AN OPEN-LABEL PHASE 2 STUDY OF DENINTUZUMAB MAFODOTIN (SGN-CD19A) IN COMBINATION WITH RCHOP (RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE) OR RCHP (RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE) COMPARED WITH RCHOP ALONE AS FRONTLINE THERAPY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) OR FOLLICULAR LYMPHOMA (FL) GRADE 3B

Test Drug: Denintuzumab mafodotin

Protocol Number: SGN19A-004 **IND number:** 114874
Study Phase: 2

Date and Version: 18 February 2016, Version 01

Sponsor: Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021 US 1-855-473-2436	**Clinical Research Organization (CRO):** PRA Health Sciences 4130 ParkLake Avenue, Suite 400 Raleigh, NC 27612 US
Medical Monitor: [redacted] PRA Health Sciences Phone: [redacted] Fax:	**Safety Contact (SAE reporting):** 24-hour FAX: 1-425-527-4308 DRUG.SAFETY@SEAGEN.COM

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

CONFIDENTIAL

1. SIGNATURE

Representatives of Sponsor

I have read and agree to the protocol SGN19A-004 entitled 'An open-label phase 2 study of denintuzumab mafodotin (SGN-CD19A) in combination with RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) compared with RCHOP alone as frontline therapy in patients with diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) Grade 3b'. I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities.

Accepted for the Sponsor - Seattle Genetics, Inc.:

Investigator

I have read and agree to the protocol SGN19A-004, entitled 'An open-label phase 2 study of denintuzumab mafodotin (SGN-CD19A) in combination with RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) compared with RCHOP alone as frontline therapy in patients with diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) Grade 3b'. I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Site Principal Investigator:

Print Name	Title
Signature	Date

2. SYNOPSIS

NAME OF SPONSOR: Seattle Genetics, Inc.	**PROTOCOL No.:** SGN19A-004
NAME OF STUDY TREATMENT: Denintuzumab mafodotin	
TITLE OF STUDY: An open-label phase 2 study of denintuzumab mafodotin (SGN-CD19A) in combination with RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) compared with RCHOP alone as frontline therapy in patients with diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) Grade 3b	
PHASE OF DEVELOPMENT: Phase 2	

OBJECTIVES:

Primary Objectives:

- To compare the complete response (CR) rate at the end of treatment (EOT) in treatment-naive patients with high-intermediate or high-risk systemic DLBCL or FL Grade 3b treated with denintuzumab mafodotin plus RCHOP or RCHP versus RCHOP alone (Part B)
- To assess the safety profile of denintuzumab mafodotin administered in combination with RCHOP or RCHP in treatment-naive patients with high-intermediate or high-risk systemic DLBCL or FL Grade 3b (Part A and Part B)

Secondary Objectives:

- To compare event-free survival (EFS) between study arms (Part B)
- To compare progression-free survival (PFS) between study arms (Part B)
- To compare overall survival (OS) between study arms (Part B)
- To compare the objective response rate (ORR) at EOT between study arms (Part B)
- To compare the duration of objective response and of CR between study arms (Part B)

Additional Objectives:

- To evaluate the pharmacokinetics (PK) of denintuzumab mafodotin administered in combination with RCHOP or RCHP (Parts A and B)
- To evaluate the incidence of antitherapeutic antibodies (ATAs) against denintuzumab mafodotin (Parts A and B)
- To assess denintuzumab mafodotin-mediated pharmacodynamic effects and potential biomarkers of response to denintuzumab mafodotin in combination with RCHOP or RCHP (Parts A and B)

STUDY DESIGN AND METHODOLOGY: This open-label study has 2 parts (Part A and Part B). Part A of the study is a safety evaluation of denintuzumab mafodotin in combination with either RCHOP or RCHP in patients with newly diagnosed, treatment-naive DLBCL or FL Grade 3b. Up to approximately 24 patients will be randomized 1:1 to receive denintuzumab mafodotin plus RCHOP or denintuzumab mafodotin plus RCHP to assess the safety, including peripheral neuropathy, of these 2 combination regimens. Patient randomization will be stratified by high-intermediate or high-risk disease. Study treatment is up to six 21-day cycles of either RCHOP or RCHP combined with up to 3 doses of denintuzumab mafodotin administered on Day 1 of Cycles 1, 3, and 5.

The safety of the combinations will be assessed at predefined interim safety evaluations as well as over the course of the treatment period by a Safety Monitoring Committee (SMC) comprised of the study investigators, medical monitor, biostatistician, and sponsor medical expert. In Part A, at each interim safety evaluation, the SMC will review the cumulative safety data of denintuzumab mafodotin in combination with RCHOP or RCHP. At the last formal safety evaluation in Part A, a comprehensive evaluation of the safety and antitumor activity data will be performed to determine the regimen (RCHOP or RCHP) to be tested in combination with denintuzumab mafodotin in the Experimental Arm in Part B of the study.

Part B of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of denintuzumab mafodotin in combination with either RCHOP or RCHP (Experimental Arm) compared with RCHOP alone (Comparator Arm). Approximately 136 patients will be randomized 1:1 to either the Experimental or Comparator Arm. Randomization will be stratified by high-intermediate or high-risk disease and cell of origin (COO). Up to six 21-day cycles of either RCHOP or RCHP (as determined using the safety data from Part A) will be administered with up to 3 doses of denintuzumab mafodotin administered on Day 1 of Cycles 1, 3, and 5 in the Experimental Arm versus up to six 21-day cycles of RCHOP in the Comparator Arm. The SMC will continue to monitor the safety of the combination of denintuzumab mafodotin and either RCHOP or RCHP at predefined interim safety evaluations and throughout the study period.

In Part A and Part B, lymphoma response and progression will be assessed using the Lugano Classification Revised Staging System (Cheson, 2014) for malignant lymphoma. Diagnostic quality computed tomography (CT) scans (neck, chest, abdomen, and pelvis with IV and oral contrast) and positron emission tomography (PET) scans will be performed at baseline and at 5 weeks after the last dose of study treatment; all other EOT evaluations will be assessed 30 to 37 days after the last dose. Follow-up assessments will be performed every 4 months from the last scan until 24 months, then every 6 months until 48 months, and then annually until study closure. For all follow-up assessments, both PET and CT scans are required until disease is PET negative; responses will then be followed by CT scan only. A CT scan will also be performed at the time of suspected clinical progression. Follow-up assessments will continue until disease progression, initiation of a new anti-cancer treatment, or study closure, whichever comes first. Survival status follow-up will continue until patient death or study closure, whichever comes first.

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:
Patients cannot be enrolled or randomized before all inclusion and exclusion criteria (including test results) are confirmed.

Inclusion Criteria: Eligible patients must meet the following criteria:

1. treatment-naive patients with histologically confirmed systemic de novo or transformed DLBCL (from follicular or marginal zone lymphoma), or FL Grade 3b; patients must have high-intermediate or high-risk disease based on standard International Prognostic Index (IPI) (score ≥3 for patients >60 years of age) or age-adjusted IPI (aaIPI) (score 2 or 3 for patients ≤60 years of age), and stage IAX (bulk defined as single lymph node mass >10 cm in diameter)–IV disease
2. tumor tissue available from most recent biopsy to determine COO by immunohistochemistry using Hans algorithm, as assessed by site pathologist. In addition, tumor tissue must be submitted for central pathological review during the trial; if such tissue is not available, a fresh biopsy must be obtained.
3. fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1 nodal lesion greater than 1.5 cm in the longest diameter or a non-nodal tumor lesion greater than 1.0 cm in the longest diameter by CT, as assessed by the site radiologist
4. an Eastern Cooperative Oncology Group (ECOG) performance status ≤2
5. age 18 years or older
6. patients must have the following baseline laboratory data:
    a. bilirubin ≤1.5 × upper limit of normal (ULN) or ≤3 × ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma
    b. alanine aminotransferase and aspartate aminotransferase ≤3 × ULN or ≤5 × ULN for patients with documented hepatic involvement with lymphoma
    c. creatinine clearance ≥30mL/min (calculated using the Cockcroft-Gault formula)
    d. absolute neutrophil count ≥1000/µL (unless documented bone marrow involvement with lymphoma, in which case ANC ≥500/µL)
    e. platelet count ≥75,000/µL (unless documented bone marrow involvement with lymphoma, in which case platelets ≥50,000/µL)
    f. urine protein:creatinine ratio (UPC) ratio <1
7. females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin pregnancy test result within 7 days prior to the first dose of study drug. Females of non-childbearing potential are those who are postmenopausal for more than 1 year or who have

had a bilateral tubal ligation, hysterectomy, or bilateral oophorectomy

8. females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraception methods during the study and for 12 months following the last dose of study drug, as well as 12 months following the last dose of rituximab
9. patients must provide written informed consent

Exclusion Criteria: If any of the following apply, the patient MUST NOT enter the study:

1. previous history of treated indolent lymphoma. Newly diagnosed patients with DLBCL who are found to have small cell infiltration of the bone marrow or other diagnostic material (representing a discordant lymphoma) are eligible.
2. history of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years (exceptions include non-melanoma skin cancer, curatively treated localized prostate cancer, ductal carcinoma in situ, and cervical carcinoma in situ by biopsy or a squamous intraepithelial lesion by papanicolaou smear)
3. history of progressive multifocal leukoencephalopathy (PML)
4. cerebral/meningeal disease related to the underlying malignancy
5. baseline peripheral neuropathy ≥Grade 2 (per the National Cancer Institute's [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03) or patients with the demyelinating form of Charcot-Marie-Tooth syndrome
6. left ventricular ejection fraction less than 45% or symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), or myocardial infarction within the past 6 months or previous treatment with complete cumulative doses of doxorubicin or other anthracyclines
7. patients with the following ocular conditions:
    a. corneal disorders: corneal dystrophies, history of corneal or limbal stem cell transplantation (including endothelial keratoplasty), evidence of limbal stem cell deficiency (ie, deep pannus, poor epithelial healing)
    b. monocular vision (ie, best corrected visual acuity ≥20/200 in one eye)
    c. active ocular disorders requiring treatment such as corneal ulcer, herpetic keratitis, uncontrolled glaucoma (stable topical medication is allowed), uncontrolled diabetic retinopathy, evolving wet macular degeneration, iritis or vitritis, papilledema, or optic nerve disorder
8. any active ≥Grade 3 (per the NCI CTCAE, Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study treatment. Routine antimicrobial prophylaxis is permitted.
9. current therapy with other systemic anti-neoplastic or investigational agents
10. females who are breastfeeding
11. known hypersensitivity to any excipient contained in any of the drug formulations of study treatments
12. patients with known urinary outflow obstruction
13. patients with a positive polymerase chain reaction assay who have also tested positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody; patients with a negative polymerase chain reaction assay are permitted with appropriate anti-viral prophylaxis
14. known or suspected active hepatitis C infection or known human immunodeficiency virus infection

NUMBER OF SUBJECTS: Approximately 160 patients (24 patients in Part A and 136 patients in Part B)

STUDY TREATMENT:

Test Product, Dose and Mode of Administration:

Denintuzumab mafodotin at 3 mg/kg will be administered every 6 weeks via intravenous (IV) infusion to all patients in Part A and to patients in the Experimental Arm in Part B. Denintuzumab mafodotin will be administered on Day 1 of Cycles 1, 3, and 5; the timing of denintuzumab mafodotin administration will be approximately 30 minutes, but no longer than 60 minutes, following rituximab completion on Day 1, after which it will then be followed by the remaining components of the combination therapy, ie, CHOP or CHP.

Reference Therapy, Dose and Mode of Administration:

RCHOP: rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (dose capped at 2 mg total) will be administered IV on Day 1 of every 21-day cycle together

with prednisone 100 mg administered orally on Days 1 to 5 of every 21-day cycle
RCHP: rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, and doxorubicin 50 mg/m^2 will be administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1 to 5 of every 21-day cycle

DURATION OF TREATMENT: Study treatment consist of up to six 21-day cycles of either RCHOP or RCHP with or without up to 3 doses of denintuzumab mafodotin given on Day 1 of Cycles 1, 3, and 5.

STUDY EVALUATIONS:

Efficacy Assessment: Disease response will be assessed by the investigator, based on the Lugano classification criteria (Cheson, 2014). Radiographic assessments will include PET and diagnostic quality CT scans. For all follow-up response assessments, both PET and CT scanning will be required until disease is PET negative; responses will then be followed by CT scan of diagnostic quality only and evaluated by CT-based response criteria per the Lugano classification criteria.

Pharmacokinetic and Antitherapeutic Antibody Measurements: Concentrations of denintuzumab mafodotin antibody drug conjugate and released cysteine maleimidocaproyl monomethyl auristatin F in plasma and ATA in serum will be measured. Concentrations of rituximab in serum will be measured. Pharmacokinetic samples will also be collected and archived for possible analysis of other denintuzumab mafodotin-related species.

Biomarker Assessments: Biomarker evaluations may include, but are not limited to, baseline pre- and post-treatment peripheral blood evaluation for circulating B cells by flow cytometry and for soluble mediator quantification, which may include soluble CD19. Peripheral blood will be collected and assessed for cell-free circulating tumor DNA to detect minimal residual disease. Peripheral blood cell pellets will be collected for assessment of Fc-gamma receptor (FcγR) polymorphisms. The evaluation of pre-treatment tumor biopsies may include, but is not limited to, therapeutic target CD19 and other immune cell marker expression by immunohistochemistry, COO by gene expression profiling, as well as somatic mutations that are prognostic or predictive of denintuzumab mafodotin response.

Safety Assessment: Safety assessments will include the evaluation of the type, incidence, severity, seriousness, and relatedness of adverse events, and the type, incidence, and severity of laboratory test abnormalities. Ophthalmologic exams and ocular health surveys will be conducted at protocol-specific time points.

STATISTICAL METHODS:

Sample Size Considerations

In Part A of the study, up to approximately 24 patients will be enrolled to receive denintuzumab mafodotin with either RCHOP or RCHP (approximately 12 patients per treatment arm). With 12 patients in each arm, the probability of observing at least 1 patient with a clinically relevant adverse event is 72% if the true event rate is 10%. The probability becomes 93% if the true event rate is 20%.

In Part B of the study, with approximately 136 patients randomized in a 1:1 to each treatment arm (approximately 68 patients per treatment arm) for the primary analysis, the study is designed to have approximately 80% power to detect an increase in the CR rate of 18% (eg, from 70% in the RCHOP treatment arm to 88% in the denintuzumab mafodotin plus RCHOP (or RCHP) treatment arm. This calculation is based on a 2-sided chi-squared test with significance level of alpha =0.1 using EAST 6.3.1

Randomization

In Part A, randomization will be stratified by high-intermediate or high-risk disease.
In Part B, randomization will be stratified based on the following factors for both randomization and analysis:

- COO by local immunohistochemical assessment per Hans algorithm (germinal center B [GCB] versus non-GCB)
- IPI or aaIPI (high-intermediate risk versus high-risk disease)

Analysis Methods

The efficacy endpoints of response rates (CR rate and ORR) at EOT assessment will be summarized by descriptive statistics and exact 90% confidence intervals (CIs) will be calculated. The CR rate comparison between the 2 treatment arms for Part B will be performed using a Cochran-Mantel-Haenszel test stratified by the randomization strata at a 2-sided alpha level of 0.1.

EFS, PFS and OS will be estimated using the Kaplan-Meier methodology. The safety analysis will evaluate the type, incidence, severity, seriousness, and relatedness of adverse events, and the type, incidence, and severity of laboratory abnormalities for Parts A and B.
DATE AND VERSION: 18 February 2016, Version 01

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
aaIPI	age-adjusted International Prognostic Index
ADC	antibody-drug conjugate
ADL	activities of daily living
ATA	antitherapeutic antibody
CBC	complete blood count
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CMR	complete metabolic response
COO	cell of origin
CR	complete response
CRO	Clinical Research Organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
cys-mcMMAF	cysteine maleimidocaproyl monomethyl auristatin F
DDT	dose-delaying toxicity
DLBCL	diffuse large B-cell lymphoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EFS	event-free survival
EOT	end of treatment
FcγR	Fc-gamma receptor
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
GCB	germinal center B cell
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
IP	immunophenotyping
IPI	International Prognostic Index

IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous(ly)
LDH	lactate dehydrogenase
MMAF	monomethyl auristatin F
MRD	minimal residual disease
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetics
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PMR	partial metabolic response
PT	prothrombin time
PTT	partial thromboplastin time
RCHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RCHP	rituximab, cyclophosphamide, doxorubicin, and prednisone
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCD19	soluble CD19
SCT	stem cell transplant
SGN-CD19A	denintuzumab mafodotin
SNP	single-nucleotide polymorphism
SMC	Safety Monitoring Committee
ULN	upper limit of normal
UPC	urine protein:creatinine ratio
US	United States

5. ETHICS

5.1 Ethics Committee

This study will be conducted in compliance with Institutional Review Board (IRB) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - including Title 21 Part 56 of the United States (US) Code of Federal Regulations (CFR) relating to IRBs and GCP as described in the US Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B[R3]), and with ICH regulations regarding scientific integrity (E4, E8, E9, and E10). In addition this study will adhere to all local regulatory requirements and requirements for data protection.

Before initiating a trial/study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, patient recruitment procedures (eg, advertisements), and any written information to be provided to patients and a statement from the IRB that they comply with GCP requirements. The IRB approval must identify the protocol version as well as the documents reviewed.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 (R1); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Fortaleza, Brazil, October 2013), and all applicable regulatory requirements.

5.3 Patient Information and Consent

The Investigator will explain the benefits and risks of participation in the study to each patient and obtain written informed consent. Written informed consent must be obtained prior to the patient entering the study and before initiation of any study-related procedure (including administration of study drug).

The Sponsor will provide a sample informed consent form. The final, version-dated form must be agreed to by the Sponsor and the IRB, and will contain all elements in the sample form in language readily understood by the patient. Each patient's original consent form, personally signed and dated by the patient and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled patients with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the patient. In this instance approval should always be given by the IRB. Patients on treatment should be informed of the changes and reconsented if the consent was updated for safety reasons. This is documented in the same way as previously described.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Study Medical Monitor/ Sponsor's Medical Expert:

[redacted]
PRA Health Sciences
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Fax:
DRUG.SAFETY@SEAGEN.COM or 24-hour FAX: 425-527-4308

[redacted]
Medical Director
Seattle Genetics, Inc.
Phone: [redacted]
Email: [redacted]

Monitoring and Evaluation Committee:

Members of the Study Monitoring Committee (SMC) will include the study investigators, medical monitor, biostatistician, and Sponsor's medical expert.

Clinical Laboratories:

Central clinical laboratory services will be provided by a central laboratory (refer to the study manual). Additional analyses of clinical laboratory samples may be conducted by certified local laboratories. Documentation of certification will be filed with study documentation.

