

**A RANDOMIZED, OPEN LABEL, PHASE 2 STUDY OF RITUXIMAB AND  
BENDAMUSTINE WITH OR WITHOUT BRENTUXIMAB VEDOTIN FOR  
RELAPSED OR REFRACTORY CD30-POSITIVE DIFFUSE LARGE B-CELL  
LYMPHOMA**

**Protocol Number:** SGN35-023  
**Study Phase:** 2

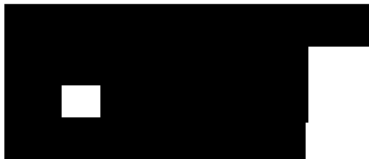
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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

**CONFIDENTIAL**

This document is a confidential communication of Seattle Genetics, Inc. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein shall be published or disclosed without prior written approval, except that this document may be disclosed to the appropriate Institutional Review Board(s)/Independent Ethics Committee(s) under the condition that they keep it confidential.

## **1. SIGNATURES**

### **Representatives of Sponsor**

I have read and agree to the protocol SGN35-023, titled 'A Randomized, Open Label, Phase 2 Study of Rituximab and Bendamustine with or without Brentuximab Vedotin for Relapsed or Refractory CD30-Positive Diffuse Large B-Cell Lymphoma'. I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities.

**Accepted for the Sponsor - Seattle Genetics, Inc:**



### **Investigator**

I have read and agree to the protocol SGN35-023, titled 'A Randomized, Open Label, Phase 2 Study of Rituximab and Bendamustine with or without Brentuximab Vedotin for Relapsed or Refractory CD30-Positive Diffuse Large B-Cell Lymphoma'. I am aware of my responsibilities as an Investigator under the guidelines of GCP, local regulations (as applicable), and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

**Clinical Site:** \_\_\_\_\_

**Site Number:** \_\_\_\_\_

**Site Principal Investigator:**

\_\_\_\_\_  
Print Name

\_\_\_\_\_  
Title

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

## 2. SYNOPSIS

<b>NAME OF SPONSOR:</b> Seattle Genetics, Inc.		<b>PROTOCOL No.:</b> SGN35-023
<b>NAME OF STUDY TREATMENT:</b> Rituximab and Bendamustine with or without Brentuximab Vedotin		
<b>TITLE OF STUDY:</b> A Randomized, Open Label, Phase 2 Study of Rituximab and Bendamustine with or without Brentuximab Vedotin for Relapsed or Refractory CD30-Positive Diffuse Large B-Cell Lymphoma		
<b>STUDY CENTERS:</b> Subjects will be enrolled at approximately 50 sites in Europe and North America.		
<b>STUDY PERIOD:</b> First subject in: September 2015 All subjects completed treatment: January 2018 End of follow-up: January 2020		<b>PHASE OF DEVELOPMENT:</b> Phase 2
<b>OBJECTIVES:</b> <b>Primary Objective:</b> <ul style="list-style-type: none"> <li>To compare the objective response rate (ORR) among subjects with relapsed or refractory CD30-positive diffuse large B-cell lymphoma (DLBCL) or follicular non-Hodgkin lymphoma (NHL) grade 3b receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)</li> </ul> <b>Secondary Objectives:</b> <ul style="list-style-type: none"> <li>To compare progression-free survival (PFS) among subjects with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)</li> <li>To compare the complete remission (CR) rate between the 2 arms of the study</li> <li>To compare duration of response (DOR) between the 2 arms of the study</li> <li>To compare overall survival (OS) between the 2 arms of the study</li> <li>To evaluate the safety and tolerability of the 2 arms of the study</li> </ul> <b>Exploratory Objectives:</b> <ul style="list-style-type: none"> <li>To characterize the incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin among subjects with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b receiving rituximab and bendamustine plus brentuximab vedotin</li> <li>To explore the relationship between CD30 expression and clinical responses</li> <li>To explore the relationship between potential patient stratification biomarkers and clinical responses</li> <li>To evaluate brentuximab vedotin (and monomethyl auristatin E [MMAE]) exposures when administered in combination with rituximab and bendamustine</li> <li>To characterize pharmacodynamic markers such as soluble CD30 in the 2 treatment arms</li> </ul>		
<b>STUDY DESIGN AND METHODOLOGY:</b> This is a randomized, open-label, multicenter, Phase 2 clinical trial designed to evaluate the efficacy and safety of brentuximab vedotin in combination with rituximab and bendamustine for the treatment of patients with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b after failure of second-line salvage therapy or as second-line treatment in patients ineligible for autologous stem cell transplant (ASCT). Patients will be randomized in a 1:1 manner to receive rituximab plus bendamustine with or without brentuximab vedotin (stratified by second-line age-adjusted International Prognostic Index [sAAPII] score [0 vs 1 vs 2-3] and duration of remission after initiation of frontline therapy [refractory or relapse <12 months vs relapse ≥12 months]). Patients who respond to combination treatment containing brentuximab vedotin and do not experience excessive toxicity may receive additional single-agent brentuximab vedotin following combination treatment, for up to an		

additional 10 cycles (up to 16 total cycles of treatment).

DLBCL or follicular NHL grade 3b will be histologically determined by local pathology assessment, and CD30 expression will be determined by local or central laboratory visual assessment of any detectable level of CD30 on tumor cells by immunohistochemistry (IHC; using anti-CD30 BerH2 antibody) to determine eligibility for enrollment. Tissue will be sent to a central laboratory for disease confirmation and retrospective evaluation of biomarkers including, but not limited to, CD30 expression by IHC and computer-assisted image analysis.

**STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:**

Subjects cannot be enrolled before all inclusion criteria (including test results) are confirmed.

