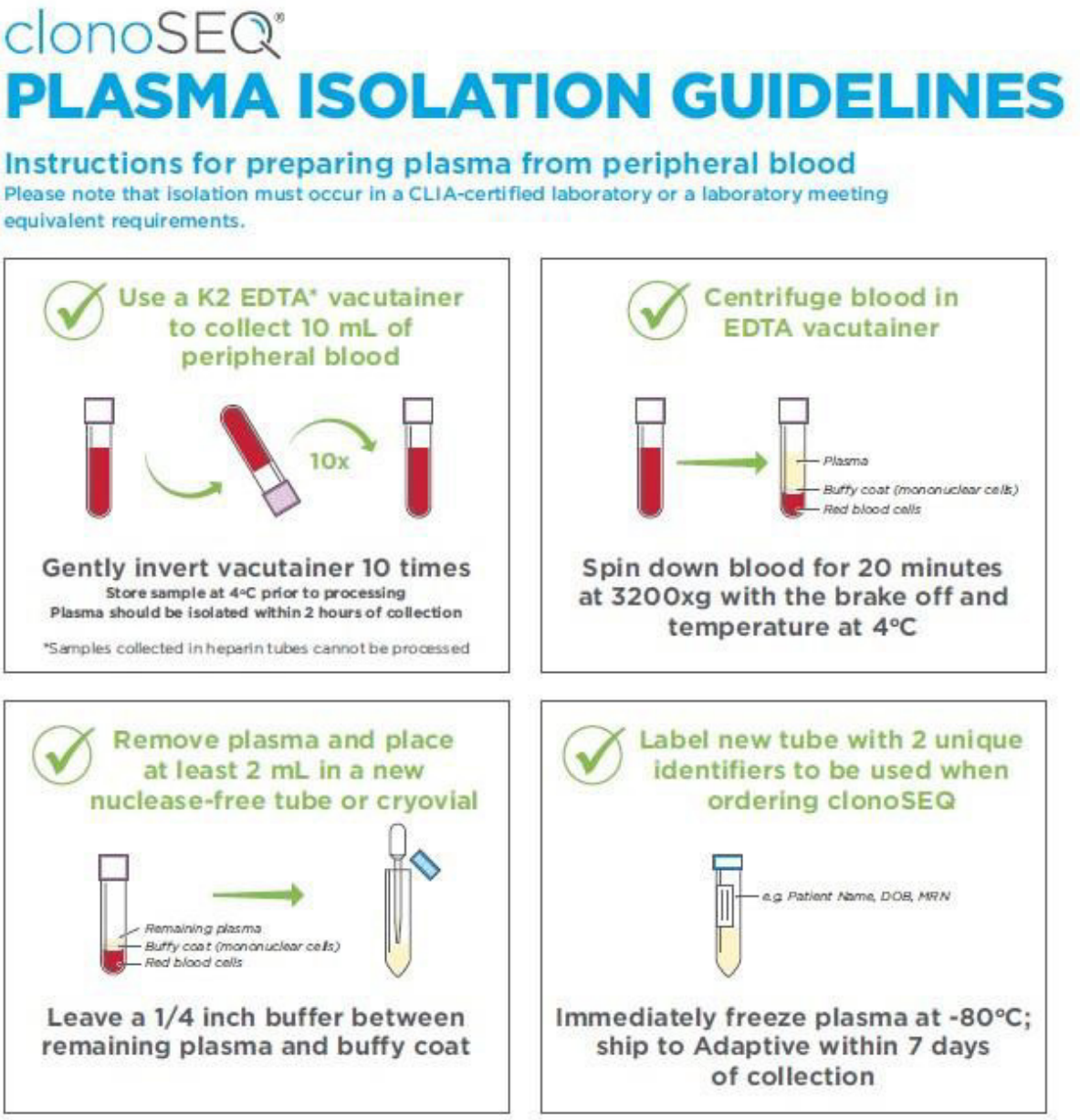
Subject ID: Time point: Date:

Height (*from patient's chart*) _____ cm

Weight (*from patient's chart*) _____kg

Weight approximately 6 months ago *(from patient's chart or patient's self- report)*_____kg

Appendix I: ClonoSEQ Plasma Isolation and Whole Blood Storage and Shipping Guidelines



WHOLE BLOOD SAMPLE:

>2mL (ideally up to 10mL) of fresh peripheral blood should be collected in EDTA tubes and stored locally on site to be shipped to Adaptive every 12-18 months from the first patient enrolled into the trial. . Freeze stored PB samples at -80°C if storing greater than six months, or at -20°C if storing less than six months. Stored frozen peripheral blood should be sent on dry ice and shipped in batch of samples collected. Adaptive will provide shipping containers for frozen samples. See batch shipping instruction below. **BATCH WHOLE BLOOD SHIPPING INSTRUCTIONS**:

1.) Email ISTSampleMgmt@adaptivebiotech.com with the number of PB samples, size of PB tube and the shipping contact name and address to receive the batch PB shipping materials.

2.) Site will receive an email from customercare@adaptivebiotech.com containing packing instructions, FedEx tracking number of the shipper(s) and a blank manifest. The shipper will contain all the necessary materials needed to ship the batch samples (including a pre-paid FedEx return label), except dry ice. Site will need to provide 10lb dry ice per shipper.

3.) When site is ready to ship, print a hard copy of the completed manifest and include in each shipper. Email ISTSampleMgmt@adaptivebiotech.com the completed manifest and the FedEx tracking number(s). *Sites are welcome to send Adaptive the completed manifest for review prior to shipping the samples.

4.) Once Adaptive receives the shipment, the sample management team will review the manifest for any discrepancies, as well as any discrepancies against the tube labels.

Appendix J: Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl): (Cockcroft, 1976; Luke 1990)

Male $$\frac{\text{CrCl (mL/min)} = (140 - \text{subject age, years}) \times (\text{subject weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

Female $$\frac{\text{CrCl (mL/min)} = (140 - \text{subject age, years}) \times (\text{subject weight, kg}) \times 0.85}{72 \times (\text{serum creatinine, mg/dL})}$$