



Protocol Number: SGN19A-003

Version: Amendment 2; 28-Oct-2017

Protocol Title: A randomized, open-label phase 2 study of denintuzumab mafodotin (SGN-CD19A) plus rituximab, ifosfamide, carboplatin, and etoposide (19A+RICE) chemotherapy vs. RICE in the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are candidates for autologous stem cell transplant

Investigational Drug: Denintuzumab mafodotin (SGN-CD19A)

Phase: 2

IND Number: 114874

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PROTOCOL SYNOPSIS

Protocol Number SGN19A-003	Product Name Denintuzumab mafodotin (SGN-CD19A)
Version Amendment 2; 28-Oct-2017	Sponsor Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Phase 2	

Protocol Title

A randomized, open-label phase 2 study of denintuzumab mafodotin (SGN-CD19A) plus rituximab, ifosfamide, carboplatin, and etoposide (19A+RICE) chemotherapy vs. RICE in the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are candidates for autologous stem cell transplant

Study Objectives

Primary:

- To compare the complete remission (CR) rates in patients with relapsed/refractory DLBCL who are candidates for autologous stem cell transplant (ASCT) treated with denintuzumab mafodotin plus RICE (19A+RICE) versus RICE

Secondary:

- To evaluate the safety of denintuzumab mafodotin given in combination with RICE
- To compare progression-free survival (PFS) between study arms
- To compare overall survival (OS) between study arms
- To compare the proportion of patients who are able to adequately mobilize peripheral blood stem cells (PBSC) between study arms
- To compare the proportion of patients receiving ASCT following study treatment between study arms
- To compare other measures of antitumor activity between study arms

Additional:

- To evaluate the pharmacokinetics (PK) of denintuzumab mafodotin (antibody-drug conjugate [ADC] and cys-mcMMAF) when denintuzumab mafodotin is given in combination with RICE chemotherapy
- To evaluate the incidence of antitherapeutic antibodies (ATA) against denintuzumab mafodotin
- To assess denintuzumab mafodotin-mediated pharmacodynamic (PD) effects and potential biomarkers to stratify response

Study Population

Eligible patients are aged 18 years and older with histologically confirmed CD20-positive (*CD20-positivity requirement not applicable to Amendment 2*), relapsed or refractory DLBCL (including de novo and transformed DLBCL, Grade 3b follicular lymphoma, and patients with DLBCL found to have small-cell infiltration of the bone marrow or other diagnostic material), have received frontline treatment with CD20-directed immunotherapy with anthracycline- or anthracenedione-based multi-agent chemotherapy, and are candidates for high-dose chemotherapy followed by ASCT. All patients must have achieved a response of stable disease or better (when compared to the baseline, pre-treatment disease assessment) following the last cycle of frontline treatment with multi-agent chemo-immunotherapy regimens delivered with curative intent, and for patients enrolled under Amendment 2, patients must have relapsed less than or equal to 6 months from the completion of frontline therapy at the time of initial dosing in this clinical trial. A representative tissue sample from the most recent biopsy after last therapy must be available, or a fresh biopsy must be obtained at baseline. Fluorodeoxyglucose (FDG)-avid disease by positive emission tomography (PET), measurable disease

of >1.5 cm by computed tomography (CT), an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 , and adequate renal, hepatic and hematologic function are required at baseline.

Patients are not eligible if they have previous history of any of the following: indolent lymphoma treated with more than 1 multi-agent chemotherapy regimen or previous cancer therapy for recurrent DLBCL or Grade 3b follicular lymphoma; autologous or allogeneic stem cell transplant (SCT); another primary invasive cancer, hematologic malignancy or myelodysplastic syndrome that has not been in remission for at least 1 year; or progressive multifocal leukoencephalopathy (PML). Patients are not permitted in the study if they have any of the following: cerebral/meningeal disease related to the underlying malignancy; corneal disorders, monocular vision, or certain active ocular disorders requiring treatment; Class III or IV congestive heart failure; active Grade 3 or higher (per the NCI CTCAE, Version 4.03 or higher) viral, bacterial, or fungal infection within 2 weeks of the first dose of study drug; positive polymerase chain reaction (PCR) assay with positive hepatitis surface antigen and/or anti-hepatitis B core antibody, known or suspected active hepatitis C infection, or known human immunodeficiency virus (HIV) infection; or known urinary tract obstruction. Chemotherapy, radiotherapy, biologics, and/or other antitumor treatment with immunotherapy must be completed 4 weeks prior to study entry; however, radiotherapy within 4 weeks prior to study entry is acceptable if the underlying disease has progressed on treatment.

Number of Planned Patients

Approximately 100 patients will be randomized in a 1:1 ratio to 1 of 2 study arms (~50 patients in each arm). If dose modification of denintuzumab mafodotin is necessary, up to 50 additional patients (25 in each arm) may be randomized. If a subset of patients appears to potentially derive benefit from 19A+RICE versus RICE at a pre-planned evaluation, the Sponsor may continue enrolling those patients beyond the planned sample size (approximately 100 patients), but will not exceed the planned maximum number of patients to be randomized in this study (up to approximately 150 patients).

Study Design

This is a randomized, open-label phase 2 study designed to compare the CR rates in patients with relapsed or refractory DLBCL who are candidates for ASCT. Patients will be randomized in a 1:1 ratio to 1 of 2 study arms:

1. Control, RICE Arm: 3 cycles (3 weeks per cycle) of RICE
2. Investigational, 19A+RICE Arm: 3 cycles (3 weeks per cycle) of denintuzumab mafodotin administered on Day 1 of every cycle, in conjunction with 3 cycles (3 weeks per cycle) of RICE

Lymphoma response and progression will be assessed using the Lugano Classification Revised Staging System for malignant lymphoma ([Cheson 2014](#)). CT scans (neck, chest, abdomen, and pelvis) and PET scans will be performed at baseline and at end of treatment (EOT). Follow-up assessments will be performed at 3, 6, 12, 18, 24 months, and then annually after ASCT or EOT (for patients who don't receive ASCT). 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. A CT scan of diagnostic quality will also be performed at the time of suspected clinical progression. Follow-up assessments will continue until disease progression, initiation of a new anticancer treatment (with the exception of a stem cell transplant), or study closure, whichever occurs first. Survival status follow-up will continue until patient death or study closure, whichever occurs first.

A safety monitoring committee (SMC) comprising the study investigators, medical monitor, and study biostatistician will monitor the safety of patients at predefined interim safety evaluations and over the course of the treatment period.

Test Product, Dose, and Mode of Administration

Both arms: RICE administered in 21-day cycles, with rituximab 375 mg/m² given as the first component of RICE via intravenous (IV) infusion on Day 1; and followed by etoposide (100 mg/m² per day), ifosfamide (5000 mg/m²) with mesna, and carboplatin (area under the curve 5 mg/mL x min; maximum dose, 800 mg) administered during each cycle in an order as per institutional standard of care.

19A+RICE Arm only: denintuzumab mafodotin 3 mg/kg administered via IV infusion on Day 1 of every 21-day cycle prior to the rituximab component of RICE therapy. The SMC may recommend modification of the dose of

denintuzumab mafodotin (e.g., to 2 mg/kg) in subsequently enrolled patients upon evaluation of the data at the predefined interim safety evaluations.

Duration of Treatment

Patients may receive a maximum of 3 cycles (3 weeks per cycle) of treatment, either 19A+RICE or RICE alone.

Efficacy Assessments

Disease response will be assessed by both the investigator and an independent review facility (IRF) based on the Lugano classification criteria ([Cheson 2014](#)).

Pharmacokinetic and Antitherapeutic Antibody Assessments

Patients in both treatment arms will have blood samples collected for pharmacokinetic and antitherapeutic antibody (ATA) evaluation at protocol-defined timepoints.

Biomarker Assessments

Biomarker evaluation may include but not be limited to baseline measurement and change of circulating B cells by flow cytometry. Pre- and post-treatment serum and plasma will be obtained and evaluated for soluble mediator quantification. Peripheral blood cell pellets will be collected for assessment of FC gamma receptor (FcγR) polymorphisms. In addition, evaluation of tumor biopsies may include but not be limited to therapeutic target CD19 and other immune cell marker expression by immunohistochemistry, cell of origin, as well as somatic mutations that are prognostic or predictive of denintuzumab mafodotin response.

Safety Assessments

Safety assessments will include the surveillance and recording of adverse events (AEs), physical examination findings, and laboratory tests. Ophthalmologic exams and ocular health surveys will be conducted at protocol-specific timepoints. PBSC collection will also be assessed as a measure of safety. Additionally, transplant-related data following ASCT will be collected and will include, but not be limited to, the time to neutrophil and platelet engraftment in each treatment arm.

Statistical Methods

Sample Size Considerations

With approximately 100 patients randomized in a 1:1 ratio to each treatment arm (~50 patients per arm) for the primary analysis, the study is designed to have approximately 80% power to detect an increase in the CR rate of 25% (e.g., from 35% in RICE Arm to 60% in 19A+RICE Arm). This calculation is based on a two-sided χ^2 test with significance level of $\alpha = 0.1$ using EAST 5.4.

If the dose of denintuzumab mafodotin in the investigational 19A+RICE Arm is modified, up to 50 additional patients may be randomized (25 in each arm) so that a total of 100 patients will be randomized in a 1:1 ratio to either the 19A (modified dose) + RICE arm or the RICE only arm. Up to approximately 150 patients may be randomized in this study. If a subset of patients appears to potentially derive benefit from 19A+RICE versus RICE at a pre-planned evaluation, the Sponsor may continue enrolling those patients beyond the planned sample size (approximately 100 patients), but will not exceed the planned maximum number of patients to be randomized in this study (up to approximately 150 patients).

Randomization

Stratified block randomization will be performed centrally. Patients will be stratified by 3 factors:

- Disease status
- Second-line age-adjusted International Prognostic Index (saIPI) score or standard IPI score, as appropriate to patient age, at randomization
- Disease type

Safety Analysis

The safety analysis will evaluate the type, incidence, severity, seriousness, and relatedness of AEs, the ability to mobilize stem cells, and the type, incidence, and severity of laboratory abnormalities.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

19A	denintuzumab mafodotin
19A+RICE	denintuzumab mafodotin plus RICE
ADC	antibody-drug conjugate
ADCC	antibody dependent cellular cytotoxicity
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
β-hCG	beta human chorionic gonadotropin
CBC	complete blood count
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CMR	complete metabolic response
CNS	central nervous system
CR	complete remission
CRF	case report form
CT	computed tomography
CYP	cytochrome P450
DDT	dose-delaying toxicity
DHAP	dexamethasone, cytarabine, cisplatin
DLBCL	diffuse large B-cell lymphoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FcγR	FC gamma receptor
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FOCBP	female of childbearing potential
GCB	germinal center B cell
GCP	good clinical practice
Hgb A1c	hemoglobin A1c
IB	Investigator's Brochure
ICE	ifosfamide, carboplatin, etoposide
ICH	International Council on Harmonization
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
IPI	International Prognostic Index
IRB	institutional review board
IRF	independent review facility
ITT	intent-to-treat

IV	intravenous
mc	maleimidocapryol
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMAF	monomethyl auristatin F
MRD	minimum residual disease
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NYHA	New York Heart Association
OR	objective response
ORR	overall response rate
OS	overall survival
PBSC	peripheral blood stem cell
PCR	polymerase chain reaction
PD	pharmacodynamic
PEG	polyethylene glycol
PET	positive emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PP	per-protocol
PR	partial remission
PT	prothrombin time
PTT	partial thromboplastin time
RICE	rituximab, ifosfamide, carboplatin, etoposide
saaIPI	second-line, age-adjusted International Prognostic Index
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneously
sCD19	soluble CD19
SCT	stem cell transplant
SD	stable disease
SGN-CD19A	denintuzumab mafodotin
SMC	safety monitoring committee
TLS	tumor lysis syndrome
ULN	upper limit of normal
UPC	urine protein:creatinine
USPI	United States Prescribing Information
VFQ	Visual Function Questionnaire

1 INTRODUCTION

1.1 Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a subset of non-Hodgkin lymphomas (NHL) that comprises approximately 30% of all newly diagnosed cases of NHL in the United States, representing the most common lymphoid neoplasm in adults ([Swerdlow 2008](#)). Although the majority of patients with newly diagnosed DLBCL achieve long-term remissions with rituximab and multi-agent chemotherapy, approximately 30% of patients will experience relapse or progression. At the time of relapsed disease, the treatment approach is based on whether the patient is a candidate for autologous stem cell transplant (ASCT). In patients considered to be transplant eligible, the decision to proceed to ASCT is determined by the response to salvage treatment ([Ghielmini 2013](#); [NCCN 2015](#)). The goals of salvage therapy are typically to minimize disease burden and induce remission, providing the best opportunity to benefit from consolidative ASCT.

Various multi-agent salvage regimens incorporating rituximab have been explored in DLBCL patients. A large randomized comparison of the most commonly used salvage regimens demonstrated the equivalence of rituximab combined with either ICE (ifosfamide, carboplatin, etoposide) or DHAP (dexamethasone, cytarabine, cisplatin) ([Gisselbrecht 2010](#)). There were no significant differences overall between these regimens, and the combined results supported an overall response rate (ORR) of 63%, with 37% of patients achieving a complete remission (CR of 25%, unconfirmed CR of 12%). The median progression-free survival (PFS) was found to be approximately 1 year, with a 3-year event-free survival of 31% and 3-year overall survival (OS) of 50%. Patients with chemo-sensitive disease who achieved a CR or partial remission (PR) and had adequate stem cell collection were candidates to proceed to ASCT; only 50% of patients were able to proceed to ASCT following salvage therapy. The most common reason to not proceed to ASCT was induction treatment failure to induce remission. Additionally, the study incorporated a second randomization to evaluate the benefit of maintenance rituximab following ASCT; preliminary results suggested there was no benefit.

In general, treatment guidelines support ASCT as the treatment of choice for patients with chemo-sensitive relapsed or refractory DLBCL ([Ghielmini 2013](#); [NCCN 2015](#)). Patients who are candidates for ASCT should be treated with multi-agent chemotherapy regimens combined with rituximab, such as DHAP, ESHAP, GDP, GCD, GemOx, ICE or MINE; there is no clear advantage of one regimen over another. Patients achieving remissions should then proceed to consolidative ASCT ([Ghielmini 2013](#); [NCCN 2015](#)).