Clinical Research Organization (CRO):

PRA Health Sciences
4130 ParkLake Avenue, Suite 400
Raleigh, NC 27612 US

7. INTRODUCTION

7.1 Disease Review

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative disorders originating in the B-lymphocytes, T-lymphocytes, and natural killer cells. In the US, the majority (80% to 85%) are of B-cell origin (Armitage, 1998). Non-Hodgkin lymphoma is the most common hematological malignancy, and it was estimated that 71,850 new cases would be diagnosed in the US in 2015 and that 19,790 people would die as a result of the disease (American Cancer Society, 2015). Diffuse large B-cell lymphoma (DLBCL) is a subset of NHL that comprises 37% of cases of NHL (American Cancer Society, 2014), representing the most common lymphoid neoplasm in adults (Swerdlow, 2008). According to the 2008 World Health Organization classification schema, DLBCL (not otherwise specified) is a heterogeneous grouping of lymphomas comprising neoplasms of large B-lymphoid cells that do not belong to other specific subtypes or disease entities (Swerdlow, 2008). DLBCL (not otherwise specified) cases can be further subclassified based on morphological, molecular, and immunophenotypical features. Follicular lymphoma (FL) is the most common indolent form of NHL, and comprises approximately 20% to 30% of all NHLs (Lymphoma Research Foundation, 2015). Grade 3b FL histologically is characterized by solid sheets of centroblasts, has an aggressive clinical course, and is typically treated similar to DLBCL (Cancer Research UK, 2015; Dreyling 2011). Over time, about 1 in 3 FLs transform into a fast-growing DLBCL (American Cancer Society, 2015).

Outcomes for patients with DLBCL have improved over the past decade, with the addition of rituximab to standard anthracycline-based multi-agent chemotherapy. The standard of care for newly diagnosed, treatment-naive patients with DLBCL consists of six 21-day cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) (Tilly, 2012). In large randomized trials, the benefit of RCHOP has been demonstrated by a 3-year progression-free survival (PFS) rate of approximately 70% and a 3-year overall survival (OS) rate of approximately 75% (Pfreundschuh, 2008; Cunningham, 2011). Complete response (CR) rates of 75% to 78% have been reported in analyses that included both high and low risk patients (Coiffier, 2002; Pfreundschuh, 2008). Despite the good outcomes achieved with RCHOP in newly diagnosed patients with DLBCL, high-risk patient populations still remain underserved. The International Prognostic Index (IPI) identifies patients with a score of 3 to 5 as having inferior outcomes compared to those with a score of 0 to 2. Higher-risk patients with an IPI score of 3 to 5 have a 3-year PFS rate of approximately 55%; these patients comprise approximately 40% of the frontline DLBCL population (25% IPI 3, 15% IPI 4 to 5) (Pfreundschuh, 2008). Younger patients (≤60 years of age) with age-adjusted International Prognostic Index (aaIPI) scores of 2 to 3 have similarly inferior outcomes as the traditional higher risk patients with IPI scores 3 to 5 (Shipp, 1993; Ziepert 2010).

A component of multi-agent RCHOP chemotherapy is vincristine, which is an antitubulin vinca alkaloid. Neurotoxicity is the dose-limiting toxicity of vincristine and appears to be cumulative. Neurologic manifestations that have been associated with vincristine include

paresthesia, tingling of the hands and feet, numbness, sensory loss, neuritic pain, pharyngeal and parotid gland pain, loss of deep tendon reflexes, and difficulty in walking (gait disturbances), including slapping gait. Infrequently, hoarseness of voice, ocular palsies, atony of the urinary bladder, and autonomic neuropathy presenting as postural hypotension have occurred (Tangun, 1977; Legha, 1986; Tobias, 1991). As a result of toxic neuropathy, vincristine is often dose-reduced or eliminated after several cycles of RCHOP. The expected incidence of peripheral neuropathy with vincristine, delivered as part of RCHOP, is approximately 50%; the majority of neuropathy events are sensory in nature and low grade (Grade 1 or 2). Grade 3 peripheral sensory neuropathy is observed in approximately 10% of patients; Grade 3 peripheral motor neuropathy events have been infrequently reported in the literature and are typically rare in clinical practice (Coiffier, 2002; Pfreundschuh, 2008). There is a paucity of data supporting the use of vincristine as a single agent in relapsed or refractory lymphomas, with no available single-agent prospective studies or retrospective case series. Vincristine sulfate liposome injection, a formulation of vincristine designed to provide targeted, increased, and sustained delivery to tumor tissues, was evaluated in a phase 2 study of patients with relapsed or refractory aggressive NHL (Rodriguez, 2009). In this study of 119 patients, 25% achieved an objective response; of these, 5% achieved CR. In addition, Grade 3 or 4 neurotoxicity was observed in 32% of patients. While vincristine has not been evaluated as a single agent in either the frontline or relapsed/refractory setting, the contribution of activity to RCHOP appears minimal to moderate at best based on response rate of vincristine sulfate liposome injection in the relapsed or refractory aggressive NHL setting.

RCHOP currently under-serves this high risk population, resulting in an unmet need, and an opportunity to introduce novel agents to improve the treatment paradigm.

7.2 CD19

CD19 is an internalizing transmembrane surface protein that is a member of the immunoglobulin superfamily, and is one of the earliest markers of B-cell differentiation. It is not known to be expressed by any cell outside of the B-cell lineage. B-lineage commitment coincides with surface expression of CD19, and, thus, CD19 is found on normal and malignant B cells as early as the pro-B-cell stage (Huh, 2000; Del Nagro; 2005; Bryder, 2010). Unlike other markers, such as CD20 and CD21 (Chu, 2002; Echeverri, 2002; Gervasi, 2004), CD19 is rarely lost during malignant transformation or treatment. CD19 is expressed in almost all B-cell malignancies; and accordingly, CD19 is a standard marker of B-lineage NHL and is found in almost all clinical immunohistochemistry (IHC) and flow cytometry diagnostic panels.

7.3 Denintuzumab Mafodotin

Denintuzumab mafodotin (SGN-CD19A) is an antibody-drug conjugate (ADC) directed against the CD19 antigen. The antibody backbone of denintuzumab mafodotin, hBU12, is a humanized anti-CD19 monoclonal antibody that is chemically conjugated to a synthetic analog (monomethyl auristatin F [MMAF]) of the naturally occurring tubulin-disrupting

drug, dolastatin 10. The maleimidocaproyl linker is used to conjugate MMAF to hBU12 on the cysteine residues that comprise the interchain disulfide bonds of the antibody. An average of 4 MMAF molecules is present on each antibody molecule.

7.3.1 Mechanism of Action

Subsequent to cell surface binding to CD19, denintuzumab mafodotin is internalized and trafficked through the endocytic pathway to reach the lysosomes. Proteolytic degradation of the hBU12 in lysosomes releases the cysteine adduct of the drug linker in the form of cysteine maleimidocaproyl monomethyl auristatin F (cys-mcMMAF), which becomes available for tubulin binding. Interaction between cys-mcMMAF and tubulin disrupts the cellular microtubule network, arrests cells at the G2/M phase of the cell cycle, prevents cell division, and eventually leads to cellular apoptosis. Antitumor activity and immunospecificity of denintuzumab mafodotin have been demonstrated in vitro and in vivo with animal models representing B-lineage NHL and disseminated leukemia.

7.3.2 Preclinical Experience

A complete summary of the preclinical data relevant to denintuzumab mafodotin is provided in the Investigator's Brochure (IB).

7.3.3 Clinical Studies

The safety and efficacy of denintuzumab mafodotin are being evaluated in an ongoing phase 1 dose-escalation tolerability study in patients with relapsed or refractory B-cell NHL (Protocol SGN19A-002). Denintuzumab mafodotin is administered on Day 1 of 3-week cycles (doses 0.5 to 6 mg/kg) or on Day 1 of 6-week cycles (dose 3 mg/kg). In the 62 patients treated to date, including 54 patients with DLBCL, the maximum tolerated dose (MTD) was not exceeded after escalating to 6 mg/kg every 3 weeks. Toxicity profiles and antitumor activity were similar across both schedules. Denintuzumab mafodotin was generally well tolerated, and the most common adverse events of any grade included blurred vision, dry eye, fatigue, and keratopathy. Hematopoietic toxicity and peripheral neuropathy were uncommon. Of the 60 patients evaluable for response, 23 patients (38%) achieved an objective response, including 14 patients (23%) with a complete remission (Moskowitz, 2015). Antitumor activity appeared to be higher in those who achieved an objective response to their most recent therapy (ie, relapsed patients). Of the 25 patients who relapsed to their most recent prior therapy, 15 patients (60%) achieved an objective response, including 10 patients (40%) with a best response of CR.

Please see the IB for complete clinical safety information.

7.4 Clinical Study Rationale

Overall, the rationale to evaluate the administration of denintuzumab mafodotin in combination with RCHOP as well as a substitution in place of vincristine in RCHOP (ie, RCHP) as frontline multiagent chemotherapy is manifold:

- Denintuzumab mafodotin monotherapy has demonstrated preliminary activity in aggressive, relapsed or refractory DLBCL after failure of second-line salvage and beyond. As discussed in Section 7.3.3, of the 60 patients evaluable for response, 38% achieved an objective response with a CR rate of 23% (Moskowitz, 2015). Antitumor activity appeared to be higher in those who achieved an objective response to their most recent therapy; of 25 such patients, 60% achieved an objective response with a CR rate of 40%. Given the activity observed with denintuzumab mafodotin in the relapsed DLBCL setting, there is rationale to support the hypothesis that denintuzumab mafodotin will have substantial single-agent activity in patients with newly diagnosed DLBCL. DLBCL patients with adverse risk factors (IPI score of 3 or higher for patients >60 years of age or an aaIPI score of 2 or 3 for patients who are ≤60 years of age), have poor outcomes with RCHOP therapy and new agents are needed (Section 7.1). It is hypothesized that a treatment approach combining denintuzumab mafodotin with RCHOP may yield an improved CR rate, with the potential to prolong PFS and OS.

- Due to the neurotoxicity profile of vincristine when administered as a component of RCHOP, there is a potential concern for additive neurotoxicity in combination with another microtubule inhibitor, even though clinically denintuzumab mafodotin monotherapy was generally well tolerated and peripheral neuropathy was uncommon. With denintuzumab mafodotin monotherapy, the most common adverse events of any grade included blurred vision, dry eye, fatigue, and keratopathy. Hematopoietic toxicity was infrequent. The expected incidence of peripheral neuropathy with vincristine, delivered as part of RCHOP, is approximately 50%; the majority of neuropathy events are sensory in nature and low grade (Grade 1 or 2). Grade 3 peripheral sensory neuropathy is observed in approximately 10% of patients; Grade 3 peripheral motor neuropathy events have been infrequently reported in the literature and are typically rare in clinical practice (Coiffier 2002; Pfreundschuh 2008). In addition, denintuzumab mafodotin has demonstrated better single agent antitumor activity when compared to that published for vincristine sulfate liposomal injection. Therefore, it is hypothesized that a treatment approach of substituting denintuzumab mafodotin for vincristine in RCHOP (ie, denintuzumab mafodotin plus RCHP) may also yield an improved CR rate with the potential to prolong PFS and OS. Thus, this study will evaluate both (1) the addition of denintuzumab mafodotin to RCHOP, as well as (2) the substitution of denintuzumab mafodotin for vincristine (which has at most a moderate contribution to activity in RCHOP). The latter may be a safer approach than administering the 2 agents concurrently, where doses of one or both agents may be limited by resultant neurotoxicity, without a decline in potential efficacy.

- Nonclinical studies have been conducted to study the effects of denintuzumab mafodotin administered in combination with other single- and multi-agent regimens. The combined cytotoxic effects of denintuzumab mafodotin and a set of small molecule drugs with different mechanisms of action were evaluated in a panel of transformed B-cell lines. Denintuzumab mafodotin was found to be synergistic with several agents, including the DNA alkylating agent bendamustine, the DNA cross-linking agent cisplatin, and the DNA topoisomerase inhibitor etoposide, as well as the anti-CD20 monoclonal antibody rituximab. Murine in vivo studies demonstrated impressive antitumor activity that exceeded that of denintuzumab mafodotin alone in NHL lymphoma models when combined with the therapeutic regimens of rituximab and RCHOP. In inherently denintuzumab mafodotin insensitive tumor xenograft models, the combined antitumor activity of both denintuzumab mafodotin and rituximab, and denintuzumab mafodotin and RCHOP was found to be considerably stronger than either agent or regimen alone in FL and DLBCL models, leading to prolonged tumor delay as well as complete remissions. Similarly, the combinations of denintuzumab mafodotin and CHOP demonstrated stronger antitumor activity in the DLBCL models when compared to denintuzumab mafodotin or CHOP alone. In vitro studies demonstrated that denintuzumab mafodotin internalizes faster and delivers more free drug (cys-mcMMAF) in the presence of rituximab, creating a synergistic combination (Van Epps, 2015).

Taken together, these data support further evaluation of incorporating denintuzumab mafodotin as part of multi-agent front-line therapy such as RCHOP or RCHP and may yield an improvement in the CR rate, as well as PFS and OS benefit, in treatment naive DLBCL or FL Grade 3b patients.

8. STUDY OBJECTIVES

8.1 Primary Study Objectives

- To compare the CR rate at the end of treatment (EOT) in treatment-naive patients with high-intermediate or high-risk systemic DLBCL or FL Grade 3b treated with denintuzumab mafodotin plus RCHOP or RCHP versus RCHOP alone (Part B)

- To assess the safety profile of denintuzumab mafodotin administered in combination with RCHOP or RCHP in treatment-naive patients with high-intermediate or high-risk systemic DLBCL or FL Grade 3b (Part A and Part B)

8.2 Secondary Study Objectives

- To compare event-free survival (EFS) between study arms (Part B)

- To compare PFS between study arms (Part B)

- To compare OS between study arms (Part B)

- To compare the objective response rate (ORR) at EOT between study arms (Part B)

- To compare the duration of objective response and of CR between study arms (Part B)

8.3 Additional Objectives

- To evaluate the pharmacokinetics (PK) of denintuzumab mafodotin administered in combination with RCHOP or RCHP (Parts A and B)

- To evaluate the incidence of antitherapeutic antibodies (ATA) against denintuzumab mafodotin (Parts A and B)

- To assess denintuzumab mafodotin-mediated pharmacodynamic (PD) effects and potential biomarkers of response to denintuzumab mafodotin in combination with RCHOP or RCHP (Parts A and B)

9. INVESTIGATIONAL PLAN

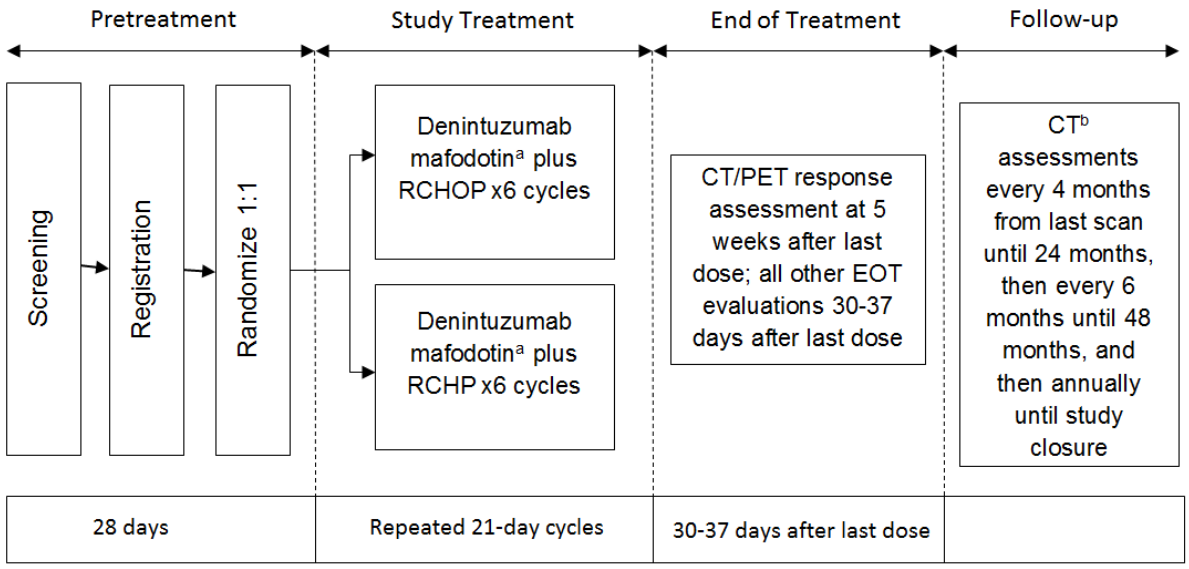
9.1 Overall Study Design and Plan

This is an open-label phase 2 multicenter study of denintuzumab mafodotin in combination with RCHOP or RCHP compared with RCHOP alone as frontline therapy in patients with DLBCL or FL Grade 3b. This study has 2 parts (Part A and Part B). Part A of the study is a safety evaluation of denintuzumab mafodotin in combination with either RCHOP or RCHP. Results from Part A will be used to determine the regimen (RCHOP or RCHP) to be tested in combination with denintuzumab mafodotin in Part B. Part B is a multicenter study designed to evaluate the antitumor activity and safety of denintuzumab mafodotin in combination with either RCHOP or RCHP compared with RCHOP alone.

9.1.1 Part A – Safety Evaluation

In Part A of the study, up to approximately 24 patients will be randomized 1:1 to receive denintuzumab mafodotin plus RCHOP or denintuzumab mafodotin plus RCHP to assess safety in these 2 combination regimens. Patient randomization will be stratified by high-intermediate or high-risk disease (see Section 9.2.1 for definition of high-intermediate and high-risk disease). Study treatment is up to six 21-day cycles of either RCHOP or RCHP combined with up to 3 doses of denintuzumab mafodotin administered on Day 1 of Cycles 1, 3, and 5. The study schema for Part A is depicted in Figure 1.

Figure 1: Part A Study Schema



CT = computed tomography; EOT = end of treatment; PET = positron emission tomography; RCHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCHP = rituximab, cyclophosphamide, doxorubicin, and prednisone

a Administered on Day 1 of Cycles 1, 3, and 5

b Follow-up PET and CT scans required until disease is PET negative; responses will then be followed by CT scans of diagnostic quality. Follow-up assessments continue until disease progression, initiation of a new anti-cancer treatment, death, or study closure, whichever comes first. Survival status follow-up until death or study closure, whichever comes first.

The SMC, comprising the study investigators, medical monitor, and biostatistician, and Sponsor's medical expert, will periodically monitor the safety of patients at predefined interim safety evaluations and at regular intervals during the treatment period. Formal safety evaluations of cumulative data from both treatment groups will be conducted at the following 6 time points in Part A of the study:

- after 6, 12, and 24 patients have completed Cycle 1
- after 6, 12, and 24 patients have completed EOT

At each interim safety evaluation, the SMC will review the cumulative safety data, including the incidence of dose-delaying toxicities (DDTs) that are associated with denintuzumab mafodotin in combination with RCHOP or RCHP, as well as the rates of adverse events of interest such as peripheral neuropathy in each treatment group. A DDT is defined as any study treatment-related toxicity that necessitates a delay of >14 days in the start of RCHOP or RCHP treatment in the next cycle. With respect to hematologic recovery, it is recommended that the next cycle of RCHOP or RCHP be given once the patient's absolute neutrophil count recovers to ≥ 1000/μL and the platelet count recovers to ≥ 75,000/μL, as applicable. Upon its evaluation of the data, the SMC will make one of the following recommendations to the Sponsor:

- continue the trial as planned

- modify the dose of denintuzumab mafodotin in subsequently enrolled patients
- temporarily halt enrollment for additional evaluation

If the SMC determines that the risks outweigh the benefits of the study treatment in both combination regimens, no further patients will be enrolled at that dose and schedule.