**Inclusion Criteria:**

1. Patients with histologically confirmed CD30-positive DLBCL or follicular NHL grade 3b, defined as any detectable CD30 expression on tumor cells based on local or central pathologic assessment.
2. Patients must have relapsed or refractory disease following:
  - a. second-line or greater salvage systemic therapy, or
  - b. frontline cytotoxic systemic therapy, for patients who are ineligible for stem cell transplant (SCT).
3. Age 18 and older.
4. Fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) and measurable disease of at least 1.5 cm by CT, as assessed by the site radiologist.
5. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2.
6. The following baseline laboratory data:
  - a. Absolute neutrophil count (ANC)  $\geq 1000/\mu\text{L}$  (unless documented bone marrow involvement)
  - b. Platelet count  $\geq 75,000/\mu\text{L}$  (unless documented bone marrow involvement)
  - c. Serum bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN) or  $\leq 3 \times$  ULN for patients with Gilbert's disease
  - d. Estimated creatinine clearance (CrCL)  $\geq 40$  mL/min (calculated using the Cockcroft-Gault formula)
  - e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $\leq 2.5 \times$  ULN.
7. Females of childbearing potential must have a negative serum beta human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test result within 7 days prior to the first dose of study drug. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or bilateral oophorectomy or hysterectomy.
8. Females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraceptive methods during the study and for 6 months following the last dose of brentuximab vedotin or 12 months following the last dose of rituximab, whichever is later.
9. Patients must be willing and able to provide written informed consent.

**Exclusion Criteria:**

1. History of another invasive malignancy that has not been in remission for at least 1 year. The following are exempt from the 1-year limit: nonmelanoma skin cancer, curatively treated localized prostate cancer, ductal carcinoma in situ (DCIS), and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear.
2. History of progressive multifocal leukoencephalopathy (PML).
3. 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 (CNS) disease has been definitively treated.
4. Any active Grade 3 or higher (per the National Cancer Institute [NCI, US] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of brentuximab vedotin. Routine antimicrobial prophylaxis is

<p>permitted.</p> <ol style="list-style-type: none"> <li>Chemotherapy, radiotherapy, biologics, and/or other antitumor treatment with immunotherapy that is not completed 4 weeks prior to first dose of study drug. Concomitant use of other systemic antineoplastic agents (including bleomycin) while on study is excluded.</li> <li>Females who are pregnant or breastfeeding.</li> <li>Known hypersensitivity to any study drug or excipient contained in the drug formulation of any of the study drugs.</li> <li>Known to be positive for hepatitis B by surface antigen expression (HBsAg) and hepatitis B core antibody (HBcAb). Known to have active hepatitis C infection (positive by polymerase chain reaction) or on antiviral therapy for hepatitis C within the last 6 months.</li> <li>Known to be positive for human immunodeficiency virus (HIV).</li> <li>Patients with previous allogeneic SCT.</li> <li>Previous treatment with brentuximab vedotin or bendamustine.</li> <li>Intolerable toxicity to prior rituximab therapy (per Investigator discretion).</li> <li>Current therapy with other investigational agents.</li> <li>Grade 3 or higher pulmonary disease unrelated to underlying malignancy.</li> <li>Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III-IV within 6 months prior to the first dose of brentuximab vedotin.</li> <li>Congestive heart failure, Class III or IV, by the NYHA criteria.</li> <li>Grade 2 or higher (per NCI CTCAE, Version 4.03) peripheral sensory or motor neuropathy at baseline.</li> <li>Major surgery less than 30 days prior to first dose of study drug. Major surgery is any invasive operative procedure in which a more extensive resection is performed, eg, a body cavity is entered, organs are removed, or normal anatomy is altered.</li> <li>Live vaccines (in particular yellow fever vaccination) within 1 month prior to the first dose of study drug.</li> <li>Current severe immunodeficiency, or history of recurring or chronic infections, or with underlying conditions which may further predispose patients to serious infection.</li> </ol>
<p><b>NUMBER OF SUBJECTS:</b> Approximately 110 patients with relapsed or refractory DLBCL or follicular NHL grade 3b will be enrolled in the study (approximately 55 patients in each treatment arm).</p>
<p><b>STUDY TREATMENT(S):</b></p> <p><b>Test Product, Dose and Mode of Administration:</b>  Brentuximab vedotin: 1.8 mg/kg IV infusion (over 30 minutes) on Day 1 of each 21-day cycle  Rituximab: 375 mg/m<sup>2</sup> IV infusion (per institutional standard of care) on Day 2 (+1) of each 21-day cycle  Bendamustine: 90 mg/m<sup>2</sup> IV infusion (over 60 minutes) on Day 1 AND Day 2 (+1) of each 21-day cycle</p> <p><b>Reference Therapy, Dose and Mode of Administration:</b>  Rituximab: 375 mg/m<sup>2</sup> IV infusion (per institutional standard of care) on Day 1 OR Day 2 (+1) of each 21-day cycle  Bendamustine: 90 mg/m<sup>2</sup> IV infusion (over 60 minutes) on Day 1 AND Day 2 (+1) of each 21-day cycle</p> <p><b>Bendamustine Timing</b>  On days when bendamustine is administered with other study drugs (brentuximab vedotin or rituximab), bendamustine will be the last study drug administered, beginning 30-60 minutes after completion of the brentuximab vedotin or rituximab infusion.</p>
<p><b>DURATION OF TREATMENT:</b> Study treatment consists of six 3-week cycles of combination treatment. The maximum total duration of combination therapy is 6 cycles, or approximately 4 months. Patients who respond to combination treatment containing brentuximab vedotin and do not experience excessive toxicity may receive additional treatment with single-agent brentuximab vedotin for up to an additional 10 cycles</p>

(up to 16 total cycles of treatment) or until progression or unacceptable toxicity.

## **STUDY EVALUATIONS:**

### **Primary Efficacy Criteria:**

The primary efficacy endpoint of this study is objective response rate (ORR) as assessed by the 2014 Lugano Classification.