Obtaining a positive emission tomography (PET)-negative CR following second-line salvage therapy has been associated with improvement in outcome in relapsed DLBCL patients who proceed to ASCT ([Dickinson 2010](#); [Johnston 2008](#); [Terasawa 2010](#)). A meta-analysis, including 300 patients with DLBCL, demonstrated that a positive PET scan pre-ASCT was associated with a significantly shorter PFS interval (random effects hazard ratio 4.3; 95% CI 3.1, 6; $p < 0.0001$) ([Terasawa 2010](#)). A PET-positive status pre-ASCT resulted in a 4 to 5-fold

higher risk for treatment failure versus a PET-negative status. A smaller study evaluating the prognostic value of pre-ASCT PET scanning in relapsed DLBCL patients found a striking difference in long term outcome, with a 3-year PFS of 81% for patients with a negative scan versus 35% for those with a positive scan. This translated into similar 3-year OS findings, with 81% of patients alive with a negative scan versus 39% with a positive scan ([Dickinson 2010](#)).

Recent literature indicates that patients with DLBCL who experience primary treatment failure (PTF) have a poor prognosis. PTF includes patients who have progressed while on frontline therapy, patients with residual disease at the end of frontline therapy, or patients who relapse early (<6 months from end of therapy after achieving a CR). Often, patients with PTF are subsequently salvaged in the same way as patients who experience much later relapse of disease ([Costa 2017](#); [Gisselbrecht 2010](#)). Previous trials, such as the CORAL, BMT CTN 04-01, and ORCHARRD studies, have included early relapse patients with the later relapsed patients ([Gisselbrecht 2009](#); [van Imhoff 2016](#); [Vose 2013](#)). The recently published results from the multi-center retrospective study REFINE indicate that the use of more refined clinical and genetic characterization in patients with PTF can identify those who appear to do poorly with conventional approaches, and thus stand to benefit from investigational therapies ([Costa 2017](#)). Additionally, preliminary data from the patients with PTF enrolled to date on our study (SGN19A-003) suggest that these high-risk patients may potentially benefit from combining 19A+RICE relative to RICE alone.

Novel treatment strategies are needed to improve outcomes for relapsed, transplant-eligible DLBCL patients. The goal of treatment in this population is to achieve a high-quality remission that enables subsequent ASCT. The primary unmet need is the failure to achieve a high rate of CR. Achieving a CR with salvage therapy prior to ASCT has been associated with improved long-term outcomes. Chemo-immunotherapy regimens, such as RICE (rituximab, ifosfamide, carboplatin, etoposide) or RDHAP, result in less than half of patients achieving CR; adding a novel agent with demonstrated activity in relapsed DLBCL to these regimens has the potential to improve outcomes.

1.2 CD19

CD19 is a member of the immunoglobulin superfamily and is one of the earliest markers of B-cell differentiation. 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 ([Bryder 2010](#); [Del Nagro 2005](#); [Huh 2000](#)). 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 non-Hodgkin lymphomas such as DLBCL and is found in almost all clinical immunohistochemistry (IHC) and flow cytometry diagnostic panels.

1.3 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 maleimidocapryol (mc) 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.

1.3.1 Mechanism of Action of Denintuzumab Mafodotin

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 maleimidocapryol 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.

1.3.2 Experience with Denintuzumab Mafodotin

1.3.2.1 Preclinical Experience

A complete summary of the nonclinical data relevant to denintuzumab mafodotin (SGN-CD19A) and its study in human subjects is provided in the Investigator's Brochure (IB).

1.3.2.2 Clinical Experience

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 NHL (Protocol SGN19A-002). In the 52 patients treated to date, including 45 patients with DLBCL, the maximum tolerated dose (MTD) was not exceeded after escalating to 6 mg/kg every 3 weeks. Denintuzumab mafodotin was generally well tolerated, and the most common adverse events of any grade included blurred vision, dry eye, fatigue, constipation, and keratopathy. Hematopoietic toxicity and peripheral neuropathy were uncommon. Of the 51 patients evaluable for response, 18 patients (35%) achieved an objective response, including 10 patients (20%) with a complete remission (as presented by Moskowitz CH, et al. at ASH 2014). Antitumor activity appeared to be higher in relapsed patients. Of the 22 patients relapsed to their most recent prior therapy, 12 patients (55%) achieved an objective response, including 7 patients (32%) with a best response of CR and 5 (23%) with a PR.

See the IB for complete clinical safety information.

1.4 Rationale for Study

As described above, novel treatment strategies are needed to improve outcomes for relapsed, transplant-eligible DLBCL patients, where the goal is to achieve a high-quality remission that enables subsequent ASCT. The primary unmet need is the failure to achieve a high rate

of CR, as achievement of a PET-negative CR following second-line salvage therapy has been associated with improvement in outcome in relapsed DLBCL patients who proceed to ASCT (Dickinson 2010; Johnston 2008; Terasawa 2010).

Preliminary activity has been observed with denintuzumab mafodotin monotherapy in patients with relapsed or refractory DLBCL after failure of second-line salvage (unless transplant-ineligible) and beyond (Moskowitz 2014). Introduction of denintuzumab mafodotin into second-line treatment may be both clinically meaningful and associated with a favorable risk-benefit ratio. Denintuzumab mafodotin has not previously been combined with RICE. However, given the known safety profiles of RICE and denintuzumab mafodotin alone, few overlapping toxicities are anticipated. Safety data to date in Protocol SGN19A-002 have shown a favorable toxicity profile for denintuzumab mafodotin, with hematopoietic toxicity and peripheral neuropathy uncommon (Moskowitz 2014). Although myelosuppression is an expected consequence of RICE therapy, only transient thrombocytopenia that recovered prior to the subsequent 3-week cycle has been consistently associated with treatment with denintuzumab mafodotin in the NHL population.

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 RICE. In inherently denintuzumab mafodotin insensitive tumor xenograft models, the combined antitumor activity of both denintuzumab mafodotin and rituximab, as well as denintuzumab mafodotin and RICE was found to be considerably stronger than either agent or regimen alone in follicular lymphoma and diffuse large B-cell lymphoma (DLBCL) models, leading to prolonged tumor delay as well as complete remissions. Similarly, the combinations of denintuzumab mafodotin and ICE also demonstrated stronger antitumor activity in the DLBCL models when compared to denintuzumab mafodotin or ICE 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 (as presented by VanEpps H, et al. at the Annual Meeting of the American Association for Cancer Research, 2015).

Taken together, these data support further evaluation of incorporating denintuzumab mafodotin as part of multi-agent second-line therapy such as RICE and may yield an improvement in the CR rate, as well as PFS and OS benefit, in relapsed or refractory, transplant-eligible DLBCL patients.

2 OBJECTIVES

2.1 Primary Objective

- To compare the complete remission (CR) rates in patients with relapsed/refractory DLBCL who are candidates for autologous stem cell transplant (ASCT) treated with denintuzumab mafodotin plus RICE (19A+RICE) versus RICE

2.2 Secondary Objectives

- To evaluate the safety of denintuzumab mafodotin given in combination with RICE
- To compare progression-free survival (PFS) between study arms
- To compare overall survival (OS) between study arms
- To compare the proportion of patients who are able to adequately mobilize peripheral blood stem cells (PBSC) between study arms
- To compare the proportion of patients receiving ASCT following study treatment between study arms
- To compare other measures of antitumor activity between study arms

2.3 Additional Objectives

- To evaluate the pharmacokinetics (PK) of denintuzumab mafodotin (ADC and cys-mcMMAF) when denintuzumab mafodotin is given in combination with RICE chemotherapy
- To evaluate the incidence of antitherapeutic antibodies (ATA) against denintuzumab mafodotin
- To assess denintuzumab mafodotin-mediated pharmacodynamic (PD) effects and potential biomarkers to stratify response

2.4 Endpoints

2.4.1 Primary Endpoint

- Complete remission (CR) rate as determined by an independent review facility (IRF) following the completion of study treatment

2.4.2 Secondary Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities
- Objective response rate (ORR) per IRF following the completion of study treatment
- Duration of response (objective response [OR] and CR)
- Progression-free survival (PFS)

- Overall survival (OS)
- Proportion of patients achieving PBSC mobilization
- Proportion of patients receiving ASCT

2.4.3 Additional Endpoints

- Estimates of selected PK parameters of denintuzumab mafodotin and released cys-mcMMAF
- Incidence of antitherapeutic antibodies (ATA)
- Exploratory biomarkers of denintuzumab mafodotin-mediated PD effects

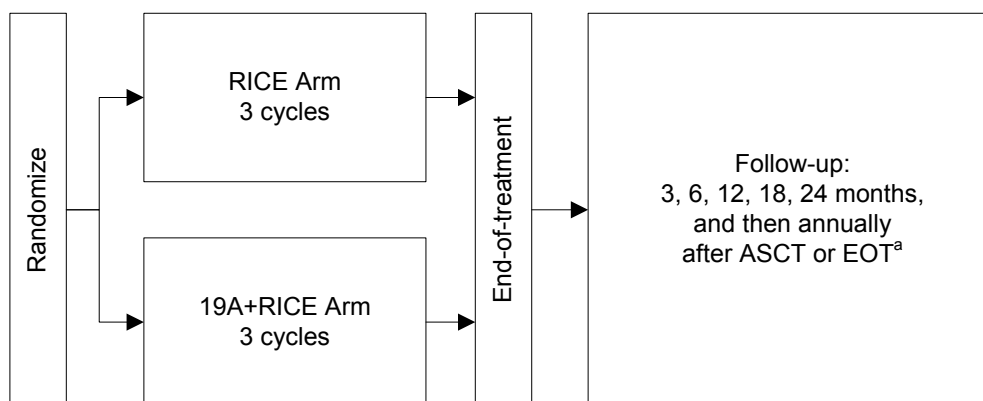
3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a randomized, open-label phase 2 study designed to compare the CR rates in patients with relapsed or refractory DLBCL who are candidates for ASCT. Approximately 100 patients will be randomized in a 1:1 ratio to 1 of 2 study arms (see [Figure 1](#)):

- Control, RICE Arm: 3 cycles (3 weeks per cycle) of rituximab 375 mg/m² administered as the first component of RICE on Day 1 of every cycle; and followed by etoposide (100 mg/m² per day), ifosfamide (5,000 mg/m²) infused continuously with mesna, and carboplatin (area under the curve 5 mg/mL x min; maximum dose, 800 mg) administered during each cycle in an order as per institutional standard of care
- Investigational, 19A+RICE Arm: 3 cycles (3 weeks per cycle) of denintuzumab mafodotin 3 mg/kg on Day 1 of every cycle in conjunction with 3 cycles (3 weeks per cycle) of RICE; denintuzumab mafodotin is administered prior to the rituximab component of RICE therapy given on Day 1 of each cycle

Figure 1: Study design



^a 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 anticancer treatment (with the exception of stem cell transplant), death, or study closure, whichever comes first. Survival status follow-up until death or study closure, whichever comes first.

A safety monitoring committee (SMC) comprising the study investigators, medical monitor, and study biostatistician will periodically monitor the safety of patients at predefined interim safety evaluations and during the treatment period (See Section 3.1.2). Upon its evaluation of the data, the SMC may recommend modification of the dose of denintuzumab mafodotin in the 19A+RICE Arm (e.g., to 2 mg/kg) in subsequently enrolled patients. If dose modification is necessary, up to 50 additional patients may be randomized (25 in each arm) so that a total of 100 patients will be randomized in a 1:1 ratio to receive either 19A (modified dose) + RICE or RICE alone.

If a subset of patients appears to potentially derive benefit from 19A+RICE versus RICE at a pre-planned evaluation, the Sponsor may continue enrolling those patients beyond the planned sample size (approximately 100 patients), but will not exceed the planned maximum number of patients to be randomized in this study (up to approximately 150 patients).

PET scans and computed tomography (CT) scans of the neck, chest, abdomen, and pelvis, will be assessed at baseline and at end of treatment (EOT). CT scans will be of diagnostic quality (i.e., contrast-enhanced with IV and oral contrast, unless contrast is medically contraindicated). Follow-up assessments will be performed at 3, 6, 12, 18, 24 months, and then annually after ASCT or EOT (for patients who don't receive ASCT). 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. Follow-up assessments will continue until disease progression, initiation of a new anticancer treatment (with the exception of a stem cell transplant), or study closure, whichever occurs first.

At screening and/or at any time on study, if a bone marrow biopsy is performed as part of standard of care, the results from the biopsy report for the presence of lymphoma will be recorded in the case report form (CRF). 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 occurs first.

Subsequent ASCT is permitted, based on investigator discretion and standard of care, and is recommended to occur within 8 weeks of Cycle 3 Day 1 (Philip 1995). Data will be recorded to assess adequacy of hematopoietic stem cell collection and transplant.

3.1.1 Dose-Delaying Toxicity

A dose-delaying toxicity (DDT) is defined as any study treatment-related toxicity that necessitates a delay of >14 days in the start of RICE treatment in the next cycle. With respect to hematologic recovery, it is recommended that the next cycle of RICE treatment be given once the patient's absolute neutrophil count (ANC) recovers to $\geq 1000/\mu\text{L}$ and the platelet count recovers to $\geq 75,000/\mu\text{L}$, as applicable.

See Section 5.8 for dose delay guidelines for DDTs; dose modifications for ocular events are described in Section 5.8.1.

3.1.2 Interim Safety Evaluations

An initial evaluation of the safety data will be conducted by the SMC after approximately 12 patients (6 patients in the 19A+RICE Arm) have been randomized and evaluated for DDTs delaying the Cycle 2 dose. Enrollment will be paused at this initial evaluation while the SMC assesses the cumulative safety data, including the incidence of DDTs that are associated with denintuzumab mafodotin in combination with RICE. After its review, the SMC will make one of the following recommendations to the sponsor regarding further conduct of the trial:

- Continue the trial as planned
- Modify the dose of denintuzumab mafodotin (e.g., to 2 mg/kg) in patients subsequently enrolled to the 19A+RICE Arm
- Temporarily halt enrollment

A second planned evaluation of the cumulative safety data will be conducted once the first 12 patients in the 19A+RICE Arm have been randomized and evaluated for DDTs delaying the Cycle 2 dose. The SMC will make a recommendation either to continue the trial as planned, modify the dose of denintuzumab mafodotin (e.g., to 2 mg/kg, if not already modified) in subsequently enrolled patients, or to temporarily halt enrollment.