The evaluation of the safety and antitumor activity data at the end of Part A will be used to determine the regimen (RCHOP or RCHP) to be tested in combination with denintuzumab mafodotin in Part B. If Grade 3 neuropathy (sensory or motor) is observed in >20% of patients in the denintuzumab mafodotin plus RCHOP treatment group (n = 12), then that combination will have exceeded the stopping criteria for that regimen, and RCHP may be selected for administration in combination with denintuzumab mafodotin in Part B of the study, with the support of the overall safety and antitumor activity data from both arms.

During the treatment period, the SMC may also recommend conducting additional safety analyses or temporarily halting enrollment until an appropriate evaluation of the cumulative safety data, including review of unanticipated safety issues, has been completed.

PET scans and computed tomography (CT) scans of the neck, chest, abdomen, and pelvis with intravenous (IV) and oral contrast, will be assessed at baseline and at EOT. CT scans will be contrast-enhanced (unless contrast is contraindicated) and of diagnostic quality. Follow-up assessments will be performed every 4 months from last scan until 24 months from EOT scan, then every 6 months until 48 months from EOT scan, and then annually until study closure. For all follow-up assessments, both PET and CT scans are required until disease is PET negative; responses will then be followed by CT scans of diagnostic quality only. Follow-up assessments will continue until disease progression, initiation of a new anticancer treatment, or study closure, whichever comes first.

Results from a bone marrow biopsy will be recorded at screening and/or EOT, and at any time on study if a bone marrow biopsy is performed as part of standard of care. A CT scan of diagnostic quality will be performed at the time of suspected clinical progression. Survival status follow-up will continue until patient death or study closure, whichever comes first.

9.1.2 Part B – Randomized, Open-Label Phase 2

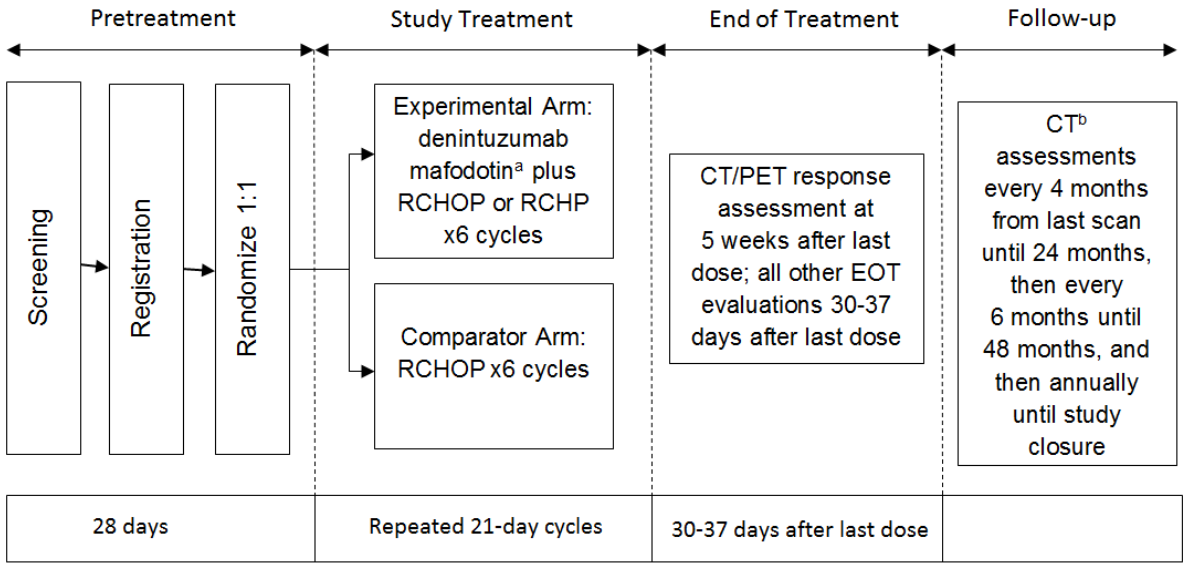
Part B of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of denintuzumab mafodotin in combination with either RCHOP or RCHP (Experimental Arm) compared with RCHOP alone (Comparator Arm). Approximately 136 patients will be randomized 1:1 to either the Experimental or Comparator Arm. Randomization will be stratified by high-intermediate or high-risk disease and by cell of origin (COO). The study treatments per arm are summarized in Table 9-1. The study schema for Part B is depicted in Figure 2.

Table 9-1: Study Treatments by Arm in Part B

Part B Study Treatment	Treatment Arm	
	Experimental	Comparator
RCHOP		X
RCHOP or RCHP (pending Part A analysis) plus denintuzumab mafodotin	X	

RCHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RCHP = rituximab, cyclophosphamide, doxorubicin, and prednisone

Figure 2: Part B Study Schema



CT = computed tomography; EOT = end of treatment; PET = positron emission tomography; RCHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCHP = rituximab, cyclophosphamide, doxorubicin, and prednisone

a Administered on Day 1 of Cycles 1, 3, and 5

b Follow-up PET and CT scans required until disease is PET negative; responses will then be followed by CT scans of diagnostic quality. Follow-up assessments continue until disease progression, initiation of a new anti-cancer treatment, death, or study closure, whichever comes first. Survival status follow-up until death or study closure, whichever comes first.

The SMC will continue to monitor the safety of the combination of denintuzumab mafodotin and either RCHOP or RCHP at predefined interim safety evaluations and during the treatment period. The SMC will review cumulative safety data after 10 patients in each arm (N=approximately 20) have completed treatment, after 20 patients in each arm (N=approximately 40) have completed treatment, and after all patients in both arms have completed treatment.

During the treatment period, the SMC may also recommend conducting additional safety analyses or temporarily halting enrollment until an appropriate evaluation of the cumulative safety data, including review of unanticipated safety issues, has been completed.

PET scans and CT scans of the neck, chest, abdomen, and pelvis with IV and oral contrast,

will be assessed at baseline and at EOT. CT scans will be contrast-enhanced (unless contrast is contraindicated) and of diagnostic quality. Follow-up assessments will be performed every 4 months from the last scan until 24 months after the EOT scan, then every 6 months until 48 months after the EOT scan, and then annually until study closure. For all follow-up assessments, both PET and CT scans are required until disease is PET negative; responses will then be followed by CT scans of diagnostic quality only. Follow-up assessments will continue until disease progression, initiation of a new anticancer treatment, or study closure, whichever comes first.

Results from a bone marrow biopsy will be recorded at screening and/or at EOT, and at any time on study if a bone marrow biopsy is performed as part of standard of care. A CT scan of diagnostic quality will be performed at the time of suspected clinical progression. Survival status follow-up will continue until patient death or study closure, whichever comes first.

9.2 Discussion and Rationale for Study Design

The FDA's Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA, 2007) was considered prior to the selection of primary and secondary endpoints for this study. The primary endpoint for this study is the CR rate at EOT as assessed by the investigator utilizing the Lugano classification criteria (Cheson, 2014). In this population where the ability to achieve a CR directly influences long-term outcomes, CR is the most appropriate endpoint to assess early treatment benefit. Complete response, which provides a direct comparison of the effectiveness of each treatment regimen, is directly correlated with the long-term clinical benefit of prolonging PFS and OS, and minimizes potential biases in interpretation. Therefore, CR rate is the most appropriate primary endpoint in this phase 2, randomized, open-label clinical trial.

The endpoints of this study are appropriate for evaluating efficacy and safety in this patient population. The frequency of blood draws for evaluation of PK is appropriate based on prior experience with denintuzumab mafodotin.

9.2.1 Method of Assigning Patients to Treatment Groups

In Part A, following informed consent and screening, patients will be randomly assigned to 1 of 2 treatment regimens combined with denituzumab mafodotin in a 1:1 ratio using a centralized randomization system. Randomization in this part of the study is for the purpose of evaluating the safety of denituzumab mafodotin in combination with RCHOP versus RCHP. Patients will be stratified according to high-intermediate risk (IPI =3 for age >60 years and aaIPI =2 for age ≤60 years) versus high-risk (IPI =4 or 5 for age >60 years and aaIPI =3 for age ≤60 years) disease based on standard IPI for patients >60 years of age or aaIPI for patients ≤60 years of age.

In Part B, following informed consent and screening assessments, patients will be randomly assigned to 1 of 2 arms in a 1:1 ratio using a centralized randomization system.

Randomization in this part of the study is for the purpose of evaluating the efficacy and safety of denituzumab mafodotin in combination with either RCHP or RCHOP versus RCHOP alone. Randomization will be stratified by the following 2 factors:

- COO by local IHC assessment per Hans algorithm (germinal center B [GCB] versus non-GCB)

- high-intermediate risk versus high-risk disease based on standard IPI for patients >60 years of age and aaIPI for patients ≤60 years of age

Randomization strata are specified in Section 9.4.11. Randomization procedures are detailed in the study manual.

9.2.2 Rationale for Selection of Doses

In the ongoing phase 1 dose-escalation study in B-lineage NHL (Protocol SGN19A-002), denintuzumab mafodotin has been administered at dose levels from 0.5 mg/kg up to 6 mg/kg IV every 3 weeks. Denintuzumab mafodotin has been generally well tolerated, and the MTD was not exceeded at 6 mg/kg every 3 weeks. Following characterization of a mean terminal-phase half-life for denintuzumab mafodotin of approximately 2 weeks, the safety and antitumor efficacy of 3 mg/kg administered once every 6 weeks was evaluated. The toxicity profiles and efficacy were similar across both schedules.

The dose of denintuzumab mafodotin selected for this study (3 mg/kg) is half of the maximum dose tested of 6 mg/kg. Denintuzumab mafodotin given every 3 weeks or every 6 weeks has demonstrated antitumor activity in 60 efficacy-evaluable patients with an ORR of 38% and CR rate of 23% (Moskowitz, 2015). While responses were seen at all dose levels >0.5 mg/kg, there is very limited experience for the 1 mg/kg (n=3) and 2 mg/kg (n=2) dose levels. Following expansion, patients treated at 3 mg/kg every 3 weeks (n=14) had the same rate of response (CR/partial remission) as those at the higher dose levels (unpublished data). A similar response rate was observed in patients treated with 3 mg/kg every 6 weeks (n=10) (4 CR out of 9 efficacy-evaluable patients) (Moskowitz, 2015). Additionally, the 3 mg/kg dose level was well tolerated with fewer Grade 3 or 4 hematological adverse events than that observed with higher doses. Thus, 3 mg/kg every 6 weeks is expected to be a safe and efficacious dose of denintuzumab mafodotin for evaluation in combination with RCHOP or RCHP.

The dose of rituximab (375 mg/m^2) is the standard approved dose for patients with previously untreated DLBCL when given in combination with CHOP or other anthracycline-based chemotherapy regimens. Additionally, the selected dose and schedule have been safely and effectively employed in combination with various single- and multi-agent chemotherapy regimens for this patient population (Gisselbrecht, 2012; Tilly, 2012). In theory, rituximab and denintuzumab mafodotin are partly eliminated via binding to CD19/CD20-positive B-cells, therefore changes in this cell population could potentially alter the PK of these molecules. In patients with relapsed/refractory NHL,

denintuzumab mafodotin demonstrated linear PK in the dose range of 1 to 6 mg/kg every 3 weeks. However, treatment naïve NHL patients generally have more normal circulating B-cells than relapsed/refractory NHL patients. Therefore, it is expected that in the current study of treatment naïve NHL patients, part of the rituximab and denintuzumab mafodotin doses will bind to the normal circulating B-cells, resulting in potentially reduced systemic exposures. However, dose adjustment of rituximab based on pre-treatment CD19 count is not necessary (Rituxan Prescribing Information, 2013). The reduction in denintuzumab mafodotin exposure is expected to be mild and transient because the dose of denintuzumab mafodotin (3 mg/kg) may be high enough to overcome this target-mediated disposition. Furthermore, both denintuzumab mafodotin and rituximab deplete the normal circulating B-cells after a single dose so that these are unlikely to affect the PK of denintuzumab mafodotin beyond the first cycle of treatment.

The doses of cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and vincristine (1.4 mg/m^2) (dose capped at 2 mg total) are the standard doses when given in a combination setting that will be administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1 to 5 of every 21-day cycle. Additional considerations for these dosing regimens include the following:

- Cyclophosphamide is excreted unchanged in the urine (approximately 10% to 20%) and converted to active metabolite(s) (approximately 75%) by multiple cytochrome P450 (CYP) enzymes, with CYP2B6 showing the highest activity. The active metabolite(s) can undergo oxidation/inactivation by aldehyde dehydrogenases (Cyclophosphamide Prescribing Information, Baxter, March 2013).
- Doxorubicin is eliminated predominantly by metabolism (by CYP3A4 and CYP2D6) and biliary excretion (by P-glycoprotein 1) (Doxorubicin Prescribing Information, Pfizer, October 2013).
- Vincristine is predominantly eliminated by the liver either by CYP 3A metabolism or biliary excretion (Vincristine Prescribing Information, Hospira, July 2013).
- Prednisone is completely converted by CYP3A4 to the active metabolite prednisolone, which is further metabolized mainly in the liver and excreted in the urine as sulfate and glucuronide conjugates (Prednisone Prescribing Information, Horizon Pharma USA, June 2013).

Cys-mcMMAF at the concentration of 0.1 µM was a substrate of multiple transporters including P-glycoprotein 1 in vitro. Cys-mcMMAF was metabolically stable in human microsomal preparations and, at concentrations up to 1 µM (roughly 100-fold higher than circulating levels after a 3 mg/kg dose of denintuzumab mafodotin), did not inhibit multiple CYP enzymes including CYP2B6, CYP2D6, or CYP3A4/5, nor induce CYP2B6 or CYP3A4/5 in vitro (denintuzumab mafodotin IB).

Based on known metabolism and elimination information for denintuzumab mafodotin (ADC), cys-mcMMAF, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, the risk of drug-drug interactions between RCHOP/RCHP components and denintuzumab mafodotin is considered low, therefore standard RCHOP/RCHP doses are considered appropriate.

9.2.3 Blinding

This study is not blinded.

9.3 Patient Population

Patients cannot be enrolled or randomized before all inclusion and exclusion criteria (including test results) are met.

9.3.1 Inclusion Criteria

Patients **MUST** satisfy all of the following entry criteria before they will be allowed to participate in the study:

1. treatment-naive patients with histologically confirmed systemic de novo or transformed DLBCL (from follicular or marginal zone lymphoma), or FL Grade 3b; patients must have high-intermediate or high-risk disease based on standard IPI (score ≥3 for patients >60 years of age) or aaIPI (score 2 or 3 for patients ≤60 years of age), and stage IAX (bulk defined as single lymph node mass >10 cm in diameter)–IV disease
2. tumor tissue available from most recent biopsy to determine COO by IHC using Hans algorithm, as assessed by site pathologist. In addition, tumor tissue must be submitted for central pathological review during the trial; if such tissue is not available, a fresh biopsy must be obtained.
3. fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) based on the Lugano classification criteria (Cheson, 2014) (Appendix 18.2), and measurable disease of at least 1 nodal lesion greater than 1.5 cm in the longest diameter or a non-nodal tumor lesion greater than 1.0 cm in the longest diameter by CT, as assessed by the site radiologist
4. an Eastern Cooperative Oncology Group (ECOG) performance status ≤2
5. age 18 years or older
6. patients must have the following baseline laboratory data:
   a. bilirubin ≤1.5 × upper limit of normal (ULN) or ≤3 × ULN for patients with Gilbert's disease or documented hepatic involvement with lymphoma
   b. alanine aminotransferase and aspartate aminotransferase ≤3 × ULN or ≤5 × ULN for patients with documented hepatic involvement with lymphoma
   c. creatinine clearance ≥30mL/min (calculated using the Cockcroft-Gault formula)
   d. absolute neutrophil count ≥1000/µL (unless documented bone marrow involvement with lymphoma, in which case ANC ≥500/µL)
   e. platelet count ≥75,000/µL (unless documented bone marrow involvement with lymphoma, in which case platelets ≥50,000/µL)
   f. urine protein:creatinine ratio (UPC) ratio <1
7. females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin pregnancy test result within 7 days prior to the first dose of study drug. Females of non-childbearing potential are those who are postmenopausal for more

than 1 year or who have had a bilateral tubal ligation, hysterectomy, or bilateral oophorectomy.
8. females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraception methods during the study and for 12 months following the last dose of study drug, as well as 12 months following the last dose of rituximab
9. patients must provide written informed consent

9.3.2 Exclusion Criteria

If any of the following apply, the patient **MUST NOT** enter the study:

1. previous history of treated indolent lymphoma. Newly diagnosed patients with DLBCL who are found to have small cell infiltration of the bone marrow or other diagnostic material (representing a discordant lymphoma) are eligible.
2. history of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 3 years (exceptions include non-melanoma skin cancer, curatively treated localized prostate cancer, ductal carcinoma in situ, and cervical carcinoma in situ by biopsy or a squamous intraepithelial lesion by papanicolaou smear)
3. history of progressive multifocal leukoencephalopathy (PML)
4. cerebral/meningeal disease related to the underlying malignancy
5. baseline peripheral neuropathy ≥Grade 2 (per the National Cancer Institute's [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03) or patients with the demyelinating form of Charcot-Marie-Tooth syndrome
6. left ventricular ejection fraction less than 45% or symptomatic cardiac disease (including symptomatic ventricular dysfunction, symptomatic coronary artery disease, and symptomatic arrhythmias), or myocardial infarction within the past 6 months or previous treatment with complete cumulative doses of doxorubicin or other anthracyclines
7. patients with the following ocular conditions:
    a. corneal disorders: corneal dystrophies, history of corneal or limbal stem cell transplantation (including endothelial keratoplasty), evidence of limbal stem cell deficiency (ie, deep pannus, poor epithelial healing)
    b. monocular vision (ie, best corrected visual acuity ≥20/200 in one eye)
    c. active ocular disorders requiring treatment such as corneal ulcer, herpetic keratitis, uncontrolled glaucoma (stable topical medication is allowed), uncontrolled diabetic retinopathy, evolving wet macular degeneration, iritis or vitritis, papilledema, or optic nerve disorder
8. any active ≥Grade 3 (per the NCI CTCAE, Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study treatment. Routine antimicrobial prophylaxis is permitted.
9. current therapy with other systemic anti-neoplastic or investigational agents
10. females who are breastfeeding
11. known hypersensitivity to any excipient contained in any of the drug formulations of study treatments
12. patients with known urinary outflow obstruction

13. patients with a positive polymerase chain reaction assay who have also tested positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody; patients with a negative polymerase chain reaction assay are permitted with appropriate anti-viral prophylaxis
14. known or suspected active hepatitis C infection or known human immunodeficiency virus infection

9.3.3 Withdrawal and Replacement of Patients

In accordance with the Declaration of Helsinki and applicable regulations, a patient 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.