Imaging (CT and PET or CT/PET; PET no longer required after documented postbaseline FDG-negative PET) at the end of Cycles 2 and 6; 6, 12, and 24 months after the start of combination treatment (Cycle 1 Day 1); and annually thereafter until disease progression or study closure).

### **Secondary Efficacy Criteria:**

Secondary efficacy endpoints are the following:

- Progression-free survival (PFS)
- Complete response (CR) rate
- Best clinical response
- Duration of response (DOR)
- Overall survival (OS)

### **Pharmacokinetic/Pharmacodynamic Measurements:**

Blood will be collected from subjects assigned to receive brentuximab vedotin (treatment arm) for measurement of ATA to brentuximab vedotin and both brentuximab vedotin and MMAE exposures.

Blood will be collected from all subjects for pharmacodynamic (soluble CD30 and other chemokines/cytokines of interest) assessments. Tumor samples will be collected from all subjects for assessment of CD30 antigen expression, mRNA levels of CD30 and related genes, and cell of origin classification.

**Safety Criteria:** Safety measurements will include type, incidence, severity, seriousness, and relatedness of adverse events and laboratory abnormalities, including incidence and severity of infusion-related and hypersensitivity reactions.

## **STATISTICAL METHODS:**

### *Stratification*

Patients will be stratified by sAAPI score (0 vs 1 vs 2–3) and duration of remission after initiation of frontline therapy (refractory or relapse <12 months vs relapse ≥12 months).

### *Sample Size Considerations*

Approximately 110 patients will be randomized in a 1:1 manner to each treatment arm (approximately 55 patients per treatment arm).

### *Analysis Methods*

ORR will be analyzed based on the intent-to-treat (ITT) population. ORR is defined as the proportion of patients who achieve a CR (including complete metabolic response [CMR]) or PR (including partial metabolic response [PMR]) as best response to combination therapy on study. The final analysis of ORR between the 2 treatment arms, which is planned to occur after all patients have completed combination therapy or discontinued therapy, will be compared and tested at a 1-sided 0.05 alpha level using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata. A statistically significant improvement of 22%, assuming a 50% ORR in the control arm and 72% in the brentuximab vedotin arm, would be considered clinically meaningful.

[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
[REDACTED]	
<b>DATE AND VERSION:</b> 13 July 2016, Version 05	



### **3. TABLE OF CONTENTS**

<b>1.</b>	<b>SIGNATURES .....</b>	<b>2</b>
<b>2.</b>	<b>SYNOPSIS .....</b>	<b>4</b>
<b>3.</b>	<b>TABLE OF CONTENTS.....</b>	<b>9</b>
<b>4.</b>	<b>LIST OF ABBREVIATIONS AND DEFINITION OF TERMS .....</b>	<b>14</b>
<b>5.</b>	<b>ETHICS.....</b>	<b>17</b>
5.1	Ethics Committee .....	17
5.2	Ethical Conduct of the Study.....	17
5.3	Subject Information and Consent .....	17
<b>6.</b>	<b>INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE .....</b>	<b>19</b>
<b>7.</b>	<b>INTRODUCTION .....</b>	<b>21</b>
7.1	Disease Review .....	21
7.2	Compound Review .....	22
7.3	Clinical Study Rationale.....	22
<b>8.</b>	<b>STUDY OBJECTIVES .....</b>	<b>24</b>
8.1	Primary Study Objective .....	24
8.2	Secondary Study Objectives.....	24
8.3	Exploratory Objectives.....	24
8.4	Endpoints.....	25
8.4.1	Primary Endpoint.....	25
8.4.2	Secondary Endpoints.....	25
8.4.3	Pharmacokinetic / Pharmacodynamic Measurements .....	25
<b>9.</b>	<b>INVESTIGATIONAL PLAN .....</b>	<b>26</b>
9.1	Overall Study Design and Plan.....	26
9.2	Discussion of Study Design .....	27
9.3	Study Duration .....	27
9.4	Study Population .....	28
9.4.1	Inclusion Criteria.....	28
9.4.2	Exclusion Criteria.....	29
9.4.3	Withdrawal and Replacement of Subjects .....	30
9.4.3.1	Discontinuation of Study Drug.....	30
9.4.3.2	Patient Withdrawal From Study .....	31
9.4.3.3	Replacement of Subjects .....	31
9.5	Treatment.....	31
9.5.1	Treatments Administered .....	31
9.5.1.1	Required Premedication and Postmedication.....	32
9.5.1.2	Brentuximab Vedotin .....	33

9.5.1.2.1	<i>Description</i> .....	33
9.5.1.2.2	<i>Method of Procurement</i> .....	33
9.5.1.2.3	<i>Dose and Administration</i> .....	33
9.5.1.2.4	<i>Preparation</i> .....	34
9.5.1.2.5	<i>Study Treatment Labeling and Packaging</i> .....	34
9.5.1.2.6	<i>Study Treatment Storage and Accountability</i> .....	34
9.5.1.3	Rituximab .....	35
9.5.1.3.1	<i>Description</i> .....	35
9.5.1.3.2	<i>Method of Procurement</i> .....	35
9.5.1.3.3	<i>Dose and Administration</i> .....	35
9.5.1.3.4	<i>Preparation</i> .....	35
9.5.1.3.5	<i>Storage and Accountability</i> .....	35
9.5.1.4	Bendamustine .....	36
9.5.1.4.1	<i>Description</i> .....	36
9.5.1.4.2	<i>Method of Procurement</i> .....	36
9.5.1.4.3	<i>Dose and Administration</i> .....	36
9.5.1.4.4	<i>Preparation</i> .....	36
9.5.1.4.5	<i>Storage and Accountability</i> .....	36
9.5.1.5	Management of Adverse Reactions.....	36
9.5.1.5.1	<i>Management of Infusion Reactions</i> .....	36
9.5.1.5.2	<i>Management of Suspected PML</i> .....	37
9.5.1.5.3	<i>Dose Modifications</i> .....	38
9.5.2	Blinding of Study Medication .....	39
9.5.3	Prior and Concomitant Therapy .....	39
9.5.4	Treatment Compliance .....	40
9.5.5	Assignment to Treatment .....	40
9.6	Efficacy and Safety Variables .....	40
9.6.1	Efficacy and Safety Measurements Assessed .....	40
9.6.1.1	Efficacy Measurements .....	40
9.6.1.2	Pharmacokinetic/Pharmacodynamic Measurements .....	41
9.6.1.3	Safety Measurements .....	41
<b>10.</b>	<b>STUDY EVALUATIONS BY VISIT .....</b>	<b>42</b>
10.1	Screening (Day -28 to 1) .....	46
10.2	Treatment Period .....	46
10.3	End of Treatment.....	49
10.4	Follow-Up.....	49
10.5	End of Study/End of Follow-up .....	50
<b>11.</b>	<b>METHODS OF ASSESSMENT.....</b>	<b>51</b>

11.1	Medical History.....	51
11.2	Histology / CD30 Assessment.....	51
11.3	Second-line Age-adjusted International Prognostic Index.....	52
11.4	Electrocardiograms.....	52
11.5	Physical Examination, ECOG Performance Status, and Weight .....	52
11.6	Lymphoma Assessment.....	53
11.7	Clinical Laboratory Tests.....	53
11.8	Pharmacokinetic, Pharmacodynamic, and Immunogenicity Samples .....	53
11.9	Imaging/Response Assessment.....	54
11.10	Long-term and Survival Status Follow-up .....	54
<b>12.</b>	<b>SAFETY MEASUREMENTS AND VARIABLES .....</b>	<b>55</b>
12.1	Adverse Events.....	55
12.1.1	Definitions .....	55
12.1.2	Procedures for Eliciting and Recording Adverse Events .....	57
12.1.3	Reporting Periods for Adverse Events and Serious Adverse Events .....	58
12.1.4	Serious Adverse Events Require Immediate Reporting .....	59
12.1.5	Sponsor Safety Reporting Requirements .....	59
<b>13.</b>	<b>DATA MANAGEMENT AND STATISTICAL ANALYSIS .....</b>	<b>61</b>
13.1	Data Management.....	61
13.2	Sample Size Estimation.....	61
13.3	Statistical Analysis Plan .....	61
13.4	Randomization.....	62
13.5	Analysis Populations .....	62
13.5.1	Intent-to-Treat Population .....	62
13.5.2	Safety Population .....	62
13.5.3	Efficacy Evaluable Population .....	62
13.5.4	Per-Protocol Population .....	62
13.6	Statistical Methods .....	62
13.6.1	Missing Data.....	62
13.6.2	Demographic and Baseline Data .....	63
13.6.3	Subject Disposition .....	63
13.6.4	Efficacy .....	63
13.6.4.1	Response to Treatment .....	63
13.6.4.2	Secondary Efficacy Endpoints .....	63
13.6.5	Pharmacokinetics and Pharmacodynamics.....	64
13.6.6	Safety.....	64
13.6.7	Additional Data .....	65
13.6.8	Interim Analysis .....	65

13.6.9	Independent Data Monitoring Committee.....	65
<b>14.</b>	<b>MONITORING PROCEDURES (QUALITY ASSURANCE) .....</b>	<b>67</b>
14.1	Routine Monitoring.....	67
14.2	Inspections and Auditing Procedures.....	67
<b>15.</b>	<b>STUDY MANAGEMENT AND MATERIALS.....</b>	<b>68</b>
15.1	Electronic Case Report Forms.....	68
15.2	Data Collection.....	68
15.3	Source Documents Maintenance.....	69
15.4	Record Maintenance.....	69
15.5	Confidentiality.....	70
<b>16.</b>	<b>ADMINISTRATION PROCEDURES .....</b>	<b>71</b>
16.1	Regulatory Approval .....	71
16.2	Protocol Amendments .....	71
16.3	Protocol Adherence and Deviations.....	71
16.4	Study Documentation, Privacy, and Records Retention .....	72
16.5	Publication Policy.....	72
16.6	Clinical Study Report.....	72
16.7	Contractual and Financial Details .....	73
16.8	Insurance, Indemnity, and Compensation .....	73
16.9	Discontinuation of the Study.....	73
16.10	Study Center File Management.....	73
<b>17.</b>	<b>REFERENCE LIST .....</b>	<b>75</b>
<b>18.</b>	<b>APPENDICES.....</b>	<b>79</b>
18.1	Appendix 1: Declaration of Helsinki .....	79
18.2	Appendix 2: Elements of Informed Consent.....	86
18.3	Appendix 3: Eastern Cooperative Oncology Group Performance Status .....	88
18.4	Appendix 4: Common Terminology Criteria for Adverse Events (CTCAE; v 4.03).....	89
18.5	Appendix 5: Second-line Age-adjusted International Prognostic Index .....	90
18.6	Appendix 6: Response Assessment – The Lugano Classification .....	91
18.7	Appendix 7: Futility Boundaries for the Interim Analysis.....	94
18.8	Appendix 8: Summary of Amendment 1.0.....	96
18.9	Appendix 9: Summary of Amendment 2.0.....	97
18.10	Appendix 10: Summary of Amendment 3.0.....	114
18.11	Appendix 11: Summary of Amendment 4.0.....	124

## LIST OF TABLES

Table 1:	Recommended dose modifications for brentuximab vedotin-associated toxicity.....	38
Table 2:	Study Schedule.....	43
Table 3:	Schedule of Follow-up Assessments.....	45
Table 4	Observed improvements in ORR and corresponding p-values .....	61

## LIST OF FIGURES

Figure 1:	Study Schematic.....	27
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#### **4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

<b><u>Term</u></b>	<b><u>Definition</u></b>
ABS	Acrylonitrile-butadiene-styrene
ADC	Antibody-drug conjugate
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase (serum glutamic-pyruvic transaminase)
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
ATA	Antitherapeutic antibodies
CDC	Complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CLL	Chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
CMR	Complete metabolic response
CNS	Central nervous system
COO	Cell of origin
CR	Complete remission
CrCL	Creatinine clearance
CRO	Clinical research organization
CSTD	Closed system transfer devices
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal carcinoma in situ
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
EU	European Union
FDA	Food and Drug Administration
FDG	[18F]fluorodeoxyglucose
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor

HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
β-hCG	Beta human chorionic gonadotropin
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IND	Investigational New Drug
INN	International Nonproprietary Name
IPI	International Prognostic Index
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous(ly)
IXRS	Interactive voice and web recognition system
JCV	John Cunningham virus
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NMR	No metabolic response
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PMD	Progressive metabolic disease
PML	Progressive multifocal leukoencephalopathy
PMR	Partial metabolic response

PR	Partial remission
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
sAAIPI	Second-line age-adjusted International Prognostic Index
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Stable disease
SmPC	Summary of Product Characteristics
SPD	Sum of the product of the diameters
Study drug	Rituximab and bendamustine with or without brentuximab vedotin
TAb	Total antibody
TEAE	Treatment-emergent AEs
ULN	Upper limit of normal
US	United States
USAN	United States adopted name
USP	United States Pharmacopeia
USPI	US prescribing information
WHO	World Health Organization



## **5. ETHICS**

### **5.1 Ethics Committee**

This study will be conducted in compliance with Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and International Conference On Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - including Title 21 Part 56 of the USA Code of Federal Regulations (CFR) relating to IRBs and GCP as described in the United States (US) Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B[R3]), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH regulations regarding scientific integrity (E4, E8, E9, and E10). In addition this study will adhere to all local regulatory requirements and requirements for data protection.

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

### **5.2 Ethical Conduct of the Study**

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 (R1); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Fortaleza, Brazil, October 2013; Appendix [18.1](#)), and all applicable regulatory requirements.

### **5.3 Subject Information and Consent**

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

The Sponsor will provide a sample informed consent form, based on the elements of informed consent in Appendix [18.2](#). The final, version dated form must be agreed to by the Sponsor and the IRB/IEC and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed informed consent.

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

## **6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE**

The study will be performed at approximately 55 sites in Europe and North America.

### **Monitoring and Evaluation Committee(s):**

The Independent Data Monitoring Committee (IDMC) will consist of individuals external to Seattle Genetics, Inc. and PRA Health Sciences, chosen for their expertise in oncology and familiarity with clinical trials. Members of the IDMC will include, at a minimum, physicians and appropriate statistical representation. The primary role of this IDMC will be to monitor safety data and to review the results of the planned futility analysis, as described further in the IDMC charter.

### **Randomization:**

Perceptive Informatics  
US: 1-877-819-6025  
Europe: +44 115 855 8220

### **Central Pathologist:**

Ventana Medical Systems, Inc.  
1910 E. Innovation Park Drive  
Tucson, Arizona 85755 USA  
1-520-887-2155  
1-800-227-2155

### **Clinical Laboratories:**

Central clinical laboratory services will be provided by Covance. Additional analyses of clinical laboratory samples may be conducted by certified local laboratories. Documentation of certification and laboratory normal ranges will be filed with study documentation.

Analyses of brentuximab vedotin antibody-drug conjugate (ADC) and monomethyl auristatin E [MMAE] concentrations; analyses of soluble CD30 and other chemokines/cytokines of interest; and analyses of CD30 antigen expression, mRNA levels of CD30 and related genes, and cell of origin (COO) classification will be performed at central facilities that will be identified in the study manual.

**Clinical Research Organization (CRO):**

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

**Medical Monitor/ Medical Expert (North America):**



**Medical Monitor/ Medical Expert (Europe):**



## 7. INTRODUCTION

### 7.1 Disease Review

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy, and it is estimated that 71,850 new cases of NHL will be diagnosed in the US during 2015 and that 19,790 people will die as a result of the disease. [1] Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL and comprises 30% of newly diagnosed cases. [2] Early stage DLBCL is frequently curable with combined modality therapy or combination chemotherapy alone [3], but most patients present with advanced disease, including rapidly enlarging masses and both local and systemic symptoms. Histologically, DLBCL is defined by the expression of B-cell markers including CD20, and approximately 25% of tumors co-express CD30. [4-6]

For patients with advanced-stage disease, over 50% of newly diagnosed patients are cured with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), the current frontline standard of care for DLBCL. [7-12] However, a significant number of patients either fail to respond or relapse following first-line treatment. [13,14] The International Prognostic Index (IPI) for aggressive NHL recognizes 5 significant risk factors prognostic of overall survival (OS): age >60 years, elevated serum lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group (ECOG) performance status  $\geq 2$ , disease stage III or IV, and  $>1$  site of extranodal involvement. [15] Patients with 2 or more risk factors have less than 50% chance of relapse-free survival and OS at 5 years. Molecular profiling of DLBCL indicates the overexpression of bcl-2, mutation of the myc gene, or both, confers a particularly poor prognosis. [16-19] Follicular NHL grade 3b, an aggressive follicular lymphoma, is often treated under the same guidelines. [31]

For patients with relapsed DLBCL, the second-line age-adjusted IPI (sAAIPI) is composed of 3 risk factors: ECOG performance status  $\geq 2$ , LDH level greater than normal, and stage III or IV disease; patients with 0, 1, 2, or 3 risk factors are considered to have low, low-intermediate, high-intermediate, or high risk disease, respectively. [20,21] Second-line treatment usually consists of salvage therapy followed by autologous stem cell transplantation (ASCT). However, ASCT results in long-term disease control for only 20% to 40% of patients. [20-28]

For patients who relapse after ASCT and those ineligible for transplant, prognosis is extremely poor, and options are limited. Recently, several studies have demonstrated that combination therapy with rituximab and bendamustine has clinical benefit in patients with relapsed or refractory DLBCL (objective response rate [ORR] 45.8% - 62.7%). Patients have included those with prior response to rituximab-containing therapy and those who were ineligible for ASCT. [13, 29-32] However, the median progression-free survival (PFS) in these studies was only 3.6 – 6.7 months, indicating an ongoing need for improved therapies in this setting.

## 7.2 Compound Review

Brentuximab vedotin (ADCETRIS™; also called SGN-35) is a CD30-directed ADC consisting of 3 components: 1) the chimeric immunoglobulin G (IgG)1 antibody cAC10, specific for human CD30, 2) the microtubule-disrupting agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell.

In patients with relapsed Hodgkin lymphoma (HL) after ASCT, a pivotal Phase 2 study using single agent brentuximab vedotin demonstrated a complete remission (CR) rate of 34%, and an ORR (CR plus partial remission [PR]) of 75%. The median duration of CR was 20.5 months, and the duration of any remission (CR or PR) was 6.7 months. [33] For further information, please refer to the Investigator's Brochure. Brentuximab vedotin has also been previously evaluated in 49 patients with relapsed or refractory CD30-positive DLBCL, demonstrating an ORR of 44% with a mean duration of 16.6 months. [34]

Rituximab (Rituxan®) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). Rituximab is marketed in the US and the European Union (EU) for use in combination chemotherapy for previously untreated NHL, including indolent B-cell lymphomas and DLBCL; it is also approved for chronic lymphocytic leukemia (CLL) and other diseases. [35]

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring, approved in the US for CLL and NHL; bendamustine is administered as an intravenous (IV) infusion on Days 1 and 2 for up to six 28-day cycles in CLL and for up to eight 21-day cycles in NHL. Though the exact mechanisms of action of bendamustine are unknown, mechlorethamine derivatives form electrophilic alkyl groups, which form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks and leading to cell death via several pathways. [36]

As brentuximab vedotin, rituximab, and bendamustine are each active agents in DLBCL and act via independent mechanisms, the combination is likely to represent an effective treatment for subjects with relapsed/refractory CD30-positive DLBCL.

## 7.3 Clinical Study Rationale

In the relapsed or refractory setting, DLBCL and follicular NHL grade 3b patients who co-express CD20 and CD30 present a unique treatment opportunity for rescue therapy targeting both CD20 and CD30 with rituximab and brentuximab vedotin, respectively, in combination with bendamustine. This combination has the potential to provide an important new treatment option for these patients.

The combination of rituximab and bendamustine has been previously evaluated for the treatment of relapsed or refractory DLBCL patients ineligible for ASCT. [31] Rituximab has been administered at a dose of 375 mg/m<sup>2</sup> on Day 1 of repeated 21-day cycles and bendamustine has been administered at a starting dose of 90 or 120 mg/m<sup>2</sup> on Days 1 and 2 [30] or Days 2 and 3 [29] of each cycle, with a treatment duration of up to 6 cycles. These regimens were well tolerated, although the degree of Grade 3 or 4 neutropenia was 76% with bendamustine at a dose of 120 mg/m<sup>2</sup>. [29]

The combination of rituximab and brentuximab vedotin has been previously evaluated in a cohort of patients with relapsed or refractory CD30-positive DLBCL, demonstrating an ORR of 46%. [33] Rituximab plus brentuximab vedotin was given at dose levels of 375 mg/m<sup>2</sup> and 1.8 mg/kg, respectively, on Day 1 of each cycle, and this regimen was well tolerated with a safety profile similar to single agent brentuximab vedotin.

The safety and efficacy of brentuximab vedotin combined with bendamustine in patients with HL is currently being evaluated in an ongoing clinical trial. Preliminary data indicate that this is both a safe and highly active regimen, with the most common adverse event (AE) being infusion-related reactions. [37] Brentuximab vedotin is given at a starting dose of 1.8 mg/kg on Day 1, and bendamustine is given at 90 mg/m<sup>2</sup> on Days 1 and 2.

In this study, the combination of brentuximab vedotin, rituximab, and bendamustine (treatment arm) will be compared with rituximab and bendamustine (control arm). Subjects on the treatment arm will receive brentuximab vedotin on Day 1 of each 21-day cycle at a starting dose of 1.8 mg/kg, rituximab on Day 2 (+1 day) at 375 mg/m<sup>2</sup> (per institutional standard of care), and bendamustine on Days 1 and 2 (+1 day) at 90 mg/m<sup>2</sup>. Subjects on the control arm will receive rituximab on Day 1 OR 2 of each 21-day cycle at 375 mg/m<sup>2</sup>, and bendamustine on Days 1 AND 2 (+1 day) at 90 mg/m<sup>2</sup>. The starting dose of 90 mg/m<sup>2</sup> bendamustine is within the effective range and is predicted to reduce toxicities, dose delays, and dose reductions compared with a starting dose of 120 mg/m<sup>2</sup>. In addition, in an ongoing trial evaluating the combination of brentuximab vedotin and bendamustine in elderly patients with HL, a decrease in the dose of bendamustine from 90 mg/m<sup>2</sup> to 70 mg/m<sup>2</sup> was required to improve tolerability. The safety of the 3-drug combination will be monitored in an ongoing process as part of the clinical study, including a scheduled evaluation by an IDMC. A formal futility assessment to assess efficacy will be performed after 50% of subjects have had the Cycle 2 disease assessment.

## **8. STUDY OBJECTIVES**

### **8.1 Primary Study Objective**

- To compare the objective response rate (ORR) among subjects with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)

### **8.2 Secondary Study Objectives**

- To compare progression-free survival (PFS) among subjects with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)
- To compare the complete remission (CR) rate between the 2 arms of the study
- To compare duration of response (DOR) between the 2 arms of the study
- To compare overall survival (OS) between the 2 arms of the study
- To evaluate the safety and tolerability of the 2 arms of the study

### **8.3 Exploratory Objectives**

- To characterize the incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin among subjects with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b receiving rituximab and bendamustine plus brentuximab vedotin
- To explore the relationship between CD30 expression and clinical responses
- To explore the relationship between potential patient stratification biomarkers and clinical responses
- To evaluate brentuximab vedotin (and MMAE) exposures when administered in combination with rituximab and bendamustine
- To characterize pharmacodynamic markers such as soluble CD30 in the 2 treatment arms



## **8.4 Endpoints**

### **8.4.1 Primary Endpoint**

The primary efficacy endpoint of this study is objective response rate (ORR) as assessed by the 2014 Lugano Classification. [38, Appendix 18.6]

### **8.4.2 Secondary Endpoints**

Secondary efficacy endpoints are the following:

- Progression-free survival (PFS)
- Complete response (CR) rate
- Best clinical response
- Duration of response (DOR)
- Overall survival (OS)
- Type, incidence, severity, seriousness, and relatedness of AEs
- Type, incidence, and severity of laboratory abnormalities
- Incidence and severity of infusion-related and hypersensitivity reactions.

### **8.4.3 Pharmacokinetic / Pharmacodynamic Measurements**

Blood will be collected from subjects assigned to receive brentuximab vedotin (treatment arm) for measurement of ATA to brentuximab vedotin and both brentuximab vedotin and MMAE exposures.

Blood will be collected from all subjects for pharmacodynamic (soluble CD30 and other chemokines/cytokines of interest) assessments. Tumor samples from prior biopsies/aspirates will be collected from all subjects for assessment of CD30 antigen expression, mRNA levels of CD30 and related genes, and cell of origin (COO) classification.

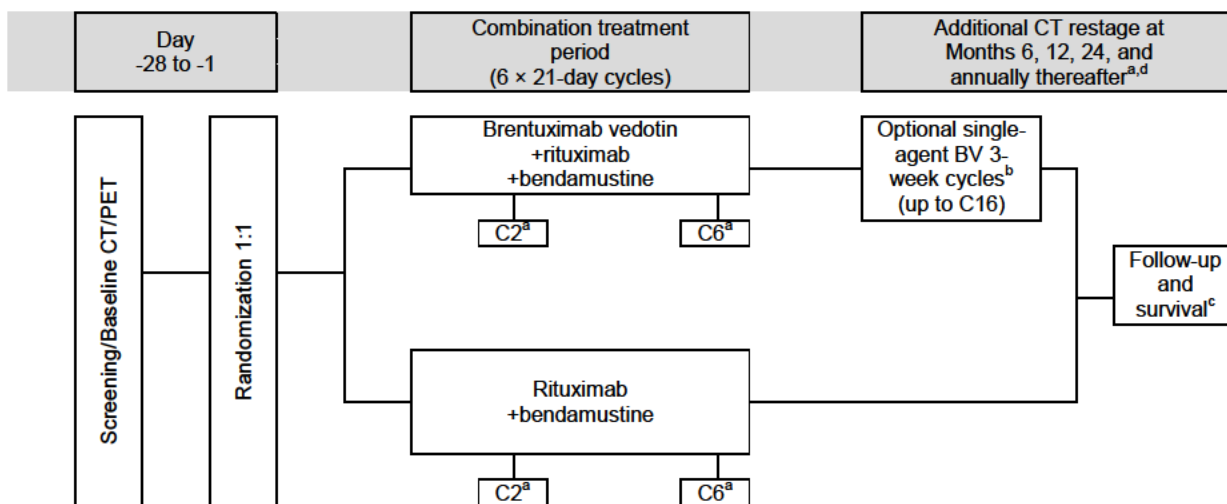
## **9. INVESTIGATIONAL PLAN**

### **9.1 Overall Study Design and Plan**

This is a randomized, open-label, multicenter, Phase 2 clinical trial designed to evaluate the efficacy and safety of brentuximab vedotin in combination with rituximab and bendamustine for the treatment of patients with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b after failure of second-line salvage therapy, or after failure of front-line treatment in patients ineligible for ASCT. The study design is presented in [Figure 1](#). Patients will be randomized in a 1:1 manner to receive rituximab plus bendamustine with or without brentuximab vedotin (stratified by sAAIPI score [0 vs 1 vs 2-3] and duration of remission after initiation of frontline therapy [refractory or relapse <12 months vs relapse ≥12 months]). Patients who respond to combination treatment containing brentuximab vedotin and do not experience excessive toxicity may receive additional single-agent brentuximab vedotin (on Day 1 of each 21-day cycle) following combination treatment, for up to an additional 10 cycles (up to 16 total cycles of treatment).

DLBCL or follicular NHL grade 3b will be histologically determined by local pathology assessment, and CD30 expression will be determined by local or central laboratory visual assessment of any detectable level of CD30 on tumor cells by immunohistochemistry (IHC; using anti-CD30 BerH2 antibody) to determine eligibility for enrollment. Tissue will be sent to a central laboratory for disease confirmation and retrospective evaluation of biomarkers including, but not limited to, CD30 expression by IHC and computer-assisted image analysis. Once stained for CD30 expression by the central pathology laboratory, slides may be retained to support future research efforts by the sponsor.

**Figure 1: Study Schematic**



- a Positron emission tomography (PET) in addition to computed tomography (CT), unless a documented negative postbaseline PET previously obtained; scans required until disease progression, death, or study closure, whichever comes first
- b Only patients who have responded to combination treatment with brentuximab vedotin and not experiencing excessive toxicity
- c Survival status should continue after disease progression until death or study closure, whichever comes first
- d Time from start of combination treatment (Cycle 1 Day1)

## 9.2 Discussion of Study Design

This is a randomized, open-label study. Randomization reduces the risk of bias in treatment allocation. For this study, an open-label design was selected as brentuximab vedotin is administered as a 30-minute infusion. The use of a placebo infusion would constitute an undue burden on subjects randomized to the control arm.

The safety and efficacy assessments are standard and well accepted measures in clinical oncology.

## 9.3 Study Duration

Study treatment consists of six 3-week cycles of combination treatment. The maximum total duration of combination therapy is 6 cycles, or approximately 4 months. Patients on the brentuximab vedotin arm may receive additional treatment with single-agent brentuximab vedotin, for up to an additional 10 cycles (up to 16 total cycles of treatment) or until progression or unacceptable toxicity. The estimated duration of the study through final primary analysis is approximately 2 years from randomization of the first patient, with an additional 2 years until the final analysis of OS and PFS.

## 9.4 Study Population

### 9.4.1 Inclusion Criteria

Subjects cannot be enrolled before all inclusion criteria (including test results) are confirmed.

1. Patients with histologically confirmed CD30-positive DLBCL or follicular NHL grade 3b, defined as any detectable CD30 expression on tumor cells based on local or central pathologic assessment.
2. Patients must have relapsed or refractory disease following:
  - a. second-line or greater salvage systemic therapy, or
  - b. frontline cytotoxic systemic therapy, for patients who are ineligible for stem cell transplant (SCT).
3. Age 18 and older.
4. Fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) and measurable disease of at least 1.5 cm by computed tomography (CT), as assessed by the site radiologist.
5. An ECOG performance status score of 0–2.
6. The following baseline laboratory data:
  - a. Absolute neutrophil count (ANC)  $\geq 1000/\mu\text{L}$  (unless documented bone marrow involvement)
  - b. Platelet count  $\geq 75,000/\mu\text{L}$  (unless documented bone marrow involvement)
  - c. Serum bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN) or  $\leq 3 \times$  ULN for patients with Gilbert's disease
  - d. Estimated creatinine clearance (CrCL)  $\geq 40$  mL/min (calculated using the Cockcroft-Gault formula)
  - e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)  $\leq 2.5 \times$  ULN.
7. Females of childbearing potential must have a negative serum beta human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test result within 7 days prior to the first dose of study drug. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or bilateral oophorectomy or hysterectomy.

8. Females of childbearing potential and males who have partners of childbearing potential must agree to use 2 effective contraceptive methods (see Section 9.5.3) during the study and for 6 months following the last dose of brentuximab vedotin or 12 months following the last dose of rituximab, whichever is later.
9. Patients must be willing and able to provide written informed consent.

#### 9.4.2 Exclusion Criteria

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

1. History of another invasive malignancy that has not been in remission for at least 1 year. The following are exempt from the 1-year limit: nonmelanoma skin cancer, curatively treated localized prostate cancer, ductal carcinoma in situ (DCIS), and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear.
2. History of progressive multifocal leukoencephalopathy (PML).
3. 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 (CNS) disease has been definitively treated.
4. Any active Grade 3 or higher (per the National Cancer Institute [NCI, US] Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of brentuximab vedotin. Routine antimicrobial prophylaxis is permitted.
5. Chemotherapy, radiotherapy, biologics, and/or other antitumor treatment with immunotherapy that is not completed 4 weeks prior to first dose of study drug. Concomitant use of other systemic antineoplastic agents (including bleomycin) while on study is excluded.
6. Females who are pregnant or breastfeeding.
7. Known hypersensitivity to any study drug or excipient contained in the drug formulation of any of the study drugs.
8. Known to be positive for hepatitis B by surface antigen expression (HBsAg) and hepatitis B core antibody (HBcAb). Known to have active hepatitis C infection (positive by polymerase chain reaction [PCR]) or on antiviral therapy for hepatitis C within the last 6 months.
9. Known to be positive for human immunodeficiency virus (HIV).
10. Patients with previous allogeneic SCT.

11. Previous treatment with brentuximab vedotin or bendamustine.
12. Intolerable toxicity to prior rituximab therapy (per Investigator discretion).
13. Current therapy with other investigational agents.
14. Grade 3 or higher pulmonary disease unrelated to underlying malignancy.
15. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III-IV within 6 months prior to the first dose of brentuximab vedotin.
16. Congestive heart failure, Class III or IV, by the NYHA criteria.
17. Grade 2 or higher (per NCI CTCAE, Version 4.03) peripheral sensory or motor neuropathy at baseline.
18. Major surgery less than 30 days prior to first dose of study drug. Major surgery is any invasive operative procedure in which a more extensive resection is performed, eg, a body cavity is entered, organs are removed, or normal anatomy is altered.
19. Live vaccines (in particular yellow fever vaccination) within 1 month prior to the first dose of study drug.
20. Current severe immunodeficiency, or history of recurring or chronic infections, or underlying conditions which may further predispose patients to serious infection.

### **9.4.3 Withdrawal and Replacement of Subjects**

In accordance with the Declaration of Helsinki (Appendix 18.1) and applicable regulations, a subject has the right to discontinue treatment or withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

#### **9.4.3.1 Discontinuation of Study Drug**

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

- Completed treatment
- Progressive disease (PD)
- AE
- Investigator decision

- Patient decision, non-AE
- Study termination by Sponsor
- Other, non-AE

Study drug must be discontinued in the case of pregnancy.

The reason for treatment discontinuation will be recorded in the clinical records and the electronic Case Report Form (eCRF). All subjects who discontinue treatment will undergo an end of treatment (EOT) visit (see Section 10.3). These subjects will continue to be followed for survival and disease status (see Section 10.4) unless they withdraw from the study (see Section 9.4.3.2). For replacement of withdrawn/discontinued subjects, see Section 9.4.3.3.

#### 9.4.3.2 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

Subjects who withdraw from study will not be further contacted. For replacement of withdrawn/discontinued subjects, see Section 9.4.3.3.

#### 9.4.3.3 Replacement of Subjects

Subjects who discontinue from treatment or study will not be replaced; the