A third planned interim evaluation for safety will be conducted once the first 12 patients in the 19A+RICE Arm have completed Cycle 3 or EOT. At this assessment, the SMC will evaluate safety including DDTs and late toxicities associated with denintuzumab mafodotin in combination with RICE, including an assessment of the ability to mobilize PBSC per institutional standard of care.

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.

3.2 Discussion and Rationale for Study Design

The Food and Drug Administration's (FDA's) "Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (May 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 the end of treatment as assessed by IRF utilizing the Lugano classification criteria ([Cheson 2014](#)). In this population where the ability to achieve a CR and proceed to ASCT directly influences long-term outcomes, CR is the most appropriate endpoint to assess treatment benefit. Complete remission measures the effect of the 2 treatment approaches being tested before ASCT is experienced by patients. The decision to proceed to subsequent transplant and subtle differences in conditioning regimens applied prior to transplant may represent sources of bias. Complete remission as the primary endpoint provides a direct comparison of treatment regimen efficacy, is directly correlated with long-term clinical benefit, and minimizes potential biases in interpretation. Therefore, CR rate is the most appropriate primary endpoint in this phase 2, randomized, open-label clinical trial.

3.2.1 Method of Assigning Patients to Treatment Groups

Following informed consent and screening assessments, patients will be assigned to 1 of 2 treatment arms in a 1:1 ratio using a central randomization system. Patients will be stratified by 3 factors:

- Disease status
- Second-line age-adjusted IPI score (saIPI) for patients ≤ 60 years of age or standard IPI score for patients > 60 years of age, as assessed at randomization
- Disease type

Randomization strata are specified in Section 9.3.1.1. Randomization procedures are detailed in the study manual.

3.2.2 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 intravenously (IV) every 3 weeks. Denintuzumab mafodotin has been generally well tolerated, and MTD was not exceeded at 6 mg/kg. 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 has demonstrated antitumor activity in 51 efficacy-evaluable patients with an ORR of 35% and CR rate of 20% (Moskowitz 2014). 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, the patients treated at 3 mg/kg (n=14) experienced the same rate of response (CR/PR) as those at the higher dose levels (unpublished data). Additionally, the 3 mg/kg dose level was well tolerated with fewer Grade 3/4 hematological adverse events than that observed with higher doses. Thus, 3 mg/kg is expected to be a safe and efficacious dose of denintuzumab mafodotin for evaluation in combination with RICE.

The dose of rituximab (375 mg/m²) is the standard approved dose for patients with previously untreated DLBCL when given in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or other anthracycline-based chemotherapy regimens. There is no standard dose or schedule for rituximab in the relapsed or refractory setting; however, the selected dose and schedule has been safely and effectively employed in combination with various single- and multi-agent chemotherapy regimens for this patient population (Gisselbrecht 2010; NCCN 2015). In theory, rituximab and denintuzumab mafodotin are partly eliminated via binding to CD19/CD20-positive B-cells, internalization, and catabolism, therefore changes in this cell population could potentially alter the PK of these molecules. However, dose adjustment of rituximab based on pre-treatment CD19 count is not necessary (Rituxan Prescribing Information, Genentech, September 2013), while denintuzumab mafodotin PK generally did not differ based on baseline CD19 levels in relapsed/refractory NHL patients (unpublished data).

The doses of ifosfamide (5000 mg/m²), carboplatin (area under the curve 5 mg/mL x min; maximum dose, 800 mg), and etoposide (100 mg/m² per day for 3 days) are the standard doses when given in a combination setting. Additionally:

- Ifosfamide is extensively metabolized (70–86% of the dose) by CYP3A4 and CYP2B6 (Ifosfamide Prescribing Information, APP Pharmaceuticals, January 2008). Cys-mcMMAF is 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), was not a direct, time- or metabolism-dependent inhibitor or inducer of CYP 3A or 2B6 in vitro (denintuzumab mafodotin IB).
- Carboplatin is mainly eliminated by renal glomerular filtration (Paraplatin Prescribing Information, Bristol-Myers Squibb, July 2010).
- Etoposide is eliminated by multiple mechanisms, including renal and biliary excretion and several metabolic pathways (sulfation, glucuronidation, and oxidation by CYP3A4) (Etopophos Prescribing Information, Bristol-Myers Squibb, March 2011).

Based on known metabolism and elimination information for cys-mcMMAF, rituximab, ifosfamide, carboplatin, and etoposide, the risk of drug-drug interactions between RICE components and denintuzumab mafodotin is considered low, therefore standard RICE doses are considered appropriate.

3.2.3 Blinding

This study is not blinded.

4 STUDY POPULATION

Patients must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of Good Clinical Practice (GCP) audit and/or health regulatory authority inspection.

4.1 Inclusion Criteria

1. Histologically confirmed CD20-positive, relapsed or refractory DLBCL, including de novo and transformed DLBCL (from follicular or marginal zone lymphoma), and Grade 3b follicular lymphoma. This includes patients with DLBCL who are found to have small cell infiltration of the bone marrow or other diagnostic material (representing a discordant lymphoma). (CD20-positivity requirement not applicable to Amendment 2.)
2. Available representative tissue from the most recent biopsy after the last therapy; if such tissue is not available, a fresh biopsy must be obtained. Archived tumor tissue from the initial biopsy, if available, is also required to be submitted during the trial.
3. Received only frontline CD20-directed immunotherapy with anthracycline- or anthracenedione-based multi-agent chemotherapy. Monotherapy rituximab or other CD20-directed immunotherapy prior to frontline chemotherapy, as maintenance therapy,

and radiotherapy in a limited field or as a part of the frontline treatment plan are permitted.

4. Achieved a response of stable disease (SD), PR, or CR (when compared to the baseline, pre-treatment disease assessment) following the last cycle of frontline treatment with multi-agent chemo-immunotherapy regimens delivered with curative intent.
 - a. Relapsed less than or equal to 6 months from the completion of frontline therapy at the time of initial dosing in this clinical trial (applicable only to patients enrolled under Amendment 2).
5. Considered eligible for high-dose chemotherapy followed by ASCT.
6. FDG-avid disease by PET, and measurable disease of >1.5 cm in the greatest transverse diameter by CT, as assessed by the site radiologist.
7. Age 18 years or older.
8. An Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 .
9. Patients must have the following baseline laboratory data:
 - serum bilirubin ≤ 1.5 x the upper limit of normal (ULN) or ≤ 3 mg/dL for patients with Gilbert's syndrome or documented hepatic involvement with lymphoma
 - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN or ≤ 5 x ULN for patients with documented hepatic involvement with lymphoma
 - serum creatinine of ≤ 1.5 mg/dL; if creatinine >1.5 mg/dL creatinine clearance must be >60 mL/min within 7 days prior to treatment either measured or calculated using a standard Cockcroft and Gault formula
 - absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$
 - platelet count $\geq 75,000/\mu\text{L}$
10. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β -hCG) pregnancy test result within 7 days prior to the first dose of study treatment. Females of non-childbearing potential are those who are post-menopausal for more than 1 year or who have had a bilateral tubal ligation or hysterectomy.
11. 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.
12. Patients must provide written informed consent.

4.2 Exclusion Criteria

1. Previous history of indolent lymphoma treated with more than 1 multi-agent chemotherapy regimen (including such therapies as rituximab-bendamustine) or previous cancer therapy for recurrent DLBCL or Grade 3b follicular lymphoma.
2. History of autologous or allogeneic stem cell transplant.
3. History of another primary invasive cancer, hematologic malignancy, or myelodysplastic syndrome that has not been in remission for at least 1 year.
4. History of progressive multifocal leukoencephalopathy (PML).
5. Cerebral/meningeal disease related to the underlying malignancy. Patients with a history of cerebral/meningeal disease related to the underlying malignancy are allowed if prior central nervous system disease has been definitively treated.
6. Patients with the following ocular conditions:
 - Corneal disorders: corneal dystrophies, history of corneal or limbal stem cell transplantation (including endothelial keratoplasty), evidence of limbal stem cell deficiency (i.e., deep pannus, poor epithelial healing)
 - Monocular vision (i.e., best corrected visual acuity $\geq 20/200$ in one eye)
 - 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
7. Congestive heart failure, Class III or IV, by the New York Heart Association (NYHA) criteria.
8. Any active Grade 3 or higher (per the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 4.03 or higher) 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. Chemotherapy, radiotherapy, biologics, and/or other antitumor treatment with immunotherapy that is not completed 4 weeks prior to study entry. Note: radiotherapy within 4 weeks prior to study entry is acceptable if the underlying disease has progressed on treatment.
11. Acute toxicities from previous chemotherapy, radiotherapy, biologics and/or other antitumor treatment must have resolved or returned to baseline.
12. Females who are breastfeeding.

13. Known hypersensitivity to any study treatment or any excipient contained in the drug formulations of study treatments.
14. Patients with a positive polymerase chain reaction (PCR) assay who have also tested positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody; patients with a negative PCR assay are permitted with appropriate anti-viral prophylaxis.
15. Known or suspected active hepatitis C infection or known human immunodeficiency virus (HIV) infection.
16. Known urinary tract obstruction.

4.3 Removal of Patients from Therapy or Assessment

Seattle Genetics 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 case report form (CRF).

4.3.1 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 (AE)
- Investigator decision
- Patient decision, Non-AE
- Study termination by sponsor
- Other, Non-AE

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

4.3.2 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

5 TREATMENTS

5.1 Treatments Administered

Patients will be randomized within 1 business day prior to the planned first dose of Cycle 1 Day 1. Patients will receive either denintuzumab mafodotin in combination with RICE (19A+RICE Arm) or RICE alone.

5.2 Investigational Study Drug

Denintuzumab mafodotin (SGN-CD19A), 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 Instructions.

5.2.1 Description

Denintuzumab mafodotin is a sterile, preservative-free, white to off-white lyophilized cake or powder supplied by Seattle Genetics in single-use glass vials for reconstitution for IV administration. Each drug product vial contains [REDACTED]

[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 (WFI), United States Pharmacopeia (USP), the reconstituted product has a concentration of 5 mg/mL. The pH of the reconstituted product is approximately 6. Before administration, reconstituted denintuzumab mafodotin must be diluted.

5.2.2 Dose and Administration

Patients randomized to the 19A+RICE Arm will receive denintuzumab mafodotin (3 mg/kg), administered on Day 1 of each 21-day cycle by IV infusion given over approximately 30 minutes. The dose of denintuzumab mafodotin may be modified (e.g., to 2 mg/kg) 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 experience a $\geq 10\%$ change in weight from baseline. If rounding, doses must be rounded to the nearest milligram.

Denintuzumab mafodotin should be given prior to and on the same day as rituximab (the first component of RICE). Denintuzumab mafodotin infusion should be completed approximately 30 to 60 minutes prior to the start of rituximab (see Section 5.3.3). 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 20–45 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 of denintuzumab mafodotin. 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.

5.2.3 Storage and Handling

Single-use vials containing denintuzumab mafodotin must be stored under refrigeration set to 2 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 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 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 to 8°C. Drug product vials and solutions should be protected from direct sunlight until the time of use. Reconstituted vials and solutions must not be shaken.

Drug accountability instructions are provided in the Pharmacy Binder.

5.2.4 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 (USAN) and the International Nonproprietary Name (INN), or as SGN-CD19A, the compound code; the 2 names can be used interchangeably.

5.2.5 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 Instructions.

5.3 Rituximab, Etoposide, Ifosfamide, and Carboplatin

In this protocol, RICE is administered either in combination with denintuzumab mafodotin (19A+RICE Arm) or alone.

5.3.1 Description

RICE is a standard chemo-immunotherapy regimen consisting of rituximab, etoposide, ifosfamide, and carboplatin. Rituximab is a CD20-directed cytolytic antibody. Etoposide is a topoisomerase inhibitor. Ifosfamide is a nitrogen mustard alkylating agent. Carboplatin is a platinum-based antineoplastic agent with a mechanism of action that interacts with DNA to interfere with DNA repair.

5.3.2 Method of Procurement

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

Rituximab, etoposide, ifosfamide, and carboplatin 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).

5.3.3 Dose and Administration

Patients in both treatment arms will receive RICE. In the 19A+RICE Arm, rituximab administration (as the first component of RICE) should be initiated approximately 30 to 60 minutes after the completion of denintuzumab mafodotin study drug infusion on Day 1.

Rituximab 375 mg/m² should be administered IV on Day 1 as the first component of RICE. The remaining RICE components may be administered in an order as per institutional standard of care. Typically, etoposide (100 mg/m² per day) is administered IV on Days 1 through 3; ifosfamide (5,000 mg/m²) is infused continuously in an inpatient setting for approximately 24 hours on Day 2 with mesna; and carboplatin (area under the curve 5 mg/mL x min; maximum dose, 800 mg) is administered IV on Day 2.

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

5.3.4 Storage and Handling

Rituximab, etoposide, ifosfamide, and carboplatin should be stored and handled per the package insert.

5.3.5 Packaging and Labeling

Rituximab, etoposide, ifosfamide, and carboplatin are commercially available in the US.

5.3.6 Preparation

Rituximab, etoposide, ifosfamide, and carboplatin should be prepared per the package insert.

5.4 Required Premedication and Postmedication

Routine premedication is not necessary for the prevention of infusion-related reactions prior to the first dose of denintuzumab mafodotin. However, patients who experience a Grade 1 or

Grade 2 infusion-related reaction may receive subsequent denintuzumab mafodotin infusions with premedication as described in Section 5.6.

Acetaminophen and an antihistamine should be given within 15 to 90 minutes prior to 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. Premedications for the rituximab infusion may be given during the 30 to 60 minute period between the completion of the denintuzumab mafodotin infusion and the start of the rituximab infusion.

Routine anti-emetic prophylaxis regimen should be administered with each cycle of RICE per institutional standard and should include oral or IV dexamethasone at a dose of at least 12 mg on Day 1, and 8 mg on Days 2 and 3. Omission or discontinuation of steroid antiemetic treatment may be allowed under certain circumstances (e.g., in the setting of intolerability, contraindication, or toxicity secondary to dexamethasone) upon discussion with the medical monitor.

Patients in both treatment arms should receive prophylactic growth factor support (e.g., filgrastim or polyethylene glycol [PEG]-filgrastim, per institutional standard) following each cycle of chemotherapy to shorten the duration of neutropenia (see Section 5.8). As per National Comprehensive Cancer Network (NCCN) guidelines, it is recommended that:

- PEG-filgrastim be given as 1 dose of 6 mg subcutaneously (sc) per cycle, administered the day after completion of chemotherapy
- Filgrastim be given as a daily dose of 5 mcg/kg (total dose rounded to the nearest vial size per institutional-defined weight limits) initiated the next day or up to 3–4 days after completion of chemotherapy until post-nadir ANC recovery to normal or near normal levels by laboratory standards. The preferred route of administration is sc, but may also be given IV

Refer to the United States Prescribing Information (USPI) for the applicable growth factor support in order to determine the appropriate administration window for use with cytotoxic chemotherapy.

There are no protocol-required pre- or postmedications for etoposide, ifosfamide, or carboplatin, other than those mentioned above.

See Section 5.5.1 for other required concomitant therapies.

5.4.1 Prophylactic Ocular Interventions for Denintuzumab Mafodotin

Prophylactic steroid eye drops must be administered daily for 7 days with each dose of denintuzumab mafodotin. Steroid eye drops should consist of prednisolone 1% administered four times daily, 1 drop in each eye or equivalent. 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 (e.g., 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 5.8.1, .See Section 7.7.5 for the ocular safety monitoring plan.

Prophylactic preservative-free artificial tears should be administered twice daily, at least one drop in each eye, beginning on Cycle 1 Day 1 until EOT. Allow at least 30 minutes between administration of artificial tears and steroid eye drops. In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed (Section 5.8.1).

While not yet clinically demonstrated, it is theoretically possible that the application of a cooling eye mask during denintuzumab mafodotin administration in the first few hours after infusion and the use of vasoconstrictor eye drops may reduce exposure of the eye tissue to denintuzumab mafodotin and may subsequently decrease ocular side effects. On the day of infusion, the following are recommended:

- Vasoconstrictor eye drops (consisting of tetrahydrozoline 0.05% or naphazoline 0.012%, or equivalent) should be administered 1 drop in each eye at the following time points: (1) start of denintuzumab mafodotin infusion, (2) start of rituximab infusion, and (3) end of rituximab infusion.
- Beginning with the start of each denintuzumab mafodotin infusion, it is recommended that patients apply cooling eye masks to their eyes for approximately 1 hour, or as much as tolerated by the patient. Patients are encouraged to continue using the cooling eye mask beyond the first hour for up to 4 hours. Further use beyond 4 hours is at the patient's discretion.

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

A summary of prophylactic ocular interventions for patients randomized to the 19A+RICE Arm is provided in Table 1.

Table 1: Prophylactic^a ocular interventions with denintuzumab mafodotin

Prophylactic Measure	Dose and Administration	Timing
Steroid eye drops	Prednisolone 1% administered 4 times daily, 1 drop in each eye or equivalent.	Begin 1 day prior to each dose of denintuzumab mafodotin ^b . Administer for 7 days.
Preservative-free artificial tears	Administer twice daily, at least 1 drop in each eye.	Administer daily beginning on Cycle 1 Day 1 until EOT. Allow at least 30 minutes between administration of artificial tears and steroid eye drops.
Vasoconstrictor eye drops	Tetrahydrozoline 0.05% or naphazoline 0.012% or equivalent, administer 1 drop in each eye.	At the time of infusion: <ol style="list-style-type: none"> 1. At the start of denintuzumab mafodotin infusion 2. At the start of rituximab infusion 3. At the end of rituximab infusion
Cooling eye mask	Apply cooling eye mask to both eyes for approximately 1 hour, or as much as tolerated by the patient. Use beyond the first hour for up to 4 hours is encouraged. Further use beyond 4 hours is at the patient's discretion.	Begin at the start of each denintuzumab mafodotin infusion.

a Dose modifications and treatment for ocular toxicities are discussed in Section 5.8.1.

b In Cycle 1, beginning steroid eye drop prophylaxis on Day 1 is acceptable.

5.5 Concomitant Therapy

All concomitant medications and blood products administered will be recorded from Day 1 (predose) through the safety reporting period, unless the concomitant medication is for an event specifically related to ASCT (see Section 6.1). Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.5.1 Required Concomitant Therapy

Patients with a negative hepatitis PCR assay who tested positive for hepatitis B surface antigen and/or hepatitis B core antibody should begin antiviral prophylaxis prior to receiving study treatment and 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.

All 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 (e.g., treatment with allopurinol or rasburicase, as well as adequate hydration (Cairo 2010).

See Section 5.4 for required pre- and post-medications.

5.5.2 Allowed Concomitant Therapy

The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed.

The use of corticosteroids to treat conditions other than DLBCL is permitted per institutional standard. The use of systemic corticosteroids to palliate DLBCL-related symptoms prior to Cycle 1 Day 1 is permitted but recommended not to exceed 14 days.

Routine antibiotic prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP) should be considered for all patients per standard of care. In addition, the NCCN 2015 guideline for the prevention and treatment of cancer-related infections is recommended ([NCCN 2015](#)).

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.

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

5.5.3 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the treatment phase of the study. Exceptions are noted in Section [5.5.2](#).

5.6 Management of Infusion Reactions

Infusion reactions related to rituximab, etoposide, ifosfamide, or carboplatin 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 experienced a Grade 1 or Grade 2 infusion-related reaction after administration of denintuzumab mafodotin should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 15–90 minutes prior to each infusion or according to institutional standards.
- Patients who experience a Grade 3 infusion-related reaction after denintuzumab mafodotin administration may potentially receive additional treatment with denintuzumab mafodotin at the discretion of the investigator after discussion with the sponsor.
- If anaphylaxis or a Grade 4 infusion-related reaction occurs after denintuzumab mafodotin administration, denintuzumab mafodotin should be immediately and permanently discontinued.

See Section [7.7.1](#) for details regarding recording adverse events.

5.7 Management of Suspected PML

PML has been associated with rituximab treatment (Rituxan Prescribing Information, Genentech, September 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 (RICE 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 (MRI)
- Polymerase chain reaction (PCR) analysis: John Cunningham virus (JCV) DNA detectable in cerebrospinal fluid

If PML is confirmed, permanently discontinue study treatment.

5.8 Dose Modifications

Dose modifications of rituximab, etoposide, ifosfamide, or carboplatin due to hematologic and non-hematologic toxicity are allowed per institutional standards and according to the product-specific United States Prescribing Information (USPI), or other 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 RICE chemo-immunotherapy and should not be used as the basis for dose reduction or elimination of denintuzumab mafodotin. All patients should receive growth factor support to shorten the duration of neutropenia (see Section 5.4). If adequate myeloid recovery has not occurred per institutional standard of care, initiation of the next cycle may be postponed. Cycle 2 and/or Cycle 3 should not begin until there has been satisfactory recovery of peripheral blood counts (i.e., recommend that platelets $\geq 75,000/\mu\text{L}$ and ANC $\geq 1000/\mu\text{L}$).

If RICE chemo-immunotherapy will be delayed at the start of Cycle 2 or Cycle 3 due to myelosuppression or other dose-delaying toxicity (DDT), denintuzumab mafodotin infusion will be delayed as well. A delay of more than 14 days in starting RICE in Cycles 2 and/or 3 is discouraged; delays of more than 21 days are not allowed without discussion with the sponsor.

If RICE chemo-immunotherapy is discontinued, no further denintuzumab mafodotin will be given and the patient will be discontinued from the treatment phase of the study (see Section 6.6).

Denintuzumab mafodotin infusion may be delayed at the start of Cycle 2 or Cycle 3 due to ocular toxicity (see Section 5.8.1). Per-patient dose modifications of denintuzumab mafodotin are permitted as described in Section 5.8.1. Dose modifications of denintuzumab mafodotin must be discussed with the medical monitor. In the absence of myelosuppression

or other DDT, RICE chemo-immunotherapy should be administered as planned on a q3week (21-day) cycle.

5.8.1 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 (see [Appendix E](#)). [Table 2](#) 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 \leq Grade 2 or corneal changes recover to \leq 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 (i.e., dry eyes), the use of preservative-free artificial tears may be increased up to every 2 hours, as needed.

Steroid eye drops administered for the treatment of \geq Grade 2 ocular symptoms or \geq 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 [7.7.5](#) for additional details of the ocular safety monitoring plan. Refer to Section [7.7.1.2](#) and [Appendix E](#) for information regarding the grading of ocular events related to the cornea.

Table 2: Evaluation, treatment, and dose modifications in the event of ocular toxicity

CTCAE ^a	Evaluation and Treatment	Dose Modifications ^b
Ocular Symptoms		
Grade 1	Use of preservative-free artificial tears may be increased up to every 2 hours, as needed	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). Use of preservative-free artificial tears may be increased up to every 2 hours, as needed.	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 \leq Grade 2 within 7 days after the start of the current cycle of RICE, 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 \leq Grade 2 within 7 days after the start of the current cycle of RICE, skip dose of denintuzumab mafodotin for this cycle. Re-evaluate subsequent denintuzumab mafodotin dosing at the end-of-cycle ophthalmologic evaluation.
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). Use of preservative-free artificial tears may be increased up to every 2 hours, as needed. 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 \leq Grade 3 within 7 days after the start of the current cycle of RICE, 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 \leq Grade 3 within 7 days after the start of the current cycle of RICE, skip dose of denintuzumab mafodotin for this cycle. Re-evaluate subsequent denintuzumab mafodotin dosing at the end-of-cycle ophthalmologic evaluation.

a Modified CTCAE grading scheme; see [Appendix E](#).

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

5.9 Peripheral Blood Stem Cell Mobilization and Collection

Peripheral blood stem cells may be mobilized during study treatment at the discretion of the investigator.

Collection of PBSC for ASCT, if applicable, should occur per institutional standard of care. If initial stem cell collection is inadequate, additional collection of peripheral blood stem cells for ASCT may be performed per institutional standards.

5.10 Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF.

6 STUDY ACTIVITIES

6.1 Schedule of Events

Adverse events (AEs) and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.7.1.3). Any study protocol-related AE should be recorded from the time of informed consent as well as any concomitant medications given for the treatment of the AE.

Beyond the safety reporting period, patients may undergo subsequent ASCT. Additional transplant-related data will be collected following ASCT and may include, but not be limited to, the time to neutrophil and platelet engraftment in each treatment arm.

A schedule of events is provided in [Appendix A](#). Study activities are listed by visit in this section, and descriptions of all study assessments are presented in Section 7.

6.2 Screening Visit (Day –28 to Day 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria (see Section 4)
- Medical history; medical history at screening includes a review of inflammatory conditions (see Section 7.1)
- Collection/acquisition of tumor specimen for central pathology review (see Section 7.1)
- Patient second-line, age-adjusted International Prognostic Index (saaIPI) score for patients ≤ 60 years of age or standard IPI score for patients > 60 years of age (see [Appendix D](#))
- Serology for hepatitis B surface antigen and anti-hepatitis B core antibody; if either is positive, PCR for hepatitis B viremia must also be performed (see Section 5.5.1)
- Blood sample for biomarker assessments ([Table 3](#))
- CT of diagnostic quality of neck, chest, abdomen, and pelvis (see Section 7.2)
- 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)

- If a bone marrow biopsy has been performed as part of standard of care, record the biopsy result for lymphoma involvement in the CRF (see Section 7.2; a result from a biopsy collected within 60 days prior to the first dose of study treatment may be used)
- Ophthalmology exam (see Section 7.7.5)
 - Ocular health survey (± 2 days from the ophthalmology exam)

6.2.1 Baseline Visit (Day –7 to Day 1)

- Physical exam (see Section 7.7.4)
- Height and weight
- B symptom assessment (see Section 7.2)
- ECOG performance status (see Appendix B)
- Electrocardiogram (ECG)
- Pregnancy test for females of childbearing potential
- Serum chemistry panel, including fasting blood glucose (see Section 7.7.3)
- Hemoglobin A1c (Hgb A1c)
- Complete blood count (CBC) with differential (see Section 7.7.3)
- Prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- Spot urine for urine protein:creatinine (UPC) ratio (see Section 7.7.3)

6.3 Randomization (Day –1 to Day 1)

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

- For the 19A+RICE Arm: Begin prophylactic steroid eye drop administration. Steroid eye drop prophylaxis is recommended to begin 1 day prior to denintuzumab mafodotin dose if possible (see Section 5.4.1); however, beginning steroid eye drop prophylaxis on Day 1 for the first cycle of treatment is acceptable.

6.4 Treatment Period (Day 1 to Day 21)

6.4.1 Cycle 1, Day 1

All Day 1 assessments should be completed prior to study drug administration.

- Vital signs (see Section 7.7.2)
- Serum chemistry panel
- CBC with differential
- PT/PTT/INR
- Spot urine for UPC ratio
- Blood samples for PK, ATA, and biomarker assessments (see Table 3)
- For the 19A+RICE Arm:
 - Denintuzumab mafodotin administration

- Prophylactic steroid eye drop administration starting 1 day before infusion, if not already started
- Recommended prophylactic ocular interventions at the time of infusion: cooling eye mask application and vasoconstrictor eye drops administration (see [Table 1](#))

If Baseline Visit activities occur within 1 day prior to Cycle 1, Day 1, 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.

6.4.2 Cycle 1, Day 1 to Day 3 (+1 day)

- RICE administration (see Section [5.3.3](#))
- Days 1 and 2: Blood samples for PK, ATA, and biomarker assessments (see [Table 3](#))

6.4.3 Cycle 1, Day 4

- Blood samples for PK and biomarker assessments (see [Table 3](#))

6.4.4 Cycle 1, Day 8 (±1 day)

- Serum chemistry panel
- CBC with differential
- Spot urine for UPC ratio
 - 24-hour urine collection if UPC >2 (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)
- Blood samples for PK and biomarker assessments (see [Table 3](#))

6.4.5 Cycle 1, Day 15 (±1 day)

- Serum chemistry panel
- CBC with differential
- Spot urine for UPC ratio
 - 24-hour urine collection if UPC >2 (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)
- Blood samples for PK and biomarker assessments (see [Table 3](#))

6.4.6 Cycle 1, Day 22 (±3 days)

For patients who do not continue on treatment or do not start the next cycle on Day 22 due to dose delay:

- Blood sample for PK (see [Table 3](#))

6.4.7 Cycles 2 and 3: Day 1 (±1 day)

- Perform the following procedures within 24 hours prior to administration of the first component of study treatment
 - Physical exam, including weight

- Vital signs (see Section 7.7.2)
- ECOG performance status
- B symptom assessment
- Serum chemistry panel
- CBC with differential
- PT/PTT/INR
- Spot urine for UPC ratio
 - 24-hour urine collection if UPC >2 (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)
- Blood samples for PK, ATA, and biomarker assessments (see Table 3)
- For the 19A+RICE Arm:
 - Denintuzumab mafodotin administration
 - Prophylactic steroid eye drop administration. Note: Eye drop prophylaxis should begin 1 day prior to denintuzumab mafodotin dose (see Section 5.4.1).
 - Recommended prophylactic ocular interventions at the time of infusion: cooling eye mask application and vasoconstrictor eye drops administration (see Table 1)

6.4.8 Cycles 2 and 3: Day 1 to Day 3 (±1 day)

- RICE administration

6.4.9 Cycles 2 and 3: Day 8 (±1 day)

- Serum chemistry panel
- CBC with differential
- Spot urine for UPC ratio
 - 24-hour urine collection if UPC >2 (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)

6.4.10 Cycles 2 and 3: Day 15 (±1 day)

- Serum chemistry panel
- CBC with differential
- Spot urine for UPC ratio
 - 24-hour urine collection if UPC >2 (prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment)
- Ophthalmology exam (performed Day 14 to Day 21 of the treatment cycle, unless alternate schedule is approved by the medical monitor; see Section 7.7.5). Review exam results prior to next dosing of denintuzumab mafodotin; dose modifications should be made based on ocular toxicity grading (see Table 2 and Appendix E).
 - Ocular health survey (±2 days from the ophthalmology exam)

6.4.11 Cycle 2, Day 22 (± 3 days)

For patients who do not continue on treatment or do not start the next cycle on Day 22 due to dose delay:

- Blood sample for PK (see [Table 3](#))

6.5 PBSC Mobilization

PBSC mobilization for ASCT should occur per institutional standard of care. Chemotherapy for the mobilization of stem cells is permitted. Information surrounding PBSC mobilization and collection, if conducted, will be collected and may include, but not be limited to, the following: date of mobilization, number of CD34-positive cells mobilized (cells/kg), and mobilization regimen.

6.6 End of Treatment Visit

End of Treatment (EOT) visits should occur 14 to 30 days after the start of the last cycle (administration of denintuzumab mafodotin in the 19A+RICE Arm, or Day 1 of RICE in the control arm), unless delayed due to an AE. However, EOT evaluations must be performed before initiation of a new therapy, inclusive of radiotherapy and ASCT. If EOT evaluations are completed before 30 days after completion of study treatment, the patient will also be contacted 30–37 days following the completion of study treatment to assess for adverse events.

- Physical examination
- Review of inflammatory conditions (only for those patients with certain inflammatory conditions of interest at Screening/Baseline)
- ECOG performance status
- B symptom assessment
- ECG
- Ophthalmology exam (not required if an exam was performed within 4 weeks prior to the EOT visit, and following the last dose of study treatment)
 - Ocular health survey (± 2 days from the ophthalmology exam)
- Pregnancy test for females of childbearing potential
- Serum chemistry panel
- CBC with differential
- PT/PTT/INR
- Spot urine for UPC calculation
 - 24-hour urine collection if UPC > 2 (within 5 days after UPC assessment)
- Blood samples for PK, ATA, and biomarker assessments (see [Table 3](#))
- For patients discontinuing treatment due to disease progression: if a tumor biopsy was performed at the time of disease progression as part of standard of care, submit sample of tumor specimen, if available (see [Section 7.4.4](#))

The following response assessments are required (unless progressive disease [PD] was documented within the previous 6 weeks by diagnostic CT/PET scan):

- CT of diagnostic quality of neck, chest, abdomen, and pelvis (see Section 7.2)
- 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)
- If patient is scheduled to undergo stem cell collection and bone marrow biopsy is performed as part of standard of care, record the bone marrow biopsy result for lymphoma involvement in the CRF.

6.7 Long-Term Follow-Up Visits

Patients who discontinue from study treatment will remain on the study for follow-up until discontinuation from the study by withdrawal of consent, loss to follow-up, death, or study closure, whichever occurs first (see Section 4.3.2).

For patients who discontinue study treatment for any reason other than disease progression or initiation of a non-protocol therapy (with the exception of ASCT) for treatment of lymphoma, long-term follow-up visits for PFS assessment will occur at 3, 6, 12, 18, 24 months (± 1 month), and then annually after ASCT or EOT (for patients who don't receive ASCT).

The following assessments will be performed at long-term follow-up visits:

- Clinical assessment of disease status by history and physical examination
- CT scan of diagnostic quality of the neck, chest, abdomen, and pelvis (see Section 7.2) until disease progression or initiation of a new anticancer treatment (with the exception of a stem cell transplant); perform at follow-up visits and at any time disease progression is suspected
- PET scan, unless disease is PET negative; required until disease is PET negative (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)
- Record subsequent anticancer therapies received
- For patients who receive ASCT, collect PBSC mobilization outcomes, and time to neutrophil and platelet engraftment

At any time during the follow-up period, if a bone marrow biopsy is performed as part of standard of care, the results from the bone marrow biopsy for lymphoma involvement will be recorded in the CRF.

For patients who proceed to ASCT, an ophthalmology exam and ocular health survey will be performed approximately 30-days post ASCT.

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

All patients who receive at least one dose of denintuzumab mafodotin in the experimental arm or RICE in the control arm will be followed for survival at 6-month intervals after ASCT or EOT for the first 24 months and then yearly thereafter until death or study closure, whichever occurs first. At the time of study closure, patients will be contacted for a final survival assessment.

6.8 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 4.3.2).

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

Only patients who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

Histologically-confirmed DLBCL must be determined by local pathology assessment. Submission of the tumor block or approximately 15 unstained slides from a biopsy of relapsed disease (or diagnostic specimen if refractory) is required for subsequent central pathology disease confirmation and further evaluation of pharmacodynamic biomarkers (see Section 7.4). 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 representative tissue from the most recent tumor biopsy after the last therapy is unavailable, a fresh biopsy must be obtained.

If available, archived tumor tissue from the initial biopsy is also required to be submitted during the trial.

A blood sample for hepatitis serology and biomarker assessments is required (Table 3).

Patient medical history includes a thorough review of:

- The patient's current and previous conditions
- Disease status after each previous systemic therapy received prior to entering this study
- Concomitant medications and prior therapies for malignancy

Included with the medical history is 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.

Patient second-line, age-adjusted International Prognostic Index (saaIPI) scores should be calculated based on the method initially published by Shipp et al, Moskowitz et al, and updated by Hamlin et al (see [Appendix D](#)) to be used for randomization of patients ≤ 60 years of age. The saaIPI is calculated by scoring 3 prognostic factors: stage of disease, lactate dehydrogenase (LDH) level, and ECOG score. The standard IPI should be used for randomization of patients > 60 years of age. The standard IPI incorporates additional scores for age and extranodal involvement. Refer to the study manual for details and scoring sheet.

Patient disease stage will be calculated to determine eligibility, per the Cotswolds Modification of Ann Arbor Staging System ([Lister 1989](#)).

Cardiac assessment will be performed with an ECG.

7.2 Response/Efficacy Assessments

The determination of antitumor activity will be based on response assessments made according to the Lugano Classification Revised Staging System for malignant lymphoma (see [Appendix F](#)) ([Cheson 2014](#)). Treatment decisions by the investigator will be based on these assessments. PET and CT scans are required per protocol as directed in [Section 6](#) and [Appendix A](#). 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. CT scans will be of diagnostic quality (i.e., contrast-enhanced with IV and oral contrast, unless contrast is medically contraindicated). 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 (PD), stable disease (SD), partial remission (PR), or complete remission (CR) 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 complete metabolic response (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 and evaluated by CT-based response criteria per the Lugano classification criteria.

At any time on study, if bone marrow biopsies are performed as part of standard of care, results from the biopsy reports will be recorded in the CRF. The results will be used to confirm the presence or absence of lymphoma in the marrow. At the screening visit, a result

from a biopsy performed within 60 days of the first dose of denintuzumab mafodotin in the 19A+RICE Arm or RICE in the control arm, as part of clinical care, is preferred, if available. 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 recorded. All available bone marrow biopsy results will also be recorded in the CRF.

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 CRF source verification. Copies of all tumor imaging studies must be submitted for IRF review as described in the study manual.

7.3 Pharmacokinetic and Antitherapeutic Antibody Assessments

Sensitive, qualified assays will be used to measure concentrations of denintuzumab mafodotin ADC and released cys-mcMMAF in plasma. PK samples will be collected and archived for possible analysis of other denintuzumab mafodotin-related species and rituximab concentrations. Samples for rituximab PK will only be collected and archived for the first 20 patients treated in the RICE Arm and the first 50 patients treated in the 19A+RICE Arm. The assays will include enzyme-linked immunosorbent assays (ELISA) and liquid chromatography/tandem mass spectrometry (LC-MS/MS) assays, as well as other assays if further characterization is required. A qualified electrochemiluminescence assay will be used to determine the levels of antitherapeutic antibodies (ATA).

The PK parameters to be estimated include, but are not limited to, maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC), plasma concentrations at trough (C_{trough}), terminal half-life ($T_{1/2}$), plasma clearance (CL), steady-state volume of distribution (V_{ss}), and accumulation ratio (AR). Related analytes of denintuzumab mafodotin may also be measured using appropriate assays.

Blood samples for PK and antitherapeutic antibodies (ATA) testing will be collected at timepoints throughout the study as described in [Table 3](#). Refer to the Central Laboratory Manual for information on collection, processing, storage, and shipment of samples.

Table 3: Pharmacokinetic, antitherapeutic antibody, and biomarker sampling timepoints

								Biomarker Samples				
	Study Day	Time	Window	Relative Time ^c	SGN-CD19A PK ^a	Rituximab PK ^b	ATA	Tumor Tissue	Whole Blood	Serum	Plasma	Cell Pellet
Screening/ Baseline	Day -28 to 1	N/A	N/A	N/A				X ^d	X			
Cycle 1	Day 1	Pre-dose	Within 24 hrs prior to start of infusion	Start of infusion	X	X	X		X	X	X	X
		End of SGN-CD19A infusion	Within 5 min post end of infusion	End of infusion	X							
		End of rituximab infusion	Within 5 min post end of infusion	End of infusion		X						
		4 h	±15 min	End of infusion	X							
		8 h	±30 min	End of infusion	X							
	Day 2	24 hr	±4 hr	Start of infusion	X	X			X	X	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	X	
	Day 15	336 hr	±24 hr	Start of infusion	X	X			X	X	X	
	Day 22 ^f	504 hr	±72 hr	Start of infusion	X	X						
Cycles 2 and 3	Day 1	Pre-dose	Within 8 hr	Start of infusion	X	X	X		X	X	X	
		End of SGN-CD19A infusion	Within 5 min post end of infusion	End of infusion	X							
		End of rituximab infusion	Within 5 min post end of infusion	End of infusion		X						
	Day 22 ^f	504 hr	±72 hr	Start of infusion	X	X						
EOT					X	X	X	X ^e	X	X	X	

^a 19A+RICE Arm only.

^b Collected for the first 20 patients treated in the RICE Arm and the first 50 patients treated in the 19A+RICE Arm.

^c Relative time is based on the denintuzumab mafodotin infusion in the 19A+RICE Arm and based on the rituximab infusion in the RICE Arm.

^d Representative tissue from the most recent biopsy after the last therapy or fresh tumor specimen for study entry (see Section 7.1) and biomarker analysis (see Section 7.4.4). If available, archived tumor tissue from the initial biopsy is also required.

^e 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 (see Section 7.4.4).

^f For Cycle 1 and Cycle 2 only. Sample obtained only for patients not continuing on treatment or not starting the next cycle on Day 22.

7.4 Biomarker Analysis

Samples from patients in both treatment arms 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 pharmacodynamic markers of denintuzumab mafodotin activity and compared to that in the RICE control treatment cohort. Circulating proteins such as soluble CD19 (sCD19) may be assessed at baseline and post treatment to understand their potential prognostic and predictive value to denintuzumab mafodotin treatment. Blood sampling timepoints for biomarker analyses are listed in [Table 3](#).

7.4.1 B-Cell Subsets 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 pharmacodynamic marker of denintuzumab mafodotin activity. Flow cytometry measurements will include but not be limited to: CD3, CD14, CD19, CD20, CD27, CD38, CD56, CD269, and IgD.

7.4.2 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 DLBCL patients at baseline may be predictive of denintuzumab mafodotin treatment response. sCD19 may be measured pre- and post-treatment with denintuzumab mafodotin to understand its value as a potential predictive marker as well as a pharmacodynamic marker. Circulating proteins related to tumor burden or other potentially prognostic characteristics of the disease will also be monitored. In addition, Minimal Residual Disease (MRD) evaluation may also be carried out to understand the depth of response to therapy and correlate with PFS and other patient outcomes. Molecular MRD status may be analyzed using the Adaptive ClonoSEQ assay.

7.4.3 Fc-γ Receptor (FcγR) Variants

Peripheral blood cell pellets will be collected for assessment of FC gamma receptor (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 anti-tumor 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 (ADCC); therefore, enhanced ADCC in patients with high-affinity FcγR variants may contribute to better anti-tumor activity.

Germline single nucleotide polymorphisms (SNPs) that may inform efficacy and toxicity may also be explored from patients who give optional pharmacogenomics (PGx) 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 (ALL). No additional blood draw is necessary.

7.4.4 Characterization of Tumor Tissue

Fresh or archived tumor tissue blocks after last relapse will be collected at screening to evaluate biomarkers potentially predictive of response to denintuzumab mafodotin treatment. If available, initial diagnostic biopsies will also be collected to understand changes in response and resistant biomarkers. If a biopsy on residual tumor is performed at the end of treatment 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 6.6). Tumor biopsies may be evaluated for CD19, CD20, CD21, and other immune-cell marker expression by immunohistochemistry (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 cell of origin and additional gene expression analysis may also be evaluated. 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.

7.5 Biospecimen Repository

In the US only, for patients who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seattle Genetics and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of antibody-drug conjugate (ADC) sensitivity and resistance mechanisms, and to identify biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed following study completion.

7.6 Patient-Reported Outcomes

7.6.1 Ocular Health Survey

The Visual Function Questionnaire (VFQ-25) 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 6 and should be completed at or around the time of each ophthalmology exam (± 2 days).

7.7 Safety Assessments

Safety assessments will include the surveillance and recording of adverse events (AEs), clinical laboratory tests, and physical examination findings during the course of this study. Ophthalmologic examinations and ocular health survey will be conducted. PBSC collection will also be assessed as a measure of safety. Additionally, transplant-related data following ASCT will be collected and will include, but not be limited to, the time to neutrophil and platelet engraftment in each treatment arm.

Safety will be monitored over the course of the study by an SMC as described in Section 3.1.2.

7.7.1 Adverse Events

7.7.1.1 Definitions

Adverse Event

According to the International Council on Harmonization (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject 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 case report form (CRF):

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE 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 AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section [7.7.1.3](#)). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, 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 AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a serious adverse event (SAE), or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

Serious Adverse Events

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

Fatal:	AE resulted in death
Life threatening:	The AEs placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE 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 AE 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

AE severity should be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, with the exception of ocular adverse events which will be graded according to a modified CTCAE version 4.03 scheme ([Appendix E](#)). The NCI CTCAE, version 4.03 criteria are provided in the study manual or may be accessed at <http://ctep.cancer.gov/reporting/ctc.html>.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for Serious Adverse Events).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (denintuzumab mafodotin or RICE) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: <ul style="list-style-type: none">• an event that is uncommon and known to be strongly associated with drug exposure (e.g., 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 (e.g., tendon rupture)
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.7.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF 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 AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-Existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met serious criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out 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 AE.

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 AE. 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 [Appendix E](#).

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form.

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 CRF.
- 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’ alone when reporting AEs, including SAEs, because it is too nonspecific. 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 (e.g., ‘malignant pleural effusion’, ‘spinal bone metastases’, ‘lymphadenopathy’, ‘brain metastases’). Otherwise, it is acceptable to report the specific disease (e.g., 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 12 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. Email or fax to 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 CRF: 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 CRF.

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 7.7.1.1) should be reported as SAEs.

7.7.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through the EOT visit or 30 days after last study treatment (denintuzumab mafodotin or any component of RICE), whichever is later. However, all study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study 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. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

7.7.1.4 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 emailed or faxed to the sponsor's Drug Safety Department (see email address or fax number included on the SAE report form) within 24 hours.

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

7.7.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section [7.7.1.4](#)).

The sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity as well 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 Food and Drug Administration (FDA) as individual Investigational New Drug (IND) safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Reporting Requirements for INDs and Bioavailability (BA) and Bioequivalence (BE) Studies (December 2012).

In this study, the SAEs that do not require individual IND safety reports to the FDA are progression of the underlying cancer. These anticipated SAEs 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 arm (19A+RICE), then an IND safety report for the SAE will be submitted to the FDA.

7.7.2 Vital Signs

Vital signs measures are to include heart rate, blood pressure, and temperature. Vital signs should be collected per institutional standard for RICE infusion. For patients in the 19A+RICE Arm, vitals will be measured and recorded prior to 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.

7.7.3 Clinical Laboratory Tests

Samples will be drawn for local labs. Local laboratory testing 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 timepoints (see [Appendix A](#)) during the course of the study:

- The chemistry panel includes, but is not limited to, the following tests: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, calcium, creatinine, chloride, glucose (fasting at baseline), lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, and uric acid.
- Hgb A1c
- 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 either is positive, PCR for hepatitis B viremia must also be performed.
- A serum or urine β -hCG pregnancy test for females of childbearing potential (FOCBP)
- Spot Urine. A spot urine will be performed to test urine samples for urine protein and creatinine values, and results will be used to calculate a UPC ratio.
- A 24-hour urine collection to test for total protein value 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.

7.7.4 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Measurements of weight will be obtained. Measurements of height obtained within the prior 12 months may be utilized.

7.7.5 Ocular Monitoring Plan

In order to assess the effects of denintuzumab mafodotin on the eye, patients in both study arms will have complete ophthalmology assessments at protocol-defined timepoints (see Section 6 and [Appendix A](#)). Ophthalmology assessments are to include, but are not limited to, visual acuity and slit lamp examination. A baseline dilated fundus examination is required; subsequent dilated fundus examinations are to be conducted as clinically indicated. In particular, corneal epithelium changes must be assessed at each timepoint. Assessments must also include evaluation of steroid eye drop-induced changes including, but not limited to, intraocular pressure measurements and subcapsular cataracts. In addition, 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 5.8.1 and [Appendix E](#)) following discussion with the medical monitor.

Ophthalmology exams and ocular health surveys are required at baseline, the end of Cycles 2 and 3 (Days 15–21), EOT, and approximately 30-days post ASCT (for those patients who proceed to ASCT). 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.

7.7.6 Monitoring for Tumor Lysis Syndrome

Patients who are in the opinion of the investigator to be at high risk for tumor lysis syndrome (TLS) should be monitored for TLS after the Cycle 1, Day 1 dose according to the institutional standard.

7.7.7 ECOG Performance Status

ECOG performance status will be evaluated at protocol-specified timepoints. See [Appendix B](#) for the ECOG scale and the Karnofsky performance status equivalents.

7.8 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. AEs 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

timepoints 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 timepoints.

ATA 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.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of patients at the site, Seattle Genetics or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's Brochure/ package insert
- Recording and reporting AE and SAE
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval process
- Informed consent process
- Good Clinical Practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Patient coding and randomization
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seattle Genetics representative will review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source 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 Seattle Genetics or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for electronic CRF (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.

8.3 Access to Source Data

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

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5 Quality Assurance Procedures

The Clinical Quality Assurance group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Clinical Quality Assurance group of Seattle Genetics as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and Institution in which the study will be conducted, or for the period specified by Seattle Genetics, whichever is longer. The investigator must contact Seattle Genetics prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seattle Genetics.

9 DATA ANALYSIS METHODS

9.1 Determination of Sample Size

With approximately 100 patients randomized in a 1:1 ratio to each treatment arm (~50 patients per arm), the study is designed to have approximately 80% power to detect an increase in the CR rate of 25%. It is assumed that the CR rates for the 19A+RICE Arm and the RICE Arm are 60% and 35%, respectively. This calculation is based on a two-sided χ^2 test with significance level of $\alpha=0.1$ using EAST (version 5.4).

If the dose of denintuzumab mafodotin in the investigational 19A+RICE arm is modified, up to 50 additional patients may be randomized (25 in each arm) so that a total of 100 patients will be randomized in a 1:1 ratio to either the 19A (modified dose) + RICE arm or the RICE only arm. Up to approximately 150 patients may be randomized in this study. If a subset of patients appears to potentially derive benefit from 19A+RICE versus RICE at a pre-planned evaluation, the Sponsor may continue enrolling those patients beyond the planned sample size (approximately 100 patients), but will not exceed the planned maximum number of patients to be randomized in this study (up to approximately 150 patients).

9.2 Study Endpoint Definitions

9.2.1 Primary Efficacy Endpoint: CR Rate per IRF

CR rate per IRF is defined as the proportion of patients with complete metabolic response by PET/CT or complete radiologic response by CT only per IRF at the end of treatment according to the Lugano Classification Revised Staging System for malignant lymphoma ([Cheson 2014](#)). Patients whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate.

CR rate by investigator assessment will also be evaluated.

9.2.2 Secondary Efficacy Endpoints

9.2.2.1 Progression-Free Survival (PFS)

PFS is defined as the time from randomization to first documentation of disease progression per investigator (including progressive metabolic disease by PET/CT or progressive disease by CT as assessed by the Lugano classification criteria ([Cheson 2014](#)), or investigator claim of clinical progression), death due to any cause, or receipt of subsequent anticancer therapy, whichever comes first. Note that patients receiving post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing PBSC, or ASCT will not be considered as having started new anticancer therapy.

PFS by IRF may also be evaluated.

9.2.2.2 Overall Survival

Overall survival (OS) is defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive. If the last recorded date where a patient is known to be alive is the date of randomization, survival time will be censored on the date of randomization (i.e., OS duration of 1 day).

9.2.2.3 Duration of Complete Remission

Duration of CR is defined as the time from the start of the first radiographic documentation of CR per investigator to the first documentation of PD (including progressive metabolic disease by PET/CT or progressive disease by CT as assessed by the Lugano classification criteria ([Cheson 2014](#)), or investigator claim of clinical progression), death due to any cause, or receipt of subsequent anticancer therapy, whichever comes first. Note that patients receiving post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing PBSC, or ASCT will not be considered as having started new anticancer therapy.

Duration of CR by IRF may also be evaluated.

9.2.2.4 Proportion of Patients Achieving PBSC Mobilization

The proportion of patients achieving PBSC mobilization is defined as the number of patients who are able to adequately mobilize PBSC (defined as 2×10^6 CD34 cells/kg) on or after completion of study treatment, prior to subsequent anticancer therapy (excluding post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing PBSCs, and consolidative autologous or allogeneic SCT), divided by the total number of patients.

9.2.2.5 Proportion of Patients Receiving ASCT

The proportion of patients receiving ASCT is defined as the number of patients receiving ASCT after completion of study treatment, prior to subsequent anticancer therapy (excluding post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing PBSCs, and consolidative autologous or allogeneic SCT), divided by the total number of patients.

9.2.2.6 Objective Response Rate

ORR is defined as the proportion of patients with CR or partial remission (PR) per IRF at the end of treatment according to the Lugano classification criteria ([Cheson 2014](#)). CR includes complete metabolic response by PET/CT or complete radiologic response by CT. PR includes partial metabolic response by PET/CT or partial remission by CT. Patients whose disease response cannot be assessed will be scored as non-responders for calculating the ORR.

ORR by investigator assessment will also be evaluated.

9.2.2.7 Duration of Objective Response

Duration of OR is defined as the time from the start of the first radiographic documentation of objective response (CR or PR) per investigator to the first documentation of PD (as assessed by the Lugano classification criteria ([Cheson 2014](#)), or investigator claim of clinical progression), death due to any cause, or receipt of subsequent anticancer therapy, whichever comes first. Note that patients receiving post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing PBSC, or ASCT will not be considered as having started new anticancer therapy.

Duration of OR by IRF may also be evaluated.

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (e.g., adding baseline assessments to define a subgroup). The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1 General Considerations

This is a phase 2, randomized, open-label study with a formal statistical hypothesis for the primary efficacy endpoint. There are no formal pre-specified statistical hypotheses for the primary safety objective.

Descriptive statistics (mean, median, standard deviation, minimum, maximum) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables.

9.3.1.1 Randomization and Blinding

This is a randomized, open-label study that may enroll up to approximately 150 patients. Approximately 100 patients will be randomized in a 1:1 ratio to receive either 19A+RICE or RICE. In the 19A+RICE Arm, the planned dose for denintuzumab mafodotin is 3 mg/kg; however, in the case that the SMC recommends modification of the dose of denintuzumab mafodotin (e.g., to 2 mg/kg), up to 50 additional patients may be enrolled and randomized (25 in each arm) so that a total of 100 patients will be randomized in a 1:1 ratio to receive either 19A (modified dose) + RICE or RICE only.

Patients will be stratified based on the following variables to ensure that patient specific risk factors are appropriately balanced between treatment arms. Randomization will be stratified by:

- Disease status
 - CR to frontline systemic therapy and relapsed more than 12 months after initial diagnosis (i.e., initiation of frontline therapy)
 - PR or SD to frontline systemic therapy, or CR to frontline and relapsed less than or equal to 12 months after initial diagnosis (i.e., initiation of frontline therapy)
- Second-line age-adjusted IPI (saaIPI) score or standard IPI score at randomization
 - Low-risk disease: saaIPI of 0 or 1, or standard IPI of 0, 1, or 2
 - High-risk disease: saaIPI of 2 or 3, or standard IPI of 3, 4, or 5
- Disease type
 - De novo DLBCL and Grade 3b follicular lymphoma
 - Transformed DLBCL

After stratification, patients will be randomized into 1 of 2 treatment arms, for a total of approximately 50 patients per arm.

Stratified randomization with a fixed block size will be performed centrally using a system that will assign both the treatment and a unique patient randomization number.

9.3.1.2 Adjustments for Covariates

Stratified analyses will include adjustment for the stratification factor as recorded at randomization (described in Section 9.3.1.1). Covariates may be considered for adjustment in exploratory regression analyses.

9.3.1.3 Handling of Dropouts and Missing Data

Missing data will not be imputed, with the exception of AE dates while calculating duration of events and treatment emergent status. Patients with missing values of a variable other than response endpoints (CR and OR) and time-to-event endpoints (PFS, duration of response, and OS) will be excluded from the analysis of that endpoint. Patients whose disease response cannot be assessed will be scored as non-responders for calculating the response rate (CR rate and ORR). Censoring rules will be applied to the estimation of the distribution of the time-to-event endpoints, details will be provided in the SAP.

9.3.1.4 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough patients to warrant an analysis by center.

9.3.1.5 Multiple Comparisons and Multiplicity

The overall two-sided alpha level for the primary endpoint is 0.1.

Formal statistical tests will be performed for the CR per IRF, and the key secondary endpoints of PFS and duration of CR. If the test for the primary analysis of CR rate is statistically significant in favor of the investigational arm at a two-sided alpha level of 0.1, formal statistical tests will be performed for the key secondary endpoints at an overall two-sided alpha level of 0.1. A fixed sequence testing procedure, where testing is carried out sequentially at an unadjusted alpha level as long as all preceding null hypotheses are rejected, will be used to ensure type I error control for key secondary endpoints. The testing order will be: 1) PFS, and 2) duration of CR. If the test for CR rate per IRF is not statistically significant, the p-value of the tests for the key secondary endpoints will still be calculated, but will be considered descriptive.

9.3.1.6 Data Transformations and Derivations

For efficacy assessments per investigator, the date of response will be the latest of all radiologic scan dates for the given restage assessment. The date of progression will be the earliest of all radiologic scan dates for the given disease assessment, or the date of investigator claim of clinical progression, whichever comes first. No other data transformations are planned for the primary or secondary endpoints.

9.3.1.7 Analysis Sets

Intent-to-Treat (ITT) Analysis Set: The 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.

Modified Intent-to-Treat (mITT) Analysis Set: The mITT analysis set will include all patients who are randomized to the recommended dose level of 19A+RICE or RICE, and receive at least 1 cycle of study treatment. If the dose of denintuzumab mafodotin is modified from 3 mg/kg (e.g., to 2 mg/kg), the mITT Analysis Set includes all patients randomized

after the dose modification decision is made. Patients will be included in the treatment arm assigned at randomization regardless of the actual treatment received.

Safety Analysis Set: The safety analysis set will include all patients who receive any amount of denintuzumab mafodotin or any component of RICE. Treatment group will be determined using the actual treatment arm received, regardless of the randomization treatment assignment.

Per-Protocol (PP) Analysis Set: The per-protocol analysis set includes patients who receive at least 1 cycle of RICE (all components) or recommended dose of 19A+RICE (with all components of RICE) combination therapy and who had both a baseline and at least one post-baseline evaluable disease assessment (per the Lugano classification criteria or determination of clinical disease progression per the investigator), and no other major protocol deviations that could potentially affect tumor response. The per-protocol analysis set is a subset of the mITT analysis, and patients will be grouped in the same manner as mITT analysis set.

9.3.1.8 Examination of Subgroups

All analyses will be presented by treatment arm.

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:

- Disease status
- Low-risk versus high-risk disease (saIPI or standard IPI score, as appropriate to patient age)
- Disease type
- Cell of origin (germinal center B cell [GCB] or non-GCB/activated B cell [ABC])

Detailed methodology will be provided in the SAP.

9.3.1.9 Timing of Analyses

Three interim evaluations for safety are planned as specified in Section 3.1.2.

There are no formal interim efficacy analyses planned for this study, however, two administrative looks at overall safety and efficacy may be performed when approximately 40 and 75 patients have completed EOT as specified in Section 9.3.1.9.

The analysis of the primary endpoint of CR per IRF will occur after all patients in the mITT analysis set have completed EOT. Comparison of the CR rates between the 2 treatment arms will be conducted. The database cutoff date for this analysis will be determined once all study patients have completed treatment.

The primary analysis of PFS and OS endpoints will occur approximately 2 years after the last patient's enrollment. If 70% of patients have experienced a PFS and/or OS event prior to 2 years after the last patient's enrollment, the primary analysis of PFS and/or OS may be

performed earlier than scheduled. Subsequent cutoff dates may be defined and corresponding database locks may occur to allow for more precise estimates of the time-to-event endpoints prior to study closure.

9.3.2 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 and listed.

9.3.3 Patient Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the SAP.

9.3.4 Treatment Compliance

The dose administered at each cycle for each treatment agent will be summarized. Details will be provided in the SAP.

9.3.5 Efficacy Analyses

Hypothesis test for primary and key secondary endpoints will be performed based on mITT analysis set. If the dose of denintuzumab mafodotin is modified (e.g., to 2 mg/kg), patients randomized after modification of the dose of denintuzumab mafodotin will be included in the testing for the primary and key secondary endpoints. Summary of all efficacy endpoints may be performed on ITT, mITT, and PP analysis sets. Response as assessed by investigator will also be summarized for associated efficacy endpoints. Concordance with response per IRF will be explored.

9.3.5.1 Primary Efficacy Analysis

Complete remission (CR) rate is defined as the proportion of patients achieving CR by IRF at the end of treatment in the mITT analysis set using the Lugano classification criteria ([Cheson 2014](#)). Patients whose disease response cannot be evaluated per the Lugano classification criteria or investigator claim of clinical progression will be scored as Not Evaluable. The primary efficacy hypotheses will be tested at a two-sided 0.1 alpha level using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata. In situations where a stratum cannot be included in a stratified analysis of an endpoint, it may be necessary to pool strata prior to the analysis. The details of pooling strategy will be specified in the SAP.

The primary efficacy hypotheses can be expressed as follows:

H_0 : The odds ratio of CR is 1 between the 19A+RICE and RICE arms, adjusting for stratification factors.

H_a : The odds ratio of CR is different from 1 between the 19A+RICE and RICE arms, adjusting for stratification factors.

CR rate and exact two-sided 90% confidence interval (CI) using the Clopper-Pearson method (Clopper 1934) will be calculated.

9.3.5.2 Secondary Efficacy Analyses

PFS, OS, duration of CR, and duration of OR will be estimated using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median survival time and its two-sided 90% CI using the log-log transformation method (Collett 1994) will be calculated. The stratified log-rank test will be used to compare PFS between the two treatment arms at a two-sided 0.1 alpha level. If the dose of denintuzumab mafodotin is modified (e.g., to 2 mg/kg), the definition of treatment arm will follow Section 9.3.5.1.

ORR, the proportion of patients achieving PBSC mobilization, and the proportion of patients receiving ASCT will be summarized. An exact two-sided 90% CI using the Clopper-Pearson method (Clopper 1934) will be calculated.

9.3.6 Pharmacokinetic and Antitherapeutic Antibody Analyses

The individual plasma concentrations of denintuzumab mafodotin ADC and unconjugated drug (cys-mcMMAF) will be summarized with descriptive statistics at each PK sampling timepoint using the Safety Analysis Set. Any additional PK and PK/PD analyses may be described in a separate analysis plan and presented in a separate report.

The ATA incidence rate is defined as the proportion of patients that develop ATA at any time during the study. ATA incidence will be summarized using the Safety Analysis Set.

9.3.7 Biomarker Analyses

Absolute and relative biomarker measurements and changes from baseline will be listed and summarized. Summary statistics may be tabulated. Relationships of absolute and relative biomarker changes from baseline to efficacy, safety and pharmacokinetic parameters will be explored. Similarly, the relationship of baseline biomarker measurements to efficacy will be explored. Details will be described in a separate analysis plan Bioinformatics Analysis Plan (BAP), SAP, or PK Analysis Plan.

9.3.8 Patient-Reported Health Outcome Analyses

VFQ-25 composite score and select sub-scale scores may be summarized with descriptive statistics by treatment arm. In addition, change from baseline may be tabulated or presented graphically by treatment arm, as appropriate.

9.3.9 Safety Analyses

9.3.9.1 Extent of Exposure

Duration of treatment, number of cycles, total dose will be summarized by treatment arm using the Safety Analysis Set. Dose modifications will also be summarized and listed.

Details will be provided in the SAP.

9.3.9.2 Adverse Events

Adverse events will be defined as treatment emergent if they are newly occurring or worsen following study treatment. The incidence of all AEs, treatment-emergent AEs, and treatment-related AEs will be tabulated using the Safety Analysis Set. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be listed and summarized by MedDRA preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one patient, the AE will be counted once as the occurrence. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

9.3.9.3 Deaths and Serious Adverse Events

Serious adverse events will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.9.4 Clinical Laboratory Results

Summary statistics for actual values and for change from baseline may be tabulated or presented graphically as appropriate for laboratory results by treatment arm and scheduled visit. Laboratory values outside of the normal reference range at any postbaseline assessment will be listed by treatment arm with grade per NCI CTCAE and out of the normal range flags.

9.3.9.5 Other Safety Analyses

Vital Signs

Vital signs will be presented graphically for each vital sign by scheduled visit. Summary statistics and change from baseline and/or predose to postdose may be tabulated where appropriate.

ECOG Status

ECOG status may be summarized for each visit. Shifts from baseline to the best and worst postbaseline score may be tabulated.

ECG

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled ECG, and shifts from baseline may be tabulated.

Ocular Toxicities

Patient incidence of ocular toxicities (as defined by the MedDRA system organ class [SOC] of eye disorders or custom queries) will be presented by treatment arm. Additional analyses may be done, including incidence of ocular toxicities by maximum severity, ocular toxicities that lead to treatment discontinuation, etc.

Transplant-Related Information Following ASCT

Time to neutrophil and platelet engraftment may be summarized and tabulated where appropriate.

9.3.10 Interim Analyses

The SMC will periodically monitor the trial for safety during the treatment period. Three formal safety interim evaluations are planned as specified in Section 3.1.2. Enrollment will only be paused during the first safety review, unless required by the SMC. The SMC will review data for both treatment arms to include, but not be limited to, the following:

- Incidence of DDT
- Adverse events
- Clinical laboratory tests
- Response assessments, if requested
- PBSC mobilization, if available

After reviewing the aggregate data, the SMC will make a recommendation to the sponsor regarding further conduct of the trial, as specified in Section 3.1.2.

An ongoing real-time review of serious AEs (SAEs) in both treatment arms will be conducted by the Seattle Genetics Program Safety Monitoring Team.

In addition, two interim administrative evaluations of overall safety are planned when approximately 40 and 75 patients have completed EOT. The hypothesis test that compares the CR rate of the 2 arms will not be performed. The study will not be discontinued unless there is a safety concern. If a subset of patients appears to potentially derive benefit from 19A+RICE versus RICE at a pre-planned evaluation, the Sponsor may continue enrolling those patients beyond the planned sample size (approximately 100 patients), but will not exceed the planned maximum number of patients to be randomized in this study (up to approximately 150 patients).

A summary of activity may be used for risk/benefit assessment. 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.

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

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 (Brazil 2013), and all applicable regulatory requirements.

10.1 Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for

ensuring patients are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each patient, or legally authorized representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

If informed consent is obtained from a legally authorized representative for a patient who is unable to provide informed consent at study entry (if applicable), but the patient is later able to provide informed consent, the investigator must obtain written informed consent from the patient.

10.2 Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1 Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study patient) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling patients who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4 Study Documentation, Privacy and Records Retention

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 applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing patient medical information must be handled in accordance with local and national laws, rules, and regulations and 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, CRFs 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.

10.5 Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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APPENDIX A: SCHEDULE OF EVENTS

		Screening	Baseline	Enrollment/ Randomization	Every cycle ^A						EOT ^B	Time of Transplant	Long-term F/U Months after ASCT or EOT						
					D1 (±1d)	D2 ^V	D4 ^V	D8 (±1d)	D15 (±1d)	D22 ^W (±3d)	14–30 days post start of last cycle		3	6	12	18	24	>24	
Visit Window		D –28 to 1	D –7 to 1										±1 month					Annually ±1 mo	
Screening/ Baseline Assessments	Informed consent	X		Eligibility documentation submitted to Sponsor prior to randomization															
	Inclusion/exclusion	X																	
	Medical history	X																	
	Inflammatory conditions review	X										X ^C							
	Tumor specimen	X ^D										X ^E							
	saaIPI score or standard IPI score ^X	X																	
	Serology (hepatitis B) ^F	X																	
	Height		X																
	Electrocardiogram		X									X							
Pregnancy test for FOCP		X									X								
Treatment	Study treatment administration					X ^{G,Y}													
Blood-based PK/Biomarker/ ATA	PK				Refer to Sections 7.3 and 7.4, and Table 3														
	ATA																		
Response Assessments	Biomarker samples	X																	
	CT (chest, neck, abdomen, pelvis) ^H	X										X ^I		X	X	X	X	X	X
	PET ^H	X										X ^I		X ^J	X ^J	X ^J	X ^J	X ^J	X ^J
	BM biopsy results ^K	X ^K										X ^K							
Safety Assessments	B symptoms		X			X ^L						X							
	Survival status														X	X	X	X	X
	Physical exam with weight		X			X ^L						X ^Z		X ^Z	X ^Z	X ^Z	X ^Z	X ^Z	X ^Z
	Vital signs (Section 7.7.2)					X													
	ECOG (Appendix B)		X			X ^L						X							
	Serum chemistry (Section 7.7.3)		X ^{AA}			X ^M		X	X			X							
	Hgb A1c		X																
	CBC with differential		X			X ^M		X	X			X							
	PT/PTT/INR		X			X ^M						X							
	Spot urine for UPC ratio (Section 7.7.3)		X			X ^M		X	X			X							
	24-hr urine collection if UPC>2					X ^{M,N}		X ^N	X ^N			X ^O							
	Ophthalmology exam (Section 7.7.5)	X							X ^{L,P}			X ^{Q,R}	X ^S	X ^R	X ^R	X ^R	X ^R	X ^R	X ^R
	Ocular health survey ^T (Section 7.6.1)	X							X ^L			X ^{Q,R}	X ^S	X ^R	X ^R	X ^R	X ^R	X ^R	X ^R
	Con meds & AEs	Collect any related to study procedures				Collect from Day 1 (predose) thru 30 days post last dose							X ^U						
	Collect PBSC mobilization info (Section 6.5)				At time of PBSC collection								Collection of PBSC mobilization outcome. Refer to Section 6.7.						

- A Cycles 2 and 3 should not begin until adequate recovery of peripheral blood counts (i.e., platelets ≥75,000/μL and ANC ≥1000/μL). A delay of >7 days is discouraged
- B Perform EOT evaluations before initiation of non-protocol therapy. If EOT visit is <30 days after completion of study treatment, conduct a phone screen 30–37 days after completion of study treatment to ensure no change in AE profile has occurred
- C Required for patients with inflammatory conditions of interest at Screening (Section 7.1)
- D For screening (Section 7.1) and biomarker analysis (Section 7.4.4) Representative tissue from the most recent biopsy after the last therapy must be available; if such tissue is not available, a fresh biopsy must be obtained
- E For patients discontinuing treatment due to PD: if a tumor biopsy was performed at the time of disease progression as part of standard of care, submit sample of tumor specimen, if available
- F If positive, PCR for hepatitis B viremia must also be performed (Section 5.5.1)

- J Required until disease is PET negative
- K Results collected at screening and/or EOT visit and at any time on study, if performed as part of standard of care (Section 7.2)
- L Not required at Cycle 1
- M If baseline activities occur within 1 day prior to Cycle 1 Day 1, assessment does not need to be repeated
- N Prior to next cycle dosing, or prior to EOT visit if discontinuing study treatment
- O Within 5 days after UPC assessment
- P Window Day 14 to 21
- Q Not required if an exam was performed within 4 weeks prior to the EOT visit, and following the last dose of study treatment
- R In the event of ocular toxicity, continue at least monthly in follow-up until resolution or return to baseline
- S Ophthalmology exam and ocular health survey approximately 30-days post ASCT
- T ±2 days from the ophthalmology exam

- G For 19A+RICE Arm: Steroid eye drop prophylaxis should begin 1 day prior to denintuzumab mafodotin dose. See Section 5.4.1 and Table 1 for additional prophylactic interventions including artificial tears, vasoconstrictor eye drops, and cooling eye mask to be given at the time of infusion.
- H 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 (i.e., contrast-enhanced with IV and oral contrast, unless contrast is medically contraindicated). Images should be submitted for central review.
- I Unless PD is documented within the previous 6 weeks by diagnostic CT scan.
- U In each treatment arm, additional transplant-related data will be collected following ASCT until time of engraftment and will include, but not be limited to, the time to neutrophil and platelet engraftment.
- V Cycle 1 only. Blood samples for PK and biomarker testing (Table 3).
- W Cycle 1 and Cycle 2 only. Only for patients not continuing on treatment or not starting the next cycle on Day 22. Blood sample for PK testing (Table 3).
- X saAPI for patients aged ≤ 60 years, and standard IPI for patients aged >60 years (Appendix D).
- Y For both treatment arms, RICE administration to occur on Days 1–3 (± 1 day).
- Z Weight not required.
- AA Fasting blood glucose at baseline.

APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		ECOG	
Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Normal activity with effort; some signs or symptoms of disease.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

APPENDIX C: NEW YORK HEART ASSOCIATION CLASSIFICATION

A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Patients

- Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.
- Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
- Class III: patients with marked limitation of activity; they are comfortable only at rest.
- Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

On-line source: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX D: SECOND-LINE AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX (IPI) SCORE AND STANDARD IPI SCORE FOR NHL

saalIPI Score for Patients Aged ≤60 Years

Risk Factor	Score	
	0 point	1 point
Serum LDH	≤1 x ULN	>1 x ULN
ECOG Performance Status	0 or 1	2, 3, or 4
Stage	I or II	III or IV

LDH = lactate dehydrogenase

ECOG = Eastern Cooperative Oncology Group

ULN = upper limit of normal

Risk Category

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

Based on ([Hamlin 2003](#); [Moskowitz 1999](#); [Shipp 1993](#)).

Standard IPI Score for Patients Aged >60 Years

Risk Factor	Score	
	0 point	1 point
Age	≤60 years	>60 years
Serum LDH	≤1 x ULN	>1 x ULN
ECOG Performance Status	0 or 1	2, 3, or 4
Stage	I or II	III or IV
Extranodal involvement	≤1 site	>1 site

LDH = lactate dehydrogenase

ECOG = Eastern Cooperative Oncology Group

ULN = upper limit of normal

Risk Category

Low	0, 1
Low-intermediate	2
High-intermediate	3
High	4, 5

APPENDIX E: 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 (i.e., preparing meals, shopping for groceries or clothes, using the telephone or computer, managing money, driving, etc.)	Symptomatic Change in vision Affects self-care ADL (i.e., 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	--

APPENDIX F: RESPONSE ASSESSMENT – THE LUGANO CLASSIFICATION

Response and Site	PET-CT–Based Response	CT-Based Response
<i>Complete Response</i>	<i>Complete metabolic response</i>	<i>Complete radiologic response (all of the following)</i>
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 (e.g., 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
<i>Partial Response</i>	<i>Partial metabolic response</i>	<i>Partial remission (all of the following)</i>
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 At end of treatment, these findings indicate residual disease	$\geq 50\%$ decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm \times 5 mm as the default value When no longer visible, 0 \times 0 mm For a node >5 mm \times 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
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
<i>No Response or Stable Disease</i>	<i>No metabolic response</i>	<i>Stable disease</i>
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 and Site	PET-CT–Based Response	CT-Based Response
<i>Complete Response</i>	<i>Complete metabolic response</i>	<i>Complete radiologic response (all of the following)</i>
<i>Progressive Disease</i>	<i>Progressive metabolic disease</i>	<i>Progressive disease requires at least 1 of the following</i>
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 $\geq 50\%$ from PPD nadir, and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by $> 50\%$ of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., 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.

- a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).
- b PET 5PS: 1, no uptake above background; 2, uptake \leq mediastinum; 3, uptake $>$ mediastinum but \leq liver; 4, uptake moderately $>$ liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma ([Barrington 2014](#)).

From: ([Cheson 2014](#))

APPENDIX G: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled, “A randomized, open-label phase 2 study of denintuzumab mafodotin (SGN-CD19A) plus rituximab, ifosfamide, carboplatin, and etoposide (19A+RICE) chemotherapy vs. RICE in the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who are candidates for autologous stem cell transplant”.

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature

Date

Investigator Name, Printed

APPENDIX H: DOCUMENT HISTORY

Version	Date
Original	16-Jun-2015
Amendment 1	23-Sep-2016
Amendment 2	28-Oct-2017

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Section 1.1	Added recently published results on patients with DLBCL who experience primary treatment failure.	To provide additional background on a subset of DLBCL patients who experience primary treatment failure.
Section 3.1, 9.1, and 9.3.10	Added that if a subset of patients appears to potentially derive benefit from 19A+RICE versus RICE at a pre-planned evaluation, the Sponsor may continue enrolling those patients beyond the planned sample size (approximately 100 patients), but will not exceed the planned maximum number of patients to be randomized in this study (up to approximately 150 patients).	To allow continued enrollment of patients who have been observed to potentially benefit from 19A+RICE versus RICE at a pre-planned evaluation.
Section 4.1	Removed the requirement for patients to have CD20-positivity for eligibility (Eligibility criterion 1).	To enroll patients who have experienced early relapse regardless of CD20 status.
Section 4.1	Added the following eligibility criterion: 4a. Relapsed less than or equal to 6 months from the completion of frontline therapy at the time of initial dosing in this clinical trial (applicable only to patients enrolled under Amendment 2).	To enroll patients who have experienced early relapse.
Section 5.5.1	Examples for tumor lysis prophylaxis, including treatment with allopurinol or rasburicase, as well as adequate hydration (Cairo 2010) were added.	Clarification.
Section 6.2 and 7.1	Added a blood sample for biomarker assessments	To allow analysis of biomarkers at screening.
Section 7.1	Clarified that a blood sample for hepatitis serology will be taken at screening	To align with other previously written sections of the protocol.
Section 7.4 and 7.4.2	Clarified that soluble CD19 may be assess rather than will be assessed.	Clarification.

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
2.4.2, 9.2.2.1, 9.2.2.3, 9.2.2.7	Secondary endpoints of duration of response (OR and CR) and PFS will be assessed using investigator-assessed response. Response by IRF may also be used to evaluate these endpoints.	For time-to-event endpoints, investigator-assessed response is more clinically relevant for the purposes of this Phase 2 study and will be used as the primary method of analysis for these secondary endpoints.
3.1, 3.2.2, 5.3.3, Synopsis	Specified units for carboplatin dosage to be area under the curve 5 <u>mg/mL x min</u> ; maximum dose, 800 mg.	Clarification
3.1, 6.2, 6.6, 6.7, 7.2, Appendix A	CT scans will be of diagnostic quality (i.e., contrast-enhanced with IV and oral contrast, unless contrast is medically contraindicated).	Clarification
3.1, 6.2, 6.6, 6.7, 7.2, Appendix A	At any time on study, if a bone marrow biopsy is performed as part of standard of care, the results from the biopsy report for the presence of lymphoma will be recorded in the CRF.	Clarification. Bone marrow biopsy is not a required procedure for this study. However, if a bone marrow biopsy is performed as part of standard of care outside of the study, the result will be recorded in the CRF.
3.2.1, 6.2, 7.1, 9.3.1.1, 9.3.1.8, Appendix A, Appendix D, Synopsis	Added standard IPI for patients aged >60 years; saalPI will be used for patients aged ≤60 years.	Measure the IPI as appropriate to the patient's age.
3.2.2	Corrected as indicated: Cys-mcMMAF is metabolically stable in human microsomal preparations and, at concentrations up to 1 µM (roughly 100 500 -fold higher than circulating levels after a 3 mg/kg dose of denintuzumab mafodotin), was not a direct, time- or metabolism-dependent inhibitor or inducer of CYP 3A or 2B6 in vitro (denintuzumab mafodotin IB).	Correction
4.1, Synopsis	Inclusion criterion #1: Added that eligible patients must have histologically confirmed CD20-positive disease.	Clarification

Section(s)	Change	Rationale
4.2, 6.2, 7.7.3, Synopsis	Hepatitis B positivity is demonstrated by testing positive for either hepatitis B surface antigen or anti-hepatitis B core antibody.	Correction. Note that this correction appears as no change in this amendment. Prior to this Protocol Amendment 1, Administrative Letter 2 (12-Oct-2015) stated that hepatitis B testing should be performed by testing for hepatitis B surface antigen only. This Protocol Amendment 1 (23-Sep-2016) reverts back to the original protocol language where positivity by either surface antigen or core antibody testing demonstrates hepatitis B positivity.
5.3.3	Rituximab administration should be initiated approximately 30 to 60 minutes after the completion of denintuzumab mafodotin study drug infusion.	Administrative correction to align with Section 5.2.2
5.4	Premedication for the rituximab infusion may be given during the 30 to 60 minute period between the completion of the denintuzumab mafodotin infusion and the start of the rituximab infusion	Clarification
5.4.1, 5.8.1, Table 1, Table 2	For patients in the 19A+RICE Arm, prophylactic preservative-free artificial tears should be administered beginning on Cycle 1 Day 1 until EOT.	Artificial tears should be used prophylactically with denintuzumab mafodotin, and may be used more frequently in the event of ocular symptoms, as needed.
5.4.1, Table 1, 6.4.1, 6.4.7, Appendix A	For patients in the 19A+RICE Arm, the use of cooling eye masks and vasoconstrictor eye drops is recommended as described.	Evaluate the use of cold eye masks and vasoconstrictor eye drops during and after denintuzumab mafodotin infusion to vasoconstrict the vessels of the eye, and potentially reduce exposure of the eye tissue to denintuzumab mafodotin.
5.5.1	Require concomitant antiviral prophylaxis for patients with negative PCR assay who also tested positive for hepatitis B surface antigen.	Patients in this situation should be administered standard of care therapy as per the institutional standard.
5.5.1	Require concomitant prophylaxis for patients assessed to be at risk for tumor lysis.	Patients in this situation should be administered standard of care therapy as per the institutional standard.

Section(s)	Change	Rationale
5.5.2	Allow prophylactic intrathecal chemotherapy as a concomitant therapy if the investigator deems it necessary.	In order to decrease the risk of relapse within the CNS, intrathecal methotrexate or Ara-C is given to patients with an increased risk of CNS involvement. Although known CNS involvement is an exclusion criterion for trial participation, patients with testicular, bone marrow, and paraspinal disease are at increased risk for relapse in the CNS (a sanctuary site). At the investigator's discretion, CNS prophylaxis may be added (to RICE) as part of standard treatment.
6.3, 6.4.1	For patients randomized to the 19A+RICE Arm, steroid eye drop prophylaxis is recommended to begin 1 day prior to denintuzumab mafodotin dose. However, for the first cycle of treatment, if beginning eye drop prophylaxis 1 day prior is not possible, starting on Day 1 is acceptable for the first cycle of treatment.	Clarification
6.4.6, 6.4.11, Table 3, Appendix A	For Cycles 1 and 2, added Day 22 PK testing for patients who are not continuing treatment or not starting the next cycle on Day 22.	To measure comparable Day 22 trough PK for denintuzumab mafodotin and/or rituximab (as applicable) if a patient does not continue treatment or start the next cycle of treatment on Day 22.
6.5	Allow the use of chemotherapy for the mobilization of stem cells.	Clarification to distinguish the use of chemotherapy for the mobilization of stem cells (an allowed concomitant medication) from its post study-treatment use to treat residual disease (a prohibited concomitant medication).
6.7	Added clinical assessments of disease status by history and physical examinations at long-term follow-up visits	To document investigator assessment of clinical progression during the long-term follow-up period.
7.1	If representative tissue from the most recent <u>tumor</u> biopsy after the last therapy is unavailable, a fresh biopsy must be obtained.	Clarification
7.7.3, Appendix A	Patients should be fasting for baseline blood glucose testing.	To determine whether a patient has a baseline predisposition to hyperglycemia.
7.7.3	Specified that a spot urine urinalysis must be performed.	Clarification. The spot urine must be performed in order to provide the urine protein and creatinine values needed to collect the UPC ratios required.

Section(s)	Change	Rationale
7.7.3	The 24-hour urine collected will be used to test for total protein value.	Clarification
9.1, Synopsis	The following correction: Up to approximately 150 patients may be treated <u>randomized</u> in this study.	Correction
9.2.1	CR rate using investigator-assessed response will also be evaluated.	Clarification
9.2.2.6	Objective response rate using investigator-assessed response will also be evaluated.	Clarification
9.3	The SAP will be finalized prior to database lock.	Clarification
9.3.1.1	Disease status is determined from the time of initial diagnosis (i.e., initiation of frontline therapy). Also, clarified the stratification group assignment for patients that were CR to frontline therapy and relapsed exactly 12 months after initial diagnosis.	Clarifications
9.3.1.5	Deleted the following paragraph: Two interim administrative evaluations of the overall safety and activity may be performed when approximately 40 and 75 patients have completed EOT. The hypothesis test that compares the CR rate of the 2 arms will not be performed. The study will not be discontinued unless there is a safety concern. No alpha adjustment is planned.	Administrative correction. This deleted paragraph is duplicated in Section 9.3.10 (Interim Analyses).
9.3.1.7, 9.3.5	Adjusted the mITT analysis set as follows: The mITT analysis set will include all patients <u>who are</u> randomized to the recommended dose level of 19A+RICE or RICE, <u>and receive at least 1 cycle of study treatment</u> .	Treated patients represent the most clinically meaningful primary analysis set to investigate the treatment activity
9.3.1.7	Adjusted the PP analysis set as follows: The pre-protocol analysis set includes patients who receive at least 1 cycle of RICE (all components) or recommended dose any amount of 19A+RICE (with all components of RICE) combination therapy and who had both a baseline and at least one post-baseline evaluable disease assessment (per the Lugano classification criteria or determination of clinical disease progression per the investigator), and no other major protocol deviations that could potentially affect tumor response.	Completing the 1st cycle of treatment is regarded as the minimal exposure to the treatment regimen, and most closely reflects the scientific model underlying the protocol.

Section(s)	Change	Rationale
9.3.5.1, 9.3.5.2	90% confidence intervals will be calculated rather than 95% confidence intervals.	Correction. The study is powered at a 0.1 alpha level.
9.3.10	The 2 interim administrative evaluations will evaluate overall safety, but not activity. However, a summary of activity may be used for risk/benefit assessment.	Clarification
Appendix A	Footnote A. Definition of platelet recovery corrected to $\geq 75,000/\mu\text{L}$.	Correction
Appendix F	Corrections and clarifications were made to response criteria, the Lugano classification criteria.	Administrative corrections to align the Lugano classification criteria to match the reference article (Cheson 2014)
Throughout protocol	Administrative changes and corrections.	To improve clarity and to achieve consistency throughout protocol.