PRA or their designee must be notified if a patient is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the patient's medical records and the electronic Case Report Form (eCRF).

9.3.3.1 Discontinuation of Study Drug

A patient's treatment with study drug may be discontinued for any of the following reasons:

- completed treatment
- progressive disease
- adverse event
- investigator decision
- patient decision, non-adverse event
- study termination by Sponsor
- other, non-adverse event

The reason for treatment discontinuation will be recorded in the clinical records and the eCRF. All patients who discontinue treatment will undergo an EOT visit (see Section 10.5) and EOT response assessments (see Section 10.6). These patients will remain on study and continue to be followed for survival and disease status (see Section 10.7) unless they withdraw from study (see Section 9.3.3.2). Withdrawn/discontinued patients will not be replaced.

9.3.3.2 Patient Withdrawal from Study

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

- patient withdrawal of consent
- study termination by Sponsor
- lost to follow-up
- death
- other

Patients who withdraw consent will not be further contacted.

9.3.3.3 Replacement of Patients

Patients who discontinue from treatment or study will not be replaced.

9.4 Treatment

9.4.1 Treatment Administered

In Part A, patients will be randomized 1:1 to receive denintuzumab mafodotin plus RCHOP or denintuzumab mafodotin plus RCHP. In Part B, patients will be randomized 1:1 to receive denintuzumab mafodotin plus either RCHOP or RCHP, or RCHOP alone.

9.4.2 Investigational Study Drug

Denintuzumab mafodotin, the investigational agent under study in this protocol, is an ADC consisting of the anti-CD19 monoclonal antibody hBU12 specific for human CD19 conjugated to MMAF, a synthetic analog of the naturally occurring microtubule-disrupting drug, dolastatin 10.

Detailed information describing the preparation, administration, and storage of denintuzumab mafodotin is located in the Pharmacy Manual.

9.4.2.1 Description

Denintuzumab mafodotin is a sterile, preservative-free, white to off-white lyophilized cake or powder for reconstitution for IV administration. Denintuzumab mafodotin is supplied by Seattle Genetics in single-use glass vials. Each drug product vial contains [redacted]. Drug product vials are labeled with a nominal content of 20 mg/vial. Each vial contains 22.5 mg of denintuzumab mafodotin. Enough overfill is included to allow for 20 mg of denintuzumab mafodotin to be withdrawn for use. When reconstituted with 4.5 mL Water for Injection, United States Pharmacopeia, the denintuzumab mafodotin product consists of 5 mg/mL. The pH of the reconstituted product is approximately 6.0. Before administration, reconstituted denintuzumab mafodotin must be diluted.

9.4.2.2 Dose and Administration

Denintuzumab mafodotin at 3 mg/kg will be administered every 6 weeks via IV infusion given over approximately 30 minutes to all patients in Parts A and to patients in the Experimental Arm in Part B. The dose of denintuzumab mafodotin may be modified upon recommendation of the SMC. Dosing of denintuzumab mafodotin is based on patient weight obtained according to the

institutional standard; however, doses must be adjusted for patients who have a ≥10% change in weight from baseline. If rounding, doses must be rounded to the nearest milligram.

Denintuzumab mafodotin should be administered immediately after and on the same day as rituximab (the first component of RCHOP and RCHP). Denintuzumab mafodotin will be administered on Day 1 of Cycles 1, 3, and 5 within approximately 30 minutes of completing treatment with rituximab (see Section 9.4.3.3 for more details). In the absence of infusion toxicities, the infusion rate for all patients should be calculated in order to achieve a 30-minute infusion period (window 20 to 45 minutes).

DENINTUZUMAB MAFODOTIN MUST NOT BE ADMINISTERED AS AN IV PUSH OR BOLUS. Denintuzumab mafodotin must be administered through a dedicated IV line without an in-line filter. Denintuzumab mafodotin cannot be mixed with other medications.

The patient should be observed for 60 minutes following the first infusion. During this observation period, the IV line should remain to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institution standards.

9.4.2.3 Storage and Handling

Single-use vials containing denintuzumab mafodotin must be stored under refrigeration set to 2°C to 8°C in an appropriate locked room accessible only to the pharmacist, investigator, or a duly designated person.

Chemical and physical stability of the reconstituted drug product has been demonstrated for 24 hours at 2°C to 8°C and at room temperature. However, denintuzumab mafodotin drug product does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials should be used immediately. After exposure to ambient temperature and light conditions, the prepared dosing solution should be administered within 8 hours if stored at ambient temperature. If not used immediately, or if it is necessary to extend the post-reconstitution hold time, the prepared dosing solution should be stored at 2°C to 8°C. The in-use storage of opened and reconstituted vials or prepared dosing solution should not be longer than 24 hours after initial vial reconstitution under refrigeration set to 2°C to 8°C. Drug product vials and solutions should be protected from light until the time of use. Reconstituted vials and solutions must not be shaken.

Drug accountability instructions are provided in the Pharmacy Manual.

9.4.2.4 Packaging and Labeling

Denintuzumab mafodotin is supplied in single-use vials. Drug product vials may be labeled as denintuzumab mafodotin, the United States adopted name and the International Nonproprietary Name, or as SGN-CD19A, the compound code; the 2 names can be used interchangeably.

9.4.2.5 Preparation

Before administration, denintuzumab mafodotin must be reconstituted and diluted. Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets. Detailed drug preparation instructions are provided in the Pharmacy Manual.

9.4.3 Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

In Part A, RCHOP or RCHP is administered with denintuzumab mafodotin. In Part B, either RCHOP or RCHP (depending on the evaluation of data from Part A) is administered with denintuzumab mafodotin in the Experimental Arm, or RCHOP is administered alone in the Comparator Arm.

9.4.3.1 Description

RCHOP is a standard chemo-immunotherapy regimen consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. RCHP is a modified version that omits vincristine. Rituximab is a CD20-directed cytolytic antibody. Cyclophosphamide is a nitrogen mustard alkylating agent. Doxorubicin is a cytoxic anthracycline antibiotic. Vincristine is a vinca alkaloid with a mechanism of action related to the inhibition of microtubule formation in the mitotic spindle. Prednisone is a synthetic corticosteroid.

9.4.3.2 Method of Procurement

Agents contained in the RCHOP regimen are commercially available and approved by the United States FDA and other regulatory agencies for use in treating patients with multiple types of cancer.

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone will be supplied by the study site and billed to patients and/or their third-party payer (insurance, a healthcare provider, or applicable government program).

9.4.3.3 Dose and Administration

In Part A, study treatment is six 21-day cycles of either RCHOP or RCHP combined with 3 doses of denintuzumab mafodotin administered on Day 1 of Cycles 1, 3, and 5. The sequence of administration of the different components of the combination therapy should be the following: rituximab administration should be the first component of RCHOP/RCHP; denintuzumab mafodotin administration should be initiated approximately 30 minutes, but no longer than 60 minutes, after the completion of rituximab on Day 1; approximately 30 minutes after the completion of denintuzumab mafodotin the remaining components CHOP or CHP should be administered in an order per institutional standard of care.

In Part B of the Experimental Arm, study treatment is six, 21-day cycles of either RCHOP or RCHP (as determined following evaluation of the safety and efficacy data from Part A) with 3 doses of denintuzumab mafodotin administered on Day 1 of Cycles 1, 3, and 5. The sequence of administration of the different components of the combination therapy should be the same as specified in Part A in the paragraph above. Study treatment in the Comparator Arm is 6 cycles of RCHOP alone; rituximab should be administered on Day 1 as the first component, while the remaining components of RCHOP may be administered as per institutional standard of care.

RCHOP: rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (dose capped at 2 mg total) will be administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1 to 5 of every 21-day cycle.

RCHP: rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, and doxorubicin 50 mg/m^2 will be administered IV on Day 1 of every 21-day cycle together with prednisone 100 mg administered orally on Days 1 to 5 of every 21-day cycle.

Dosing should be based on the patient's baseline (predose, Cycle 1 Day 1) height and weight or per institutional standards at the site.

9.4.3.4 Storage and Handling

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone should be stored and handled per their package inserts.

9.4.3.5 Packaging and Labeling

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone are commercially available in the US.

9.4.3.6 Preparation

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone should be prepared per their package inserts.

9.4.4 Required Premedication and Postmedication

Routine premedication is not necessary for the prevention of infusion-related reactions before the first dose of denintuzumab mafodotin. However, patients who have a Grade 1 or Grade 2 infusion-related reaction may receive subsequent denintuzumab mafodotin infusions with premedication as described in Section 9.4.7. Patients who have a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with denintuzumab mafodotin at the discretion of the investigator after discussion with the Sponsor.

Acetaminophen and an antihistamine should be given within 15 to 90 minutes before initiating the rituximab infusion. Additional premedications, including steroids, may be given prior to the rituximab infusion in accordance with the rituximab package insert, institutional standard of care, or as clinically indicated.

There is no protocol-required pre- or post-medications for cyclophosphamide, doxorubicin, vincristine or prednisone. Routine anti-emetic prophylaxis regimen should be administered with each cycle of RCHOP or RCHP per institutional standard.

Patients should be individually evaluated to assess the need for tumor lysis prophylaxis prior to the first dose of study treatment. Patients should receive prophylaxis as appropriate per the institutional standards.

9.4.5 Prophylactic Steroid Eye Drops for Denintuzumab Mafodotin

Prophylactic steroid eye drops must be administered daily for 7 days with each dose of denintuzumab mafodotin. Eye drops should consist of prednisolone 1%, or equivalent, administered 4 times daily, 1 drop in each eye. Prophylaxis is recommended to begin 1 day prior to each dose of denintuzumab mafodotin.

Omission or discontinuation of prophylactic steroid eye drops may be allowed under certain circumstances (eg, in the setting of intolerability, contraindication, or toxicity secondary to steroid eye drops) upon discussion with the medical monitor. The use of steroid eye drops for the treatment of ocular toxicity and dose modifications of denintuzumab mafodotin for corneal events are described in Section 9.4.9.1 and Table 9-3. See Section 12.5 for the ocular safety monitoring plan.

Patients should avoid use of contact lenses while on denintuzumab mafodotin.

9.4.6 Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be collected from Day 1 (predose) through the safety reporting period (Section 12.1.3). Any concomitant medication given for a study protocol-related adverse event should be recorded from the time of informed consent.

9.4.6.1 Required Concomitant Therapy

Patients with a negative hepatitis B PCR assay who also tested positive for hepatitis B surface antigen and/or hepatitis B core antibody must begin antiviral prophylaxis prior to receiving study treatment and continue for at least 6 months following the completion of study treatment, per institutional standard. Patients receiving antiviral prophylaxis should be regularly monitored for viral reactivation by PCR per institutional standard.

See Section 9.4.4 for required rituximab pre- and post-medications. See Section 9.4.5 for required denintuzumab mafodotin prophylactic steroid eye drops.

9.4.6.2 Allowed Concomitant Therapy

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.

Routine infectious prophylaxis for Pneumocystis jiroveci pneumonia should be considered for all patients per standard of care. In addition, the JNCCN 2012 guideline for the prevention and treatment of cancer-related infections is recommended (Baden, 2012).

Routine prophylaxis with vaccines that do not contain live micro-organisms is permitted. However, the administration of live vaccines (especially yellow fever vaccine) should be avoided.

The use of transfusions, platelet and/or colony-stimulating factors per the American Society of Clinical Oncology guideline for the use of white blood cell growth factors is recommended for the management of neutropenia and febrile neutropenia (Smith, 2015).

Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the investigator.

The use of colony-stimulating factors and/or chemotherapy for stem-cell collection to enable a future autologous stem cell transplant (SCT) is permitted per institutional standard. Chemo-mobilization of stem cells is only permitted after EOT procedures are completed.

Consolidative radiotherapy or SCT may be given at the investigator's discretion after EOT procedures are completed. At least 6 cycles of study treatment should be given prior to initiating post-treatment consolidative radiotherapy or SCT.

Any other treatment (not explicitly excluded) considered necessary for the subject's welfare may be given at the discretion of the Investigator. Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dates of administration and reasons for use.

9.4.6.3 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy from Day 1 through EOT (the treatment phase of the study). Exceptions are noted in Section 9.4.6.2.

9.4.7 Management of Infusion Reactions

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

Infusion-related reactions may occur during the infusion of denintuzumab mafodotin. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for infusion-related reactions.

- Patients who have a Grade 1 or Grade 2 infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 30 to 60 minutes prior to each infusion or according to institutional standards.

- Patients who have a Grade 3 infusion-related reaction may potentially receive additional treatment with denintuzumab mafodotin at the discretion of the investigator after discussion with the Sponsor.

- If a Grade 4 infusion-related reaction occurs, denintuzumab mafodotin administration should be immediately discontinued. It is recommended that for Grade 4 infusion reactions that it be permanently discontinued. Patients may potentially receive additional treatment with denintuzumab mafodotin at the discretion of the investigator after discussion with the Sponsor.

- If anaphylaxis occurs, denintuzumab mafodotin administration should be immediately and permanently discontinued.

See Section 12.1.2 for details regarding recording adverse events.

9.4.8 Management of Suspected Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy has been associated with rituximab treatment (Rituxan Prescribing Information, 2013) and has not been observed with denintuzumab mafodotin. Signs and symptoms of PML may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia.

If PML is suspected, hold further study treatment (RCHOP/RCHP and denintuzumab mafodotin) and undertake a diagnostic work-up including (but not limited to):

- neurologic examinations, as warranted

- brain radiologic features by magnetic resonance imaging
- PCR analysis: John Cunningham virus DNA detectable in cerebrospinal fluid

If PML is confirmed, permanently discontinue study treatment with denintuzumab mafodotin and rituximab.

9.4.9 Dose Modifications

Dose modifications of rituximab, cyclophosphamide, doxorubicin, vincristine, or prednisone due to hematologic and non-hematologic toxicity are allowed per institutional standards and according to the product-specific United States Prescribing Information, or other relevant country-specific package insert, at the discretion of the investigator. Permitted dose modifications include discontinuation of a treatment component.

Myelosuppression is an expected consequence of RCHOP/RCHP chemo-immunotherapy and should not be used as the basis for dose reduction or elimination of denintuzumab mafodotin. All patients may receive growth factor support to shorten the duration of neutropenia. If adequate myeloid recovery has not occurred per institutional standard of care, initiation of the next cycle may be postponed. Administration of Cycle 2 onwards should not be delayed if there has been adequate recovery of peripheral blood counts (ie, it is recommended that absolute neutrophil count is ≥800/μL and platelets is ≥50,000/μL).

See Table 9-2 for the recommended vincristine dose modifications for treatment-associated neuropathy. Doses reduced for treatment-related neuropathy should not be re-escalated without discussion with the sponsor.

Table 9-2: Recommended Vincristine Dose Modifications for Treatment-associated Neuropathy

Grade[a] of Treatment-Associated Neuropathy	Recommended Dose Modification	
	Sensory Neuropathy	Motor Neuropathy
1	Continue study treatment at same dose level	Continue study treatment at same dose level
2	Continue study treatment at same dose level	Reduce dose levels of vincristine[a]
3	Hold vincristine; restart vincristine[b] at reduced dose after recovery to Grade 1	Discontinue treatment with vincristine
4	Discontinue treatment with vincristine	Discontinue treatment with vincristine

[a] Severity of grade is per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
[b] The reduced dose of vincristine is 1 mg.

If RCHOP or RCHP chemo-immunotherapy will be delayed at the start of the subsequent cycle due to myelosuppression or other DDT, then denintuzumab mafodotin infusion will be delayed as well. A delay of more than 14 days in starting RCHOP or RCHP in Cycles 2 and

beyond is discouraged; delays of more than 21 days are not allowed without discussion with the medical monitor.

If RCHOP or RCHP chemo-immunotherapy is discontinued in its entirety, no further denintuzumab mafodotin will be given and the patient will be discontinued from study treatment.

Denintuzumab mafodotin infusion may be delayed at the start of Cycle 3 or 5 due to ocular toxicity (see Section 9.4.9.1). Per-patient dose modifications of denintuzumab mafodotin are permitted upon discussion with the medical monitor as described in Section 9.4.9.1. In the absence of myelosuppression or other DDT, RCHOP or RCHP chemo-immunotherapy should be administered as planned on Day 1 of 3-week cycles.

9.4.9.1 Dose Modifications for Ocular Events

Ocular adverse events are assessed as either ocular symptoms or corneal changes observed on ocular examination and are graded according to a modified CTCAE Version 4.03 scheme (Appendix 18.3). Table 9-3 describes the recommended evaluations, treatment, and dose modifications for denintuzumab mafodotin associated ocular toxicity.

Per-patient dose delays and/or reductions of denintuzumab mafodotin are permitted in the event of Grade 3 ocular symptoms or Grade 4 corneal changes. Denintuzumab mafodotin dosing should be held until ocular symptoms recover to ≤Grade 2 or corneal changes recover to ≤Grade 3. The more conservative evaluation, treatment, and dose modification should apply in cases of simultaneous ocular symptom and corneal change toxicities. Dose modifications must be discussed with the medical monitor; deviations from the recommended dose modifications must be approved by the medical monitor.

In the event of ocular symptoms (ie, dry eyes), preservative-free artificial tears may be administered up to every 2 hours, as needed.

Steroid eye drops administered for the treatment of ≥Grade 2 ocular symptoms or ≥Grade 1 corneal changes should contain prednisolone 1% (or equivalent). The frequency and duration of steroid eye drop administration for the treatment of ocular toxicity is per the discretion of the treating physician. However, it is recommended that the initial frequency should be at least 6 times per day. Treatment can be supplemented with topical steroid ointment applied overnight depending on severity.

See Section 12.5 for additional details of the ocular safety monitoring plan. Refer to Appendix 18.3 for information regarding the grading of ocular events related to the cornea.

Table 9-3: Evaluation, Treatment, and Dose Modifications in the Event of Ocular Toxicity Associated with Denintuzumab Mafodotin Administration

CTCAE[a]	Evaluation and Treatment	Dose Modifications[b]
Ocular Symptoms		
Grade 1	Start administration of preservative-free artificial tears	Continue treatment with denintuzumab mafodotin without interruption or dose reduction.
Grade 2	Obtain ophthalmologic evaluation; change from a prophylactic schedule with steroid eye drops to a treatment schedule (1% prednisolone or equivalent)	Continue treatment with denintuzumab mafodotin without interruption or dose reduction.
Grade 3	Same as Grade 2	Hold denintuzumab mafodotin and discuss with the medical monitor. If ocular symptom (in the absence of Grade 4 corneal findings) resolves to ≤Grade 2 within 7 days after the start of the current cycle of combination treatment, denintuzumab mafodotin may be resumed at the pre-hold dose level or with a dose reduction upon approval of the medical monitor. If ocular symptom does not resolve to ≤Grade 2 within 7 days after the start of the current cycle of combination treatment, skip dose of denintuzumab mafodotin for this cycle and, with the medical monitor, re-evaluate the timing of denintuzumab mafodotin administration at the start of the next cycle.
Corneal Changes (diagnosed by ocular exam)		
Grade 1–3	Change from a prophylactic schedule with steroid eye drops to a treatment schedule (1% prednisolone or equivalent). Follow-up per protocol or more frequently as suggested by ophthalmologist.	Continue treatment with denintuzumab mafodotin without interruption or dose reduction.
Grade 4	Same as Grade 3	Hold denintuzumab mafodotin and discuss with the medical monitor. If corneal change resolves to ≤Grade 3 within 7 days after the start of the current cycle of combination treatment, denintuzumab mafodotin may be resumed at the pre-hold dose level or with a dose reduction upon approval of the medical monitor. If corneal change does not resolve to ≤Grade 3 within 7 days after the start of the current cycle of combination treatment, skip dose of denintuzumab mafodotin for this cycle and, with the medical monitor, re-evaluate the timing of denintuzumab mafodotin administration at the start of the next cycle.

CTCAE = Common Terminology Criteria for Adverse Events

a Modified CTCAE grading scheme; see Appendix 18.3.

b Discuss dose modifications with the medical monitor; deviations from the recommended dose modifications must be approved by the medical monitor.

9.4.10 Treatment Compliance

Denintuzumab mafodotin, RCHOP, and RCHP will be administered by qualified study site staff, and administration information will be recorded in source documents and the eCRF.

9.4.11 Assignment to Treatment

In Part A, patients will be randomized 1:1 to denintuzumab mafodotin plus RCHOP or denintuzumab mafodotin plus RCHP. Patient randomization will be stratified by high-intermediate risk or high-risk disease based on IPI (if age >60 years) or aaIPI (if age ≤60 years).

In Part B, patients will be randomized 1:1 to receive denintuzumab mafodotin in combination with either RCHOP or RCHP or RCHOP alone. Randomization will be stratified by high-intermediate risk or high-risk disease and by COO per site pathologist.

After eligibility is determined patients are randomized within 1 business day prior to the planned first dose of Cycle 1, Day 1 of study treatment in Part A and Part B. Patients will be randomly assigned to a treatment arm using a centralized randomization system.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed

Primary Efficacy Variable:

The primary efficacy endpoint is the CR rate at the EOT as determined by investigators.

CR rate is defined as the proportion of patients who achieve complete metabolic response (CMR) by PET/CT or CR by CT scans only. Disease response will be assessed by the investigator, based on the Lugano Classification Revised Staging System for malignant lymphoma (Cheson, 2014) (Appendix 18.2). Patients whose disease responses are not evaluable/not evaluated will be regarded as non-responders for calculating the CR rate.

Secondary Efficacy Variables:

The secondary efficacy endpoints are the following:

- EFS
- PFS
- OS
- ORR following the completion of EOT
- duration of objective response
- duration of CR

See Section 13.6.4 for definitions.

9.5.2 Pharmacokinetic and Antitherapeutic Antibody Measurements

Concentrations of denintuzumab mafodotin ADC and released cys-mcMMAF in plasma and ATA in serum will be measured. Concentrations of rituximab in serum will be measured. PK samples will also be collected and archived for possible analysis of other denintuzumab mafodotin-related species.

9.5.3 Biomarker Assessments

Biomarker evaluations may include but are not limited to baseline pre- and post-treatment peripheral blood evaluation for circulating B cells by flow cytometry for soluble mediator quantification, which may include soluble CD19 (sCD19). Peripheral blood will be collected and assessed for cell-free circulating tumor DNA to detect minimal residual disease (MRD). Peripheral blood cell pellets will be collected for assessment of Fc-gamma receptor (FcγR) polymorphisms. The evaluation of pre-treatment tumor biopsies may include, but is not limited to, therapeutic target CD19 and other immune cell marker expression by IHC, COO by gene expression profiling, as well as somatic mutations that are prognostic or predictive of denintuzumab mafodotin response.

9.5.4 Safety Measurements

Safety assessments will include the evaluation of the type, incidence, severity, seriousness, and relatedness of adverse events, and the type, incidence, and severity of laboratory test abnormalities. Ophthalmologic exams and ocular health surveys will be conducted at protocol-specific time points.

Safety will be monitored over the course of the study by an SMC as described in Section 9.1.1.

10. STUDY EVALUATIONS BY VISIT

Adverse events and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 12.1.3). Any study protocol-related adverse events should be recorded from the time of informed consent as well as any concomitant medications given for the treatment of the adverse events.

A schedule of safety and efficacy procedures for the screening and treatment periods is provided in Table 18-1. PK, ATA, and biomarker assessments are provided in Table 18-2 (Part A Intense Sampling Schedule), Table 18-3 (Part B Intense Sampling Schedule) and Table 18-4 (Part B Sparse Sampling Schedule).

Study activities are listed by visit in this section, and descriptions of all study assessments are presented in Section 11 and Section 12.

10.1 Screening (Days -28 to 1)

The following procedures will be performed within 28 days before beginning treatment:

- informed consent
- study eligibility per inclusion/exclusion criteria (Section 9.3)
- medical history (includes a review of inflammatory conditions) (Section 11.1)
- collection/acquisition of tumor specimen (fresh or archived) for central pathology review (eligibility will be assessed using a local pathology lab) (Section 11.5)
- IPI or aaIPI score (Section 11.2)
- echocardiogram or multigated acquisition (MUGA) scan (Section 12.7)
- serology for hepatitis B surface antigen and anti-hepatitis B core antibody; if positive, PCR for hepatitis B viremia must also be performed (Section 12.3)
- CT scan of diagnostic quality of the neck, chest, abdomen, and pelvis with IV and oral contrast (Section 11.6)
- PET scan (Note: a combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as the CT is of diagnostic quality) (Section 11.6)
- collection of bone marrow aspirate/biopsy result, if performed as part of standard of care; the result from a biopsy collected within 60 days prior to the first dose of study treatment should be submitted (Section 11.5)
- ophthalmologic exam (Section 9.4.9.1)
- ocular health survey (±2 days from the ophthalmology exam) (Section 11.7)
- collection of COO/MRD/CD19 tumor tissue (representative tissue from fresh tumor specimen for study entry and biomarker analysis. Archived tumor tissue from the initial biopsy is also required; if such tissue is not available, a fresh biopsy must be obtained) (see Table 18-2 [Part A Intense Sampling Schedule], Table 18-3 [Part B Intense Sampling Schedule], and Table 18-4 [Part B Sparse Sampling Schedule])

10.2 Baseline (Days -7 to 1)

The following procedures will be performed within 7 days before beginning treatment:

- electrocardiogram (ECG)
- serum or urine pregnancy test for females of childbearing potential (Section 12.3)
- B symptom assessment (Section 11.4)
- physical examination, height and weight (Section 12.4)
- ECOG performance status (Section 12.6)
- serum chemistry panel (Section 12.3)
- complete blood count (CBC) with differential (Section 12.3)
- prothrombin time (PT)/partial thromboplastin time (PTT)/international normalized ratio (INR) (Section 12.3)
- spot urine for UPC ratio (Section 12.3)

10.3 Randomization (Day -1 to Day 1)

Randomization is to occur after eligibility is determined and within 1 business day prior to the planned first dose of Cycle 1 Day 1 using a centralized randomization system.

10.4 Treatment Period (Day 1 to Day 21)

Prophylactic steroid eye drops must be administered daily for 7 days with each dose of denintuzumab mafodotin. Eye drop prophylaxis should begin 1 day prior to denintuzumab mafodotin dose (see Section 9.4.5). In Cycle 1, however, if this is not possible then begin the prophylaxis on Day 1 of Cycle 1.

10.4.1 Cycles 1, 3, and 5

- **Day 1 (±1 day)**, pretreatment (all Day 1 assessments should be completed before study drug administration)
    - denintuzumab mafodotin administration (for all patients in Part A and if applicable in Part B)
        - Note: Prophylactic steroid eye drop administration required. Seven days of steroid eye drop prophylaxis should begin 1 day prior to denintuzumab mafodotin dose (see Section 9.4.5)
        - Denituzumab mafodotin administration will be approximately 30 minutes, but no longer than 60 minutes, following rituximab, after which it will then be followed by the remaining components of the combination therapy, ie, CHOP or CHP.
    - RCHOP or RCHP (Parts A and B) administration (prednisone on Days 1 to 5)
    - B symptom assessment (not required at Cycle 1 Day 1)
    - physical examination and weight (not required at Cycle 1 Day 1)
    - ECOG (not required at Cycle 1 Day 1)

- serum chemistry
- CBC with differential
- PT/PTT/INR
- spot urine for UPC ratio
  - if UPC >2: 24-hour urine collection (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)
- vitals (Section 12.2)

If the Baseline Visit activities occur within 1 day prior to Cycle 1 Day 1, then the following assessments do not need to be repeated at the Cycle 1 Day 1 visit: serum chemistry panel, CBC with differential, PT/PTT/INR, and spot urine for UPC calculation.

- **Day 8 (± 1 day)** and **Day 15 (± 1 day)**
  - serum chemistry panel
  - CBC with differential
  - spot urine for UPC ratio
    - if UPC >2: 24-hour urine collection (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)

10.4.2 Cycles 2, 4, and 6

- **Day 1 (± 1 day)**, pretreatment (all Day 1 assessments should be completed before study drug administration)
  - RCHOP or RCHP administration (prednisone on Days 1 to 5)
  - B symptom assessment
  - physical examination and weight
  - ECOG performance status
  - serum chemistry
  - CBC with differential
  - PT/PTT/INR
  - spot urine for UPC ratio
    - if UPC >2: 24-hour urine collection (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)
  - vitals
- **Day 8 (± 1 day)**
  - serum chemistry
  - CBC with differential
  - spot urine for UPC ratio
    - if UPC >2: 24-hour urine collection (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)
- **Day 15 (± 1 day)**, pretreatment
  - serum chemistry
  - CBC with differential
  - spot urine for UPC ratio

        - if UPC >2: 24-hour urine collection (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)
    - ophthalmologic exam (window Day 15 to 21 of Cycles 2, 4, and 6, unless alternate schedule is approved by the medical monitor, see Section 12.5. Review exam results before next dosing of denituzumab mafodotin; dose modifications should be made based on ocular toxicity grading (see Appendix 18.3).
    - ocular health survey ± 2 days from the ophthalmology exam

10.4.3 Part A Intense Sampling Schedule – Pharmacokinetic, Antitherapeutic Antibody, and Biomarker Assessments

For all patients enrolled in Part A.

10.4.3.1 Cycles 1 and 3

- **Day 1**, pre-dose
    - denintuzumab mafodotin PK and rituximab PK (Section 11.8)
    - ATA (Section 11.8)
    - biomarker samples – immunophenotyping (IP)/MRD (whole blood), sCD19/cytokines (serum/plasma), single-nucleotide polymorphism (SNP) (cell pellet; Cycle 1 only) (Section 11.8)
- **Day 1**, end of rituximab infusion
    - rituximab PK
- **Day 1**, end of denintuzumab mafodotin infusion
    - denintuzumab mafodotin PK
- **Day 1**, 8 hours after the end of denintuzumab mafodotin infusion
    - denintuzumab mafodotin PK
- **Days 4, 8, and 15**
    - denintuzumab mafodotin PK and rituximab PK
    - biomarker samples - IP/MRD (whole blood), sCD19 /cytokines (serum/plasma)
- **Day 22** (for patients not beginning the subsequent cycle on this day)
    - denintuzumab mafodotin PK and rituximab PK

10.4.3.2 Cycles 2 and 4

- **Day 1**, pre-dose of rituximab
    - denintuzumab mafodotin PK and rituximab PK
    - biomarker samples - IP/MRD (whole blood), sCD19/cytokines (serum/plasma)
- **Day 1**, end of rituximab infusion
    - rituximab PK

- **Days 8 and 15**
  - denintuzumab mafodotin PK and rituximab PK
- **Day 22** (for patients not beginning the subsequent cycle on this day)
  - denintuzumab mafodotin PK and rituximab PK

10.4.3.3 Cycles 5 and 6

- **Day 1**, pre-dose
  - denintuzumab mafodotin PK and rituximab PK
  - ATA (for Cycle 5 only)
  - biomarker samples - IP/MRD (whole blood), sCD19/cytokines (serum/plasma)
- **Day 1**, end of rituximab infusion
  - rituximab PK
- **Day 1**, end of denintuzumab mafodotin infusion
  - denintuzumab mafodotin PK
- **Day 22** (for patients not beginning the subsequent cycle on this day)
  - denintuzumab mafodotin and rituximab PK

10.4.4 Part B Intense Sampling Schedule – Pharmacokinetics, Antitherapeutic, Antibody, and Biomarker Assessments

For the first 25 patients enrolled in each arm.

10.4.4.1 Cycles 1 and 3

- **Day 1**, pre-dose
  - denintuzumab mafodotin PK and rituximab PK (Section 11.8)
  - ATA (Section 11.8)
  - biomarker samples - IP/MRD (whole blood), sCD19/cytokines (serum/plasma), SNP (cell pellet; Cycle 1 only) (Section 11.8)
- **Day 1**, end of rituximab infusion
  - rituximab PK
- **Day 1**, end of denintuzumab mafodotin infusion
  - denintuzumab mafodotin PK
- **Day 1**, 8 hours after the end of denintuzumab mafodotin infusion
  - denintuzumab mafodotin PK
- **Days 4, 8, and 15**
  - denintuzumab mafodotin PK and rituximab PK
  - biomarker samples - IP/MRD (whole blood), sCD19 /cytokines (serum/plasma)
- **Day 22** (for patients not beginning the subsequent cycle on this day)
  - denintuzumab mafodotin PK and rituximab PK

10.4.4.2 Cycles 2 and 4

- **Day 1**, pre-dose of rituximab
  - denintuzumab mafodotin PK and rituximab PK
  - biomarker samples - IP/MRD (whole blood), sCD19/cytokines (serum/plasma)
- **Day 1**, end of rituximab infusion
  - rituximab PK
- **Days 8 and 15**
  - denintuzumab mafodotin PK and rituximab PK
- **Day 22** (for patients not beginning the subsequent cycle on this day)
  - denintuzumab mafodotin PK and rituximab PK

10.4.4.3 Cycles 5 and 6

- **Day 1**, pre-dose
  - denintuzumab mafodotin PK and rituximab PK
  - ATA (for Cycle 5 only)
  - biomarker samples - IP/MRD (whole blood), sCD19/cytokines (serum/plasma),
- **Day 1**, end of rituximab infusion
  - rituximab PK
- **Day 1**, end of denintuzumab mafodotin infusion
  - denintuzumab mafodotin PK
- **Day 22** (for patients not beginning the subsequent cycle on this day)
  - denintuzumab mafodotin and rituximab PK

10.4.5 Part B Sparse Sampling Schedule – Pharmacokinetic, Antitherapeutic Antibody, and Biomarker Assessments

For the remaining patients in Part B following the first 25 patients enrolled in each arm.

10.4.5.1 Cycles 1 to 6

- **Day 1**, pre-dose
  - denintuzumab mafodotin PK and rituximab PK
  - ATA (for Cycles 1, 3, and 5 only)
  - biomarker samples - IP/MRD (whole blood), sCD19/cytokines (serum/plasma), SNP (cell pellet; cycle 1 only)
- **Day 1**, end of rituximab infusion
  - rituximab PK
- **Day 1**, end of denintuzumab mafodotin infusion
  - denintuzumab mafodotin PK

- **Day 22** (samples obtained only for patients not starting the next cycle on Day 22)
    - denintuzumab mafodotin PK and rituximab PK

10.5 End of Treatment (30 to 37 Days After Last Dose of Study Treatment)

EOT visits should occur 30 to 37 days after the last dose of study treatment. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the patient will be contacted 30 to 37 days following the last treatment to assess for adverse events.

At the EOT visit, the following assessments/procedures will be performed:

- review of inflammatory conditions (only required for patients with certain inflammatory conditions of interest at Screening/Baseline)
- ECG
- pregnancy test only for females of childbearing potential
- B symptom assessment
- physical examination and weight
- ECOG performance status
- serum chemistry
- CBC with differential
- PT/PTT/INR
- spot urine for UPC ratio
    - if UPC >2: 24-hour urine collection (within 5 days after urine protein creatinine PC assessment)
- ophthalmologic exam (not required if an exam was performed within 4 weeks prior to EOT and following the last dose of study treatment)
- ocular health survey (± 2 days from the ophthalmology exam)
- Blood samples for PK, ATA, and biomarker assessments (see Table 18-2 for Part A and Table 18-3 and Table 18-4 for Part B)

10.6 End of Treatment Response Assessment (5 weeks [± 1 week] After Last Dose of Study Treatment)

An EOT response assessment will be performed 5 weeks ± 1 week after the last dose of study treatment. These procedures can be performed at the same time as the EOT procedures if they occur within the appropriate visit window. At the EOT response assessment visit, the following assessments/procedures will be performed:

- bone marrow biopsy result, if bone marrow biopsy is performed as part of standard of care. In addition, bone marrow results will be recorded at any time on study if performed as part of standard of care.
- optional malignant lymphoma biopsy (Note: only for patients who are discontinuing treatment due to disease progression and who consent to the procedure. If a tumor

biopsy was performed at the time of disease progression as part of standard of care, then submit sample of tumor specimen, if available [see Section 9.5.3])
- CT scan of diagnostic quality of the neck, chest, abdomen, and pelvis with IV and oral contrast
- PET scan (Note: a combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as the CT is of diagnostic quality) physical examination and weight (can be the same as the EOT examination if within the appropriate window)

10.7 Long-Term Follow-Up

Patients who discontinue from study treatment will remain on the study for follow-up until they withdraw from the study (see Section 9.3.3).

- Optional malignant lymphoma biopsy (Note: only for patients who are discontinuing treatment due to disease progression and who consent to the procedure. If a tumor biopsy was performed at the time of disease progression as part of standard of care, then submit sample of tumor specimen, if available [see Section 9.5.3])
- Patients who discontinue study treatment for any reason other than disease progression or initiation of a non-protocol therapy for treatment of lymphoma will have PET scans and CT scans of diagnostic quality of the neck, chest, abdomen, and pelvis with IV and oral contrast every 4 months after the last scan for the first 2 years and every 6 months until 48 months and then annually thereafter until disease progression, death, or study closure, whichever comes first. Once disease becomes PET negative during the course of the study, PET scans are no longer required and all subsequent response assessments can be followed by CT scans of diagnostic quality only.
- All patients who receive at least one dose of study drug will be followed for survival and disease status at 4-month intervals after their last scan for the first 2 years, and at 6 month intervals until 48 months and then annually thereafter until death or study closure, whichever comes first.
- MRD will be evaluated at each response assessment for the first year after EOT (blood draw)
- Information will also be collected regarding subsequent anti-cancer therapies received

Patients who have disease progression or receive alternative NHL treatment will only be followed for survival thereafter.

In addition, for patients who develop ocular toxicity during study treatment, ophthalmologic exams and ocular health survey should be conducted monthly during the follow-up period (unless discussed with the medical monitor) until resolution or return to baseline.

10.8 End of Study/End of Follow-Up

The date the patient met criteria for study discontinuation and the reason for study discontinuation will be recorded (see Section 9.3.3).

11. METHOD OF ASSESSMENT

Only patients who meet all inclusion and exclusion criteria specified in Section 9.3 will be enrolled in this study.

11.1 Medical History

A full medical history, including a thorough review of significant past medical history and current conditions, any treatment for prior malignancies, and any concomitant medications, will be performed at screening. Medical history also included a review of any inflammatory conditions; patients with certain inflammatory conditions of interest at screening/baseline will have an additional review at the EOT visit.

11.2 International Prognostic Index

For patients >60 years of age at randomization, patient IPI scores should be calculated based on the International Non-Hodgkin Lymphoma Prognostic Factors Project (Shipp, 1993) to determine eligibility (see Appendix 18.4), and used for randomization into study arms. The IPI is calculated by scoring 5 prognostic factors: age, stage of disease, lactate dehydrogenase (LDH) level, ECOG score, and number of extranodal sites. For patients who are ≤60 years of age at randomization, patient aaIPI scores should be calculated based on the method initially published by Shipp et al to be used for randomization (Shipp, 1993; Ziepert, 2010). The aaIPI is calculated by scoring 3 prognostic factors: stage of disease, LDH, and ECOG score.

Refer to the Study Manual for details and scoring sheets.

11.3 Lymphoma Disease Stage

Patient disease stage is to be calculated at baseline to determine eligibility, per the Cotswolds Modification of Ann Arbor Staging System (Lister, 1989).

11.4 B Symptoms

B symptoms are defined as unexplained fevers >38°C, drenching night sweats, or weight loss >10% of body weight.

11.5 Histological Subtype and Cell of Origin Determination

Histologically confirmed DLBCL or FL Grade 3b must be determined by local pathology assessment. Also, COO by IHC using Hans algorithm must be determined by local pathologist. Submission of the tumor block or approximately 15 unstained slides from a biopsy of disease is required for subsequent central pathology review and evaluation of additional molecular biomarkers. The biopsy specimen must be from a malignant lymph

node or extranodal tissue obtained by core or excisional/incisional biopsy. Cutaneous samples alone are unacceptable. Fine needle aspiration and cytology samples are also unacceptable.

Details and shipping instructions are provided in the research specimen laboratory manual.

If additional bone marrow biopsy/aspirate samples are available at baseline, if performed at EOT or at progression as part of standard of care, or at any time while the patient is on study treatment, a sample will be collected (if available) to evaluate response at the cellular level and potential resistant biomarkers (see Section 10.5).

11.6 Response and Efficacy Assessments

Lymphoma assessments are to be performed at the time points outlined in Section 10 and Appendix 18.1. An adequate focused lymphoma assessment consists of the following:

- patient medical history, including a thorough review of the patient's current signs and symptoms, including B symptoms (fever, night sweats, or weight loss >10%) and concomitant medications
- physical examination, including evaluation of skin, head, eyes, ears, nose, and throat, and lymph nodes, heart, lungs, abdomen, back, extremities, and neurology

Radiographic assessments (PET and CT of diagnostic quality of the neck, chest**,** abdomen, and pelvis with IV and oral contrast) will be performed at protocol-specified time points or if disease progression is suspected (Appendix 18.2). After the patient is withdrawn from study treatment for any reason, a response assessment will be performed if an assessment has not been performed within the prior 6 weeks. Assessment of lymphoma progression will be made according to the Lugano Classification Revised Staging System for malignant lymphoma (see Appendix 18.2) (Cheson, 2014). Treatment decisions by the investigator will be based on these assessments. PET and CT scans are required per protocol as directed in Table 18-1. Staging will be performed by PET/CT of diagnostic quality, with disease involvement determined by focal FDG uptake in nodal and extranodal (including spleen, liver, bone marrow, and thyroid) sites that is consistent with lymphoma, according to the pattern of uptake and/or CT characteristics. Up to 6 of the largest nodes, nodal masses, or other involved lesions that are measurable in 2 diameters should be identified as target lesions; if possible, they should be from disparate regions of the body, and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

A metabolic response of progressive disease, stable disease, partial remission, or complete remission will be determined per the Lugano classification criteria. If clinical progression is determined by the investigator, radiographic staging should also be performed to determine response assessment per the Lugano classification criteria. The PET scan metabolic uptake will be graded in the 5-point Deauville scale with a score of ≤ 3 considered to represent a CMR. For all follow-up response assessments, both PET and CT scanning will be required until disease is PET negative; responses will then be followed by CT scan of diagnostic

quality only and evaluated by CT-based response criteria per the Lugano classification criteria. CT and/or PET scans may also be obtained throughout the study if clinically indicated.

If cutaneous lesions are the sole site of progressive disease, a biopsy must be obtained to histologically confirm progression.

Results from a bone marrow biopsy will be recorded at the screening and/or EOT visit and at any time on study, if performed as part of standard of care. A result from a biopsy performed within 60 days of the first dose of study treatment, as part of clinical care, may be submitted for the screening visit. At EOT, if a patient is scheduled to undergo stem cell collection and a bone marrow biopsy is performed as part of standard of care, the result will be collected. Bone marrow results will also be collected at any time on study if performed as part of standard of care.

B symptom assessment will also be performed. B symptoms are defined as unexplained fevers greater than 38°C, drenching night sweats, or weight loss greater than 10% of body weight.

Patients' clinical data must be available for eCRF source verification. Copies of all tumor imaging studies must be submitted to independent review facility as described in the study manual.

11.7 Patient-Reported Outcomes – Ocular Health Survey

The Visual Function Questionnaire is a validated 25-item patient-reported vision-targeted health survey designed to quantify the patients' perception of overall eye health, ocular symptoms, and the effect these symptoms have on the patients' regular activities (Mangione, 2001). Surveys will be administered as specified in Section 10 and should be completed at or around the time of each ophthalmology exam (± 2 days).

11.8 Pharmacokinetic and Antitherapeutic Antibody Assessments

Sensitive, qualified assays will be used to measure concentrations of denintuzumab mafodotin ADC and released cys-mcMMAF in plasma, and concentrations of rituximab in serum. PK samples will also be collected and archived for possible analysis of other denintuzumab mafodotin-related species. The assays will include enzyme-linked immunosorbent assays and liquid chromatography/tandem mass spectrometry assays, as well as other assays if further characterization is required. A qualified electrochemiluminescence assay will be used to determine the levels of ATA.

The PK parameters to be estimated include, but are not limited to, maximum plasma/serum concentration, area under the plasma/serum concentration-time curve, plasma/serum concentrations at trough, terminal half-life, clearance, steady-state volume of distribution, and accumulation ratio.

The ATA incidence rate is defined as the proportion of patients who develop ATA at any time during the study.

Pharmacokinetic, ATA, and biomarker samples will be collected at time points outlined in Table 18-2 (Part A Intense Sampling Schedule), Table 18-3 (Part B Intense Sampling Schedule), and Table 18-4 (Part B Sparse Sampling Schedule).

11.9 Biomarker Analysis

Samples from patients in both treatment arms in Part A and Part B will be analyzed and compared for target and pathway component expression that may affect the efficacy of denintuzumab mafodotin or change in response to treatment with denintuzumab mafodotin. Analysis of tumor tissue and blood may also include markers associated with prognosis, response, or resistance. Depletion of B-cell subsets in peripheral blood will be measured as potential PD markers of denintuzumab mafodotin activity and compared to that in the RCHOP Comparator Arm. Circulating proteins such as sCD19 will be assessed at baseline and post treatment to understand their potential prognostic and predictive value to denintuzumab mafodotin treatment. Blood sampling time points for biomarker analyses are listed in Table 18-2 (Part A Intense Sampling Schedule), Table 18-3 (Part B Intense Sampling Schedule), and Table 18-4 (Part B Sparse Sampling Schedule).

Biomarker evaluation may include but not be limited to baseline pre- and post-treatment peripheral blood evaluation for circulating B cells by flow cytometry for soluble mediator quantification, which may include sCD19. Peripheral blood will be collected and assessed for cell-free circulating tumor DNA to detect MRD. Peripheral blood cell pellets will be collected for assessment of FcγR polymorphisms. The evaluation of pre-treatment tumor biopsies may include but not be limited to therapeutic target CD19 and other immune cell marker expression by IHC, COO by gene expression profiling, and somatic mutations that are prognostic or predictive of denintuzumab mafodotin response.

11.9.1 B-Cell Subset Analysis

Whole blood samples will be collected for evaluation of markers of circulating B cells by flow cytometry. Reduction in circulating B cell subsets may be a PD marker of denintuzumab mafodotin activity. Flow cytometry measurements will include but are not limited to the following: CD3, CD10, CD14, CD19, CD20, CD27, CD38, CD45, CD56, CD269, and IgD.

11.9.2 Protein Markers in Blood

Serum and plasma will be obtained and evaluated for soluble mediator quantification. Soluble CD19 is elevated in autoimmune disorders. The level of sCD19 in patient with DLBCL at baseline may be predictive of denintuzumab mafodotin treatment response.

Soluble CD19 will be measured pre- and post-treatment with denintuzumab mafodotin to understand its value as a potential predictive marker as well as a PD marker.

Circulating proteins related to tumor burden or other potentially prognostic characteristics of the disease may also be monitored. In addition, MRD evaluation will be carried out to understand the depth of response to therapy and may be correlated with PFS and other patient outcomes. Peripheral blood will be collected and assessed for cell-free circulating tumor DNA to detect MRD.

11.9.3 Fc-γ Receptor (FcγR) Variants

Peripheral blood cell pellets will be collected for assessment of FcγR polymorphisms. Carriage of alleles that encode high-affinity variants of FCGR2A and FCGR3A may predict better responses to IgG1 antibody-based therapies, possibly due to increased activation of antitumor effector cells or prolonged duration of therapeutic drug levels in patients with these alleles. Denintuzumab mafodotin maintains effector functions such as antibody-dependent cellular cytotoxicity; therefore, enhanced antibody-dependent cellular cytotoxicity in patients with high-affinity FcγR variants may contribute to better antitumor activity.

Germline SNPs that may inform efficacy and toxicity may also be explored from patients who give optional pharmacogenomics consent. The genes of interest may include, but are not limited to, CEP27, an inherited genetic variant found associated with vincristine-related peripheral neuropathy in patients with acute lymphoblastic leukemia. No additional blood draw is necessary.

11.9.4 Characterization of Tumor Tissue

Fresh or archived tumor tissue from initial diagnosis will be collected at screening to evaluate biomarkers potentially predictive of response to denintuzumab mafodotin treatment; if such tissue is not available, a fresh biopsy must be obtained. Collection of tumor biopsies/samples are not required pre-treatment or during treatment, but if they are collected then they are to be submitted. If a biopsy on residual tumor is performed at EOT or at progression as part of standard of care, a sample will be collected (if available) to evaluate response at the cellular level and potential resistant biomarkers (see Section 10.5). Tumor biopsies may be evaluated for CD19, CD20, CD21, and other immune-cell marker expression by IHC. Although all B-cell lymphomas are expected to express CD19, response to therapy may vary depending on the intensity and pattern of CD19 expression.

DLBCL COO and additional gene expression analyses may also be evaluated. Cell of origin gene expression profiling of DLBCL can be used to classify the germinal center B-cell and activated B-cell subtypes, which have different prognoses. Further molecular characterization of the tumor, such as mechanism-based resistance and somatic mutations prognostic to treatment outcome such as Myc/BCL2 translocation and BCL6 expression, as well as the presence of infiltrating lymphocytes and macrophages may also be carried out if sufficient samples are available. If samples are available, correlation of response to

denintuzumab mafodotin with rates of these known mutations, as well as immune cell infiltrates, may be evaluated.

Refer to the Central Laboratory Manual for information on collection, processing, storage, and shipment of samples.

11.10 Biospecimen Samples for Future Research

Any remaining de-identified unused blood and tissue will be retained by Seattle Genetics and used for future research for patients who provide consent. The planned future research includes, but is not limited to, the identification of targets for novel ADCs, the biology of ADC sensitivity and resistance mechanisms, and the identification of predictive PD biomarkers of response to ADCs. Blood and tissue samples donated for future research will be retained for 25 years. Outside the US or if additional consent is not granted, any blood and tissue samples remaining after all study testing is completed will be destroyed following study closure.

11.11 Appropriateness of Measurements

Response will be assessed according to the Lugano classification criteria (Cheson, 2014), internationally accepted criteria for the evaluation of lymphoma. The criteria will be employed to assess tumor lesion size and extent of disease in the determination of response rate and PFS in this study. The schedule for tumor imaging is consistent with general oncological practice and appropriately balances measurement of tumor control with the expense and patient inconvenience associated with CT and PET scanning.

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. Adverse events and, when applicable, clinical laboratory data will be graded using NCI CTCAE v4.03. To detect any alteration in renal function, UPC ratios and serum creatinine levels will be obtained at specified time points and 24-hour urine collections for protein quantification will be conducted when the UPC is >2. To evaluate ocular toxicities, and to understand the ocular toxicity associated with denintuzumab mafodotin, complete ophthalmology exams and ocular health surveys will be conducted in both study arms at specified time points.

Antitherapeutic antibody is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to denintuzumab mafodotin.

Pharmacokinetic assessments are required to characterize drug effect, as are biomarker assessments, and are included in this trial.

12. SAFETY MEASUREMENTS AND VARIABLES

The assessment of safety during the course of this study will consist of the surveillance and recording of adverse events including serious adverse events (SAEs), recording of concomitant medication and measurements of protocol-specified physical examination findings and laboratory tests. Ophthalmologic examinations and ocular health survey will be conducted.

Safety will be monitored over the course of the study by an SMC as described in Section 9.1.1.

12.1 Adverse Events

12.1.1 Definition

Adverse Events

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, Investigational New Drug (IND) Safety Reporting, an adverse event is any untoward medical occurrence in a patient or clinical investigational patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing Conditions eCRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related adverse events should be recorded. A protocol-related adverse event is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All adverse events (regardless of relationship to study drug) should be recorded from study Day 1 (during and postdose) through the end of the safety reporting period (see Section 12.1.3. Complications that occur in association with any procedure (eg, biopsy) should be recorded as adverse events whether or not the procedure was protocol mandated.
- Changes in medical conditions and adverse events, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an adverse event unless it is associated with clinical signs or symptoms, requires an intervention, results in an SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an adverse event resulting from a laboratory

abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An adverse event should be classified as an SAE if it meets one of the following criteria:

Fatal:	Adverse event resulted in death
Life threatening:	The adverse event placed the patient at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	The adverse event required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	Resulted in a persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The adverse event did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

Adverse Event Severity

Adverse event severity should be graded using the NCI CTCAE, version 4.03 (Appendix 18.6), with the exception of ocular adverse events which will be graded according to a modified CTCAE version 4.03 scheme (Appendix 18.3). The CTCAE criteria are provided in the study manual or may be accessed at http://ctep.cancer.gov/reporting/ctc.html.

Adverse event severity and seriousness are assessed independently. "Severity" characterizes the intensity of an adverse event. "Serious" is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition for SAEs).

Relationship of the Adverse Event to Study Treatment

The relationship of each adverse event to each study drug (denintuzumab mafodotin or any component of or protocol-required chemotherapy [ie, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, or prednisone]) should be evaluated by the Investigator using the following criteria:

Related: There is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- An event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- An event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture)

Unrelated: Another cause of the adverse event is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the adverse event and administration of the study treatment, or a causal relationship is considered biologically implausible

12.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all adverse events and SAEs, whether elicited during patient questioning, discovered during physical examination, laboratory testing, and/or other means by recording them on the eCRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of adverse events.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions eCRF:

- description including onset and resolution dates
- whether it met serious criteria
- severity
- relationship to study treatment or other causality
- outcome

Diagnosis Versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI CTCAE terms of "cytokine release syndrome," "acute infusion reaction," or "allergic or hypersensitivity reaction." Instead, record each sign or symptom as an individual adverse event. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Events Related to Corneal Abnormalities

Corneal abnormalities observed with denintuzumab mafodotin are not well defined by the available CTCAE v4.03 toxicity categories for ocular toxicities; therefore, grading should be according to a modified CTCAE grading scheme as provided in Section 18.3.

Recording Serious Adverse Events

For SAEs, record the primary event on both the eCRF and an SAE form; events occurring secondary to the primary event should be described on the SAE form in the narrative description of the case.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and eCRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Cancer

Do not use the term "disease progression" when reporting an adverse event, including SAEs, because it is too general. Symptoms of disease progression that meet the criteria for an SAE must be reported. When possible, report the specific disease (clinical) manifestation of the progression (eg, "malignant pleural effusion", "spinal bone metastases", "lymphadenopathy from underlying NHL", "brain metastases"). Otherwise, it is acceptable to report the specific disease (eg, non-Hodgkin lymphoma) as an SAE.

Pregnancy

Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of study drug(s), including any pregnancies that occur in the partner of a male study patient. Only report pregnancies that occur in a male patient's partner if the estimated date of conception is after the male patient's first study drug dose. Fax or email the Sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy.

All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.
Collection of data on the eCRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events and Pre-Existing Conditions eCRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 12.1.1) should be reported as SAEs.

12.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all adverse events and SAEs is from study Day 1 (predose) through the EOT visit or 30 days after the last dose of study treatment (denintuzumab mafodotin or any component of or protocol-required chemotherapy [ie, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, or prednisone], whichever is later). However, all study protocol-related adverse events are to be collected from the time of informed consent.

All SAEs that occur after the end of safety reporting period (ie, more than 30 days after the last dose of study treatment) and are considered treatment-related in the opinion of the Investigator should also be reported to the Sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the Investigator, or the patient dies or withdraws consent, or study closure. All non-SAEs will be followed through the safety reporting period. Certain ongoing non-SAEs of interest (including, but not limited to, neuropathy and ocular adverse events) may be followed until resolution, return to baseline, or study closure.

12.1.4 Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, Investigators are to report the event to the Sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- patient number
- date of event onset
- description of the event
- study treatment, if known

The completed SAE form and SAE Fax Cover Sheet are to be faxed to the Drug Safety Department within 24 hours. Refer to the contact information provided on the SAE report form.

Relevant follow-up information is to be submitted to the Sponsor as soon as it becomes available.

12.1.5 Sponsor Safety Reporting Requirements

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 12.1.3).

The sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements. In the US, endpoints that assess disease-related mortality or major morbidity as well as other SAEs that are not study endpoints, but are known consequences of the underlying disease or condition that are anticipated to occur in the study population should not be reported to the FDA as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's final guidance Safety Reporting Requirements for INDs and Bioavailability and Bioequivalence Studies (December 2012) and draft guidance Safety Assessment for IND Safety Reporting (December 2015).

In this study, the SAEs that do not require individual IND safety reports are disease progression events. This anticipated SAE will be reviewed periodically by the Seattle Genetics Drug Safety Department. If, upon review, an SAE is occurring at a higher rate than that which would be expected for the investigational arms (denintuzumab mafodotin plus either RCHOP or RCHP), then an IND safety report for the SAE will be submitted to the FDA.

The Sponsor or its designee will report relevant SAEs to the relevant regulatory authorities, and participating investigators, in accordance with FDA regulations (21 CFR 312.32), ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

12.2 Vital Signs

Vital signs measures are to include heart rate, blood pressure, and temperature. Vital signs

should be collected per institutional standard for RCHOP infusion. For patients who receive denintuzumab mafodotin and RCHOP or RCHP, vital signs will be measured and recorded before the start of the denintuzumab mafodotin infusion and upon the completion of the infusion. All vitals should be measured after the patient has been sitting/resting for at least 5 minutes.

12.3 Clinical Laboratory Tests

Samples will be drawn for local laboratory testing, which will include institutional standard tests for evaluating safety and making clinical decisions. The following laboratory assessments will be performed by the local lab to evaluate safety at scheduled time points (Table 18-1) during the course of the study:

- Serum chemistry panel, including alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, calcium, creatinine, chloride, glucose, LDH, magnesium, phosphorous, potassium, sodium, total bilirubin, and uric acid.

- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit. Manual differential should be completed when clinically indicated.

- PT/PTT/INR

- Hepatitis B surface antigen and anti-hepatitis B core antibody testing; if positive, PCR for hepatitis B viremia must also be performed

- A serum or urine beta human chorionic gonadotropin pregnancy test for females of childbearing potential

- Urine samples will be tested protein and creatinine; these laboratory results will be used to calculate a UPC ratio.

- 24-hour urine collection will be required at visits where the UPC >2. If UPC >2 during a treatment cycle, only one 24-hour urine collection is required prior to the next cycle dosing.

Additional laboratory assessments may be performed by certified local laboratories. Documentation of certification and laboratory normal ranges will be filed with study documentation.

Additional and repeat laboratory safety testing may be performed at the discretion of the Investigator.

12.4 Physical Examination, Height, and Weight

Physical examinations should include assessment of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological.

Body weight will be measured and recorded at baseline and Day 1 of each cycle. Height will be determined at screening to assess body surface area (to be recorded in the eCRF).

12.5 Ocular Monitoring Plan

In order to assess the effects of denintuzumab mafodotin on the eye, patients will have complete ophthalmology assessments at protocol-defined time points (Table 18-1). Ophthalmology assessments are to include, but are not limited to the following:

- visual acuity and slit lamp examination.
- baseline dilated fundus examination is required; subsequent dilated fundus examinations are to be conducted as clinically indicated
- corneal epithelium changes must be assessed at each time point
- evaluation of steroid eye drop-induced changes including, but not limited to, intraocular pressure measurements and subcapsular cataracts
- ophthalmologic evaluations will be obtained in the event of subjective visual or ocular disturbances while on study

The results of the ophthalmological exam should be reviewed prior to the next dosing of denintuzumab mafodotin, and dose modifications of denintuzumab mafodotin should be made based on ocular toxicity grading of symptoms or corneal changes (see Section 9.4.9.1 and Appendix 18.3) following discussion with the medical monitor.

Ophthalmology exams and ocular health surveys are required at screening, during Cycles 2, 4, and 6 (Days 15 to 21), EOT (not required if conducted within 4 weeks of EOT, and following the last dose of study treatment), and during long-term follow-up. In the event of ocular toxicity, ophthalmology exams should be conducted at least monthly during the follow-up period (unless discussed with the medical monitor) until resolution or return to baseline.

12.6 ECOG Performance Status

ECOG performance status will be evaluated at protocol-specified time points indicated in Table 18-1. See Appendix 18.5 for the ECOG scale.

12.7 Cardiac Evaluation

Cardiac function will be determined by performing either an echocardiogram or a MUGA scan, and an ECG at protocol-specified time points (see Table 18-1).

13. DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data management and statistical analysis of this study will be performed by an external CRO, PRA Health Sciences.

13.1 Data Management

An eCRF will be used for the current study and a data management plan will be prepared by the CRO PRA Health Sciences. PRA Health Sciences will provide eCRF Completion Guidelines for eCRF data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

Previous and concomitant medications will be coded using the latest available World Health Organization Drug Reference Dictionary. Coexistent diseases and adverse events will be coded using the Medical Dictionary for Regulatory Activities.

13.2 Sample Size Estimation

In Part A of the study, up to approximately 24 patients will be enrolled to receive denintuzumab mafodotin with either RCHOP or RCHP (approximately 12 patients per treatment arm). With 12 patients in each arm, the probability of observing at least 1 patient with a clinically relevant adverse event is 72% if the true event rate is 10%. The probability becomes 93% if the true event rate is 20%. In evaluating the grade 3 peripheral neuropathy, the observed incidence rate for patients treated with RCHOP is approximately 10%.

One criterion for selecting the study treatment for Part B of the study is that the addition of denintuzumab mafodotin, which is another microtubule inhibitor similar to vincristine, to RCHOP should not cause significant additive neurotoxicity, and Grade 3 peripheral neuropathy should not exceed 20%. With 12 patients in each arm, if the true incidence rate is 15%, the probability of observing at least 3 patients having the event is 26%; if the true incidence rate is 25%, this probability becomes 61%.

In Part B of the study, approximately 136 patients will be randomized 1:1 to each treatment arm (approximately 68 patients per treatment arm). It is assumed that the underlying CR rates for the denintuzumab mafodotin plus RCHOP (or RCHP) treatment group is 88% and RCHOP treatment group is 70%. With a sample size of 136, an 18% improvement in CR rate in the denintuzumab mafodotin plus RCHOP (or RCHP) treatment group would provide approximately 80% power. This calculation is based on a 2-sided chi-squared test with significance level of alpha = 0.1 using EAST 6.3.1.

13.3 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand

on the details provided in the protocol. Additional analyses may be added. Tables, listing and figures shells will also be provided.

13.4 Randomization

In Part A, patients will be randomized 1:1 to denintuzumab mafodotin plus RCHOP or denintuzumab mafodotin plus RCHP. Patient randomization will be stratified by high-intermediate or high-risk disease.

In Part B, patients will be randomized 1:1 to receive denintuzumab mafodotin in combination with either RCHOP or RCHP or RCHOP alone. Randomization will be stratified by high intermediate or high-risk disease, and by COO.

13.5 Analysis Populations

13.5.1 Intent-to-Treat Population

The intent-to-treat (ITT) analysis set will include all randomized patients. Patients will be included in the treatment arm assigned at randomization regardless of the actual treatment received. Stratified analyses will be based on the stratification factor as recorded at randomization.

13.5.2 Safety Analysis Set

The safety analysis set will include all patients from Parts A and B who receive any amount of denintuzumab mafodotin or any component of RCHOP or RCHP. Treatment group will be determined using the actual treatment received, regardless of the randomization treatment assignment. In Part B, patients who received any amount of denintuzumab mafodotin will be assigned to the denintuzumab mafodotin in combination with either RCHOP or RCHP actual treatment arm.

13.5.3 Per-Protocol Analysis Set

The per-protocol analysis set will include patients in Part B who received at least of 1 cycle of study treatment, and had both a baseline and post-baseline evaluable response assessment (per the Lugano classification criteria (Cheson, 2014) (Appendix 18.2) or determination of clinical disease progression per the investigator), and no other major protocol deviations that affect response assessment. The per-protocol analysis set is a subset of the ITT analysis set, and patients will be grouped in the same manner as the ITT analysis set.

13.6 Statistical Methods

13.6.1 Missing Data

Missing data will not be imputed, with the exception of missing or partial dates or missing response assessments; imputation rules for missing or partial dates will be specified in the SAP. Patients whose responses are not evaluable/not evaluated postbaseline will be counted as non-responders in the analysis of CR rate and ORR.

13.6.2 Demographic and Baseline Data

Demographic and baseline data will be summarized descriptively by treatment arm for Part A and Part B. Details will be provided in the Statistical Analysis Plan.

13.6.3 Patient Disposition

An accounting of study patients by disposition will be tabulated and the number of patients in each analysis set will be summarized. Patients who discontinue study treatment and patients who withdraw from the study will be summarized with reason for discontinuation or withdrawal listed.

13.6.4 Efficacy

The efficacy endpoints of response rates (CR rate and ORR) at treatment completion will be analyzed based on the ITT analysis set. CR rate is defined as the proportion of patients who achieve CMR by PET/CT or CR by CT. The ORR is defined as the proportion of patients who achieved CMR or partial metabolic response (PMR) by PET/CT, or CR or PR by CT. Patients whose response is not evaluable/not evaluated postbaseline will be regarded as non-responders. The response rates will be summarized by descriptive statistics, and exact 90% confidence intervals (CIs) will be calculated for Part B only. The CR rate comparison for Part B only between the 2 treatment arms will be performed using a Cochran-Mantel-Haenszel test stratified by the randomization strata at a 2-sided alpha level of 0.1.

EFS, PFS, and OS will be analyzed based on the ITT analysis set for Part B only. EFS is defined as the time from randomization to the first documentation of disease progression, investigator-assessed clinical progression, initiation of subsequent anti-cancer therapy, or death, whichever is earliest. PFS is defined as the time from randomization to the first documentation of disease progression, investigator-assessed clinical progression, or death, whichever is earliest. OS is defined as the time from randomization to death of any cause. EFS, PFS, and OS will be summarized using the Kaplan-Meier method. The median EFS, PFS, and OS and their 2-sided 90% CIs using the complementary log-log transformation method (Collett, 1994) will be calculated as appropriate. Hazard ratio may also be estimated by the stratified Cox regression model, if appropriate.

Duration of objective response is defined as the time from the documentation of objective response at the EOT assessment to the first documentation of disease progression, investigator assessed clinical progression, initiation of subsequent anti-cancer therapy, or death, whichever is earliest. Duration of objective response will be calculated for the subgroup of patients achieving CR or PR at the EOT assessment.

Duration of CR is defined as the time from the documentation of CR at the EOT assessment to the first documentation of disease progression, investigator assessed clinical progression, initiation of subsequent anti-cancer therapy, or death, whichever is earliest. Duration of CR will be calculated for the subgroup of patients achieving CR at the EOT assessment. Duration of OR and CR will be analyzed using the Kaplan-Meier method. The median duration and its 2-sided 90% CI using the complementary log-log transformation method (Collett, 1994) will be calculated as appropriate.

As sensitivity analyses, the un-stratified analyses, and the stratified analyses using strata as recorded at baseline will be performed. Efficacy analyses will also be performed based on the safety analysis set and the PP analysis set.

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. The subgroups that may be examined include, but are not limited to, the following:

- COO (GCB versus non-GCB)
- IPI/aaIPI (high-intermediate versus high-risk)

Detailed methodology will be provided in the Statistical Analysis Plan.

The primary analysis of CR rates between the 2 treatment arms is planned to occur after all patients have completed the EOT response assessment, which occurs approximately 5 weeks after last study treatment.

13.6.5 Pharmacokinetics, Antitherapeutic Antibody, and Biomarkers

The individual plasma concentrations of denintuzumab mafodotin ADC and unconjugated drug (cys-mcMMAF) and serum concentrations of rituximab will be summarized with descriptive statistics at each PK sampling time point. Individual PK parameters will be estimated using noncompartmental analysis methods (where data allow), and summarized with descriptive statistics for each dose cohort. Additional PK and PK/PD analyses may be conducted and presented in a separate report.

The incidence of ATA to denintuzumab mafodotin will be summarized. The impact of ATA on PK, efficacy and safety may be assessed.

The biomarker data will be summarized.

13.6.6 Safety

The safety analysis will evaluate the type, incidence, severity, seriousness, and relatedness of adverse events, and the type, incidence, and severity of laboratory abnormalities for Parts A and B. The incidence, duration, and resolution of ocular adverse events (Sponsor-defined Query Terms) and neuropathy (Standardised Medical Dictionary for Regulatory Activities Queries, sensory and motor) will be summarized. The incidence and severity of infusion-related and hypersensitivity reactions will also be summarized.

13.6.7 Additional Data

All data collected on the eCRFs will be included in data listings. Additional summaries may be defined in the SAP.

13.6.8 Interim Analysis

No formal interim analysis is planned for this study. An SMC will monitor the trial for safety and will convene regularly during both parts of the study (for complete details, see Section 13.6.9).

An ongoing real-time review of SAEs in both parts of the study will be conducted by the Seattle Genetics Program Safety Monitoring Team. Additionally, interim data from the study may be presented at scientific meetings such as the annual meetings of the American Society of Clinical Oncology and the American Society of Hematology.

13.6.9 Data Safety Monitoring Committee

Members of the SMC will include the study investigators, medical monitor, and biostatistician, and Sponsor's medical expert. The primary role of this SMC will be to monitor safety data during Part A.

Formal safety evaluations of cumulative data from both treatment groups will be conducted at predefined interim safety evaluations in both Part A and Part B of the study (for complete details see Section 9.1.1 for Part A and Section 9.1.2 for Part B).

During the treatment period, the SMC may also recommend conducting additional safety analyses or temporarily halting enrollment until an appropriate evaluation of the cumulative safety data, including review of unanticipated safety issues, has been completed.

14. MONITORING PROCEDURES (QUALITY ASSURANCE)

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfill these obligations and to maintain current of study progress, the Sponsor's monitors or representatives will visit the investigative sites during study conduct, with frequency dependent on the rate of enrollment and workload at each site, in addition to maintaining telephone and written communication. During monitoring visits, the Seattle Genetics representative may review regulatory documentation, eCRFs, source documentation, and investigational product storage, preparation, and accountability, as applicable. On-site visits, telephone calls, and regular inspection of the CRFs will be conducted in order to assess patient enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of adverse events. The Investigator must provide the monitor with full access to all source and study documents pertinent to study patients, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Sponsor or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

14.1 Routine Monitoring

The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Whenever a patient name is revealed on a document that is to be collected for the Sponsor, the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the patient number as identification.

14.2 Inspections and Auditing Procedures

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor/CRO immediately if this occurs. The Investigator must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

15. STUDY MANAGEMENT AND MATERIALS

15.1 Electronic Case Report Forms

An eCRF will be used to store and transmit patient information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. The eCRF must be completed as soon as possible after any patient evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

15.2 Data Collection

During each study visit, a physician participating in the study will maintain medical records to document all significant observations. At a minimum, these notes will contain the following:

- the date of the visit and the corresponding day or visit in the study schedule (eg, screening, Cycle 1, Day 1, etc.)
- General condition and status remarks by the patient, including any *significant* medical findings. The severity, frequency, duration, and resolution of any reported adverse event, and the Investigator's assessment as to whether or not the reported adverse event is study drug-related
- changes in concomitant medications or dosages
- a general reference to the procedures completed
- the signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the patient via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialed and dated on the day the change is made by the Investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

15.3 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments.

All source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons. The original signed informed consent for each patient shall be filed with records kept by the Investigator and a copy shall be given to the patient.

15.4 Record Maintenance

All data derived from the study will remain the property of Seattle Genetics, Inc.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of patients, source documents, eCRFs, and study drug inventory must be kept on file.

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The Sponsor or their representative will notify the Principal Investigator of these events.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor, and will provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated during this study. Such documentation is patient to inspection by the Sponsor, its representatives and regulatory authorities.

If an Investigator moves, withdraws from an investigation or retires the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

15.5 Confidentiality

All information obtained during the conduct of the study with respect to the patient's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each patient's anonymity is maintained. On CRFs and other documents submitted to the Sponsor or the CRO, patient must not be identified by name. Instead, patients will only be known by their initials and by the unique patient number allocated to them in order to ensure confidentiality on all study documentation. Patients will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure patient safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the US FDA to review patient's medical records as they relate to this study. Only the patient's unique number on the eCRFs will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

Documents that are not for submission to the Sponsor or the CRO (eg, consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO, and auditing by regulatory authorities. No documents identifying subjects by name will leave the investigative site and patient identity will remain confidential in all publications related to the study.

16. ADMINISTRATION PROCEDURES

16.1 Regulatory Approval

Seattle Genetics, Inc., or their appointed agents will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No patient may enter the study until this approval has been obtained. A copy of the approval (where one is provided, according to local country requirements) will be provided to the Investigator and to the IRB(s).

16.2 Protocol Amendments

In accordance with ICH Topic E 6 (R1) Guideline for GCP the Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and documented approval from the IRB of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study patients, or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor[s], change of telephone number[s]).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the Sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IRB assuming this responsibility. The Investigator must await IRB approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to patients. In these cases, the IRB must be notified within 5 days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IRB, the Investigator and/or Sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the patient, the currently approved written informed consent form will require modification. The modified informed consent form must also be reviewed and approved by the Sponsor, appropriate regulatory authorities, and the IRB. In such cases, repeat informed consent must be obtained from patients enrolled in the study before participation continues.

16.3 Protocol Adherence and Deviations

The protocol must be read thoroughly by all site personnel participating in the trial and the instructions must be followed. No routine protocol waivers will be granted. However,

exceptions will be made in emergency situations when the protection, safety, and well-being of the patient requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the patient should continue study treatment. The Investigator, the Sponsor, and the Medical Monitor will document this decision.

16.4 Study Documentation, Privacy, and Records Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the Investigator until notified by the Sponsor in writing that retention is no longer necessary.

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the Investigator will provide the Sponsor, its licensees and collaborators, applicable regulatory agencies, and the applicable IRB with direct access to original source documents or certified copies.

Records containing patient medical information must be handled in accordance with the requirements of the Health Information Portability and Accountability Act Privacy Rule and be consistent with the terms of the patient authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, case report forms and other documents to be transferred to the Sponsor should be completed in strict accordance with the instructions provided by the Sponsor, including the instructions regarding the coding of patient identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

16.5 Publication Policy

The details of the processes of producing and reviewing publications and presentations based on the data from this study will be described in the Clinical Trial Agreement between Seattle Genetics, Inc., and the institution of the Investigator.

16.6 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated.

16.7 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

16.8 Insurance, Indemnity, and Compensation

Seattle Genetics, Inc. undertakes to maintain an appropriate clinical study insurance policy.

Deviations from the study protocol - especially the prescription of a dose other than that scheduled in the study protocol, other modes of administration, other indications, and longer treatment periods - are not permitted and shall not be covered by the statutory patient insurance scheme.

16.9 Discontinuation of the Study

This study may be terminated by the Sponsor. The study may also be terminated prematurely at any time when agreed to by both the Investigator and the Sponsor as being in the best interests of patients and justified on either medical or ethical grounds. In terminating the study, Seattle Genetics, Inc., the CRO (PRA Health Sciences), and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

16.10 Study Center File Management

The Investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but will not be limited to, the information listed below:

1. Investigator's Brochure
2. current, signed version of the protocol and any previous versions of the protocol
3. protocol amendments (if applicable)
4. operations manual (if applicable)

5. current informed consent form (blank) and any previous versions of the informed consent form

6. curricula vitae of Investigator(s) and sub-Investigator (s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US IND regulations), signed by all Principal Investigators. The names of any sub-Investigators must appear on this form. Investigators must also complete all regulatory documentation as required by ICH GCP and by local or national regulations

7. documentation of IRB approval of the protocol, the informed consent form, any protocol amendments, and any informed consent form revisions

8. all correspondence between the Investigator, IRB, and the Sponsor/CRO relating to study conduct

9. laboratory certification(s)

10. monitoring log

11. study drug invoices

12. site signature and duty delegation log

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18. APPENDICES

18.1 Schedule of Events

Table 18-1: Study Schedule

SCHEDULE OF EVENTS		Screening	Baseline	Enrollment	Cycles 1, 3, & 5			Cycles 2, 4, & 6			EOT[H]	EOT Response Assessment	Long-term follow-up
Visit Window		D–28 to 1	D–7 to 1	D–7 to 1	D1 (±1 day)	D8 (±1 day)	D15 (±1 day)	D1 (±1 day)	D8 (±1 day)	D15 (±1 day)	30+7 days post last dose	5 wks (±1 wk) post last dose	Q4 mos after last scan for 1st 2 yrs then Q6 mos[R]
Screening/ Baseline Assessments	Informed consent	X		Eligibility documentation submitted to Sponsor prior to study start									
	Inclusion/exclusion	X											
	Medical history	X											
	Inflammatory conditions review	X									X[Q]		
	Tumor specimen collection/acquisition[I]	X											
	IPI or age-adjusted IPI score	X											
	Height		X										
	Electrocardiogram		X								X		
	Echo or MUGA scan	X											
	Serology for hepatitis B[J]	X											
	Pregnancy test		X								X		
Treatment	Denintuzumab mafodotin[D]				X								
	RCHOP or RCHP				X			X[O]					
Research Sample[A]	PK/ATA samples				See Table 18-2 to Table 18-4							X	
	Soluble CD19												
	Biomarker blood samples												
	MRD												X[V]
	Biomarker bone marrow sample											X[R]	
	Optional malignant lymphoma biopsy											X[S]	X[S]
Response Assessments	CT (neck, chest, abdomen, pelvis)[B,C]	X										X[G]	X
	PET[C]	X										X[G]	X[F]
	Bone marrow aspirate/biopsy[E]	X[E]											
	B symptoms		X		X[F]			X			X		
	Survival status												X

Please refer to footnotes on the following page.

Table 18-1: Study Schedule

SCHEDULE OF EVENTS		Screening	Baseline	Enrollment	Cycles 1, 3, & 5			Cycles 2, 4, & 6			EOT[H]	EOT Response Assessment	Long-term follow-up
Visit Window		D –28 to 1	D –7 to 1	D –7 to 1	D1 (±1 day)	D8 (±1 day)	D15 (±1 day)	D1 (±1 day)	D8 (±1 day)	D15 (±1 day)	30+7 days post last dose	5 wks (±1 wk) post last dose	Q4 mos after last scan for 1st 2 yrs then Q6 mos[R]
Safety Assessments	Physical exam and weight		X		X[P]			X			X	X	
	ECOG		X		X[P]			X			X		
	Serum chemistry		X		X[O]	X	X	X	X	X	X		
	CBC with differential		X		X[O]	X	X	X	X	X	X		
	PT/PTT/INR		X		X[O]			X			X		
	Spot urine for UPC ratio		X		X[O]	X	X	X	X	X	X		
	24-hr urine collection if UPC >2				X[N,O]	X[N]	X[N]	X[N]	X[N]	X[N]	X[N]		
	Vitals				X			X					
	Ophthalmologic exam	X								X[K]	X[L]		X[M]
	Ocular health survey	X[T]								X[T]	X[L,T]		X[M]
	Concomitant medication & adverse events	Collect any related to study procedures		Collect from Day 1 (predose) thru 30 days post last dose or EOT visit, whichever is later									

ATA = antitherapeutic antibodies; CBC = complete blood count; CT = computerized tomography; D = day; echo = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; INR = international normalized ratio; IPI = International Prognostic Index; IV = intravenous; mos = months; MRD = minimal residual disease; MUGA = multigated acquisition scan; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RCHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate; prednisone; RCHP = rituximab, cyclophosphamide, doxorubicin hydrochloride, prednisone; UPC = urine protein creatinine; wk = week(s); Q = every

A. Refer to Table 18-2 to Table 18-4 for sampling schedules.
B. Diagnostic quality CT of neck, chest, abdomen, and pelvis with IV and oral contrast.
C. A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as the CT is of diagnostic quality.
D. All patients in Part A and if applicable in Part B. Note: Prophylactic steroid eye drop administration required. Seven days of steroid eye drop prophylaxis should begin 1 day prior to denintuzumab mafodotin. Denintuzumab mafodotin administration will be approximately 30 minutes, but no longer than 60 minutes, following rituximab, after which it will then be followed by the remaining components of the combination therapy, ie, CHOP or CHP.
E. If performed as part of standard of care; the result from a biopsy collected within 60 days prior to the first dose of study treatment should be submitted
F. If PET scan negativity was previously achieved during the course of the study, PET scans are not required during long-term follow-up and/or can be discontinued once PET scan negativity is achieved during long-term follow-up. Instead, CT scans only are acceptable.
G. Should be obtained if not done within the previous 6 weeks.
H. EOT evaluations should be done before initiation of non-protocol therapy. If done <30 days after the last dose of study treatment, conduct a phone screen 30 to 37 days post last treatment to ensure no change in the adverse event profile has occurred. EOT and EOT response assessments can be performed at the same time if it is within the 30 to 37 day window.
I. Tumor specimen (fresh or archived) must be submitted for central pathology review (eligibility will be assessed using a local pathology lab).
J. Hepatitis B surface antigen and anti-hepatitis B core antibody; if positive, PCR for hepatitis B viremia must also be performed
K. Window Day 15 to 21 of Cycles 2, 4, and 6.
L. Not required if conducted within 4 weeks of EOT, and following the last dose of study treatment.
M. In the event of ocular toxicity, continue at least monthly in follow up until resolution or return to baseline.
N. Prior to next cycle dosing or within 5 days of UPC if discontinuing study treatment.
O. If baseline activities occur within 1 day prior to Cycle 1 Day 1, assessment does not need to be repeated.
P. Not required at Cycle 1 Day 1.
Q. Only required for patients with certain inflammatory conditions of interest at Screening/Baseline.
R. Recorded if bone marrow biopsy is performed as part of standard of care. In addition, bone marrow results will be recorded at any time on study if performed as part of standard of care.

S. Only for patients who are discontinuing treatment due to disease progression and who consent to the procedure. If a tumor biopsy was performed at the time of disease progression as part of standard of care, then submit sample of tumor specimen, if available.
T. ±2 days from the ophthalmology exam
U. Prednisone on Days 1 to 5
V. Collected for the first year of follow-up only.

Table 18-2: Part A Intense Sampling Schedule – Pharmacokinetics, Antitherapeutic Antibody, and Biomarker Assessment - (For all Patients enrolled in Part A)

								Biomarker Samples			
									Blood Samples		
	Study Day	Time	Window	Relative Time[A]	Denintuzumab mafodotin PK[B]	Rituximab PK	ATA	COO/MRD/CD19 – Tumor Tissue	IP/MRD – Whole Blood	sCD19/ Cytokines – Serum/Plasma	SNP – Cell Pellet
Screening/ Baseline	Day –28 to 1	N/A	N/A	N/A				X[C]			
Cycles 1, 3	Day 1	Pre-dose	Within 8 hrs prior to start of infusion[E]	Start of infusion	X	X	X[F]		X	X	X[G]
		End of rituximab infusion	Within 5 min post end of infusion	End of infusion		X					
		End of denintuzumab mafodotin infusion	Within 5 min post end of infusion	End of infusion	X						
		8 hr after the end of denintuzumab mafodotin infusion	± 30 min	End of infusion	X						
	Day 4	72 hr	± 4 hr	Start of infusion	X	X			X	X	
	Day 8	168 hr	± 24 hr	Start of infusion	X	X			X	X	
	Day 15	336 hr	± 24 hr	Start of infusion	X	X			X	X	
	Day 22[D]	504 hr	± 24 hr	Start of infusion	X	X					
Cycles 2, 4	Day 1	Pre-dose of rituximab	Within 8 hr	Start of infusion	X	X			X	X	
		End of rituximab infusion	Within 5 min post end of infusion	End of infusion		X					
	Day 8	168 hr	± 24 hr	Start of infusion	X	X					
	Day 15	336 hr	± 24 hr	Start of infusion	X	X					
	Day 22[D]	504 hr	± 24 hr	Start of infusion	X	X					
Cycles 5, 6	Day 1	Pre-dose	Within 8 hr	Start of infusion	X	X	X[F]		X	X	
		End of rituximab infusion	Within 5 min post end of infusion	End of infusion		X					
		End of denintuzumab mafodotin infusion	Within 5 min post end of infusion	End of infusion	X						
	Day 22[D]	504 hr	± 24 hr	Start of infusion	X	X					
EOT					X	X	X	X[H]	X	X	

Please refer to footnotes on the following page.

ATA = antitherapeutic antibodies; COO = cell or origin; EOT = end of treatment; IP = immunophenotyping; MRD = minimal residual disease; N/A = not applicable; PK = pharmacokinetics; sCD19 = soluble CD19; SNP = single-nucleotide polymorphism

A. For patients receiving denintuzumab mafodotin plus RCHOP or RCHP: odd-cycle relative time is based on the denintuzumab mafodotin infusion, except the rituximab PK samples at the end of rituximab infusion; even-cycle relative time is based on the rituximab infusion.
B. For patients receiving denintuzumab mafodotin plus RCHOP or RCHP.
C. Representative tissue from fresh tumor specimen for study entry and biomarker analysis. If available, archived tumor tissue from the initial biopsy is also required.
D. Sample obtained only for patients not starting the next cycle on that day
E. Cycle 1 Day 1 pre-dose window is 24 hours.
F. For Cycles 1, 3 and 5 only
G. For Cycle 1 only
H. If a tumor biopsy is obtained at time of disease progression as part of institutional standard of care, submit a sample of the tumor tissue, if available.

Table 18-3: Part B Intense Sampling Schedule – Pharmacokinetics, Antitherapeutic Antibody, and Biomarker Assessments – (For the First 25 Patients in Each Arm)

								Biomarker Samples			
								COO/MRD/CD19 – Tumor Tissue	Blood Samples		
	Study Day	Time	Window	Relative Time[A]	Denintuzumab mafodotin PK[B]	Rituximab PK	ATA		IP/MRD – Whole Blood	sCD19/ Cytokines – Serum/Plasma	SNP – Cell Pellet
Screening/ Baseline	Day –28 to 1	N/A	N/A	N/A				X[C]			
Cycles 1, 3	Day 1	Pre-dose	Within 8 hrs prior to start of infusion[E]	Start of infusion	X	X	X[F]		X	X	X[G]
		End of rituximab infusion	Within 5 min post end of infusion	End of infusion		X					
		End of denintuzumab mafodotin infusion	Within 5 min post end of infusion	End of infusion	X						
		8 hr after the end of denintuzumab mafodotin infusion	± 30 min	End of infusion	X						
	Day 4	72 hr	± 4 hr	Start of infusion	X	X			X	X	
	Day 8	168 hr	± 24 hr	Start of infusion	X	X			X	X	
	Day 15	336 hr	± 24 hr	Start of infusion	X	X			X	X	
	Day 22[D]	504 hr	± 24 hr	Start of infusion	X	X					
Cycles 2, 4	Day 1	Pre-dose of rituximab	Within 8 hr	Start of infusion	X	X			X	X	
		End of rituximab infusion	Within 5 min post end of infusion	End of infusion		X					
	Day 8	168 hr	± 24 hr	Start of infusion	X	X					
	Day 15	336 hr	± 24 hr	Start of infusion	X	X					
	Day 22[D]	504 hr	± 24 hr	Start of infusion	X	X					
Cycles 5, 6	Day 1	Pre-dose	Within 8 hr	Start of infusion	X	X	X[F]		X	X	
		End of rituximab infusion	Within 5 min post end of infusion	End of infusion		X					
		End of denintuzumab mafodotin infusion	Within 5 min post end of infusion	End of infusion	X						
	Day 22[D]	504 hr	± 24 hr	Start of infusion	X	X					
EOT					X	X	X	X[H]	X	X	

Please refer to footnotes on the following page.

ATA = antitherapeutic antibodies; COO = cell or origin; EOT = end of treatment; IP = immunophenotyping; MRD = minimal residual disease; N/A = not applicable; PK = pharmacokinetics; sCD19 = soluble CD19; SNP = single-nucleotide polymorphism

A. For patients receiving denintuzumab mafodotin plus RCHOP or RCHP: odd-cycle relative time is based on the denintuzumab mafodotin infusion, except the rituximab PK samples at the end of rituximab infusion; even-cycle relative time is based on the rituximab infusion. For patients receiving RCHOP: relative time is based on the rituximab infusion for all cycles.
B. For patients receiving denintuzumab mafodotin plus RCHOP or RCHP.
C. Representative tissue from fresh tumor specimen for study entry and biomarker analysis. If available, archived tumor tissue from the initial biopsy is also required.
D. Sample obtained only for patients not starting the next cycle on that day
E. Cycle 1 Day 1 pre-dose window is 24 hours.
F. For Cycles 1, 3 and 5 only
G. For Cycle 1 only
H. If a tumor biopsy is obtained at time of disease progression as part of institutional standard of care, submit a sample of the tumor tissue, if available.

Table 18-4: Part B Sparse Sampling Schedule – Pharmacokinetics, Antitherapeutic Antibody, and Biomarker Assessments – (For the Remaining Patients in Part B Following the First 25 Patients Enrolled in Each Arm)

								Biomarker Samples			
									Blood Samples		
	Study Day	Time	Window	Relative Time[B]	Denintuzumab mafodotin PK[C]	Rituximab PK	ATA	COO/MRD/ CD19 – Tumor Tissue	IP/MRD – Whole Blood	sCD19/ Cytokines – Serum/Plasma	SNP – Cell Pellet
Screening / Baseline	Day –28 to 1	N/A	N/A	N/A				X[D]			
Cycles 1-6	Day 1	Pre-dose	Within 8 hrs prior to start of infusion[A]	Start of infusion	X	X	X[F]		X	X	X[H]
		End of rituximab infusion	Within 5 min post end of infusion	End of infusion		X					
		End of denintuzumab mafodotin infusion	Within 5 min post end of infusion	End of infusion	X						
	Day 22[E]	504 hr	± 24 hr	Start of infusion	X	X					
EOT					X	X	X	X[G]	X	X	

ATA = antitherapeutic antibodies; COO = cell or origin; EOT = end of treatment; IP = immunophenotyping; MRD = minimal residual disease; N/A = not applicable; PK = pharmacokinetics; sCD19 = soluble CD19; SNP = single-nucleotide polymorphism

A. Cycle 1 Day 1 pre-dose window is 24 hours.

B. Odd-cycle relative time is based on the denintuzumab mafodotin infusion, except the rituximab PK samples at the end of rituximab infusion; even-cycle relative time is based on the rituximab infusion.

C. For patients receiving denintuzumab mafodotin plus RCHOP or RCHP.

D. Representative tissue from fresh tumor specimen for study entry and biomarker analysis. If available, archived tumor tissue from the initial biopsy is also required.

E. Sample obtained only for patients not starting the next cycle on that day

F. For Cycles 1, 3 and 5 only.

G. If a tumor biopsy is obtained at time of disease progression as part of institutional standard of care, submit a sample of the tumor tissue, if available.

H. For Cycle 1 only.

18.2 Response Assessment – The Lugano Classification

Response and Site	PET-CT–Based Response	CT-Based Response
Complete Response	***Complete metabolic response***	***Complete radiologic response (all of the following)***
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response	***Partial metabolic response***	***Partial remission (all of the following)***
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None

Response Assessment – The Lugano Classification (continued)

Partial Response	***Partial metabolic response***	***Partial remission (all of the following)***
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No Response or Stable Disease	***No metabolic response***	***Stable disease***
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	>50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
No Response or Stable Disease	***No metabolic response***	***Stable disease***
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	>50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Response Assessment – The Lugano Classification (continued)

Progressive Disease	***Progressive metabolic disease***	***Progressive disease requires at least 1 of the following***
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or EOT assessment	PPD progression An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS=5-point scale, CT=computed tomography, FDG=fluorodeoxyglucose, IHC=immunohistochemistry, LDi-longest transverse diameter of a lesion, MRI=magnetic resonance imaging, PET=positron emission tomography, PPD=cross product of the LDi and perpendicular diameter, SDi=shortest axis perpendicular to the LDi, SPD=sum of the product of the perpendicular diameters for multiple lesions.
The Lugano Classification (Cheson 2014).

18.3 Modified* CTCAE V4.03 Grading Scheme for Ocular Toxicity

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Ocular Symptoms	Symptomatic (with or without clinical findings) Does not affect ADL	Symptomatic Possible change in vision Affects instrumental ADL (ie, preparing meals, shopping for groceries or clothes, using the telephone or computer, managing money, driving, etc.)	Symptomatic Change in vision Affects self-care ADL (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)	--
Corneal Findings (as determined by ocular examination)	Corneal findings, but no change in visual acuity from baseline	Corneal findings with change in visual acuity from baseline; see table below for visual acuity criteria	Corneal findings with change in visual acuity from baseline; see table below for visual acuity criteria	Corneal findings with change in visual acuity from baseline; see table below for visual acuity criteria

ADL=activities of daily living
* Modified portion of CTCAE refers to when patient does not have 20/20 vision at baseline.

Visual Acuity for Grading

Baseline Vision (cc or sc)	Grade 1	Grade 2	Grade 3	Grade 4
20/20	No change	20/25 – 20/40 or better	20/50 – better than 20/200	20/200 or worse
20/25	No change	20/30 – 20/50	20/60 – better than 20/200	20/200 or worse
20/30	No change	20/40 – 20/60	20/70 – better than 20/200	20/200 or worse
20/40	No change	20/50 – 20/70	20/80 – better than 20/200	20/200 or worse
20/50	No change	20/60 – 20/80	20/100 – 20/200	Worse than 20/400
20/60	No change	20/70 – 20/100	20/125 – 20/400	Worse than 20/400
20/70	No change	20/80 – 20/125	20/200 – 20/400	Worse than 20/400
20/80	No change	20/100 – 20/200	20/400	Worse than 20/400
20/100	No change	20/125 – 20/400	Worse than 20/400	--

18.4 International Prognostic Index Scales

International Prognostic Index (IPI, for patients >60 years of age)

1 point for any of the following:

- Age >60
- Serum LDH >1 x ULN
- ECOG Performance Status ≥2
- Stage III or IV
- Extranodal involvement ≥2 sites

Risk Category:

- Low: 0–1
- Low-intermediate: 2
- High-intermediate: 3
- High: 4–5

From the International Non-Hodgkin's Lymphoma Prognostic Factors Project (Shipp, 1993).

Age-adjusted International Prognostic Index (aaIPI, for patients ≤60 years of age)

1 point for any of the following:

- Serum LDH >1 x ULN
- ECOG Performance Status ≥2
- Stage III or IV

Risk Category:

- Low: 0
- Low-intermediate: 1
- High-intermediate: 2
- High: 3

Based on Shipp 1993; Moscowitz 1999; Hamlin 2003

18.5 Eastern Cooperative Oncology Group Performance Status

Grade	Criterion
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example light housework or office work.
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair.
5	Death

18.6 Common Terminology Criteria for Adverse Events (CTCAE; v 4.03)

The current version of the NCI CTCAE (Version 4.03) can be viewed on-line at the NCI web site:

http://ctep.cancer.gov/reporting/ctc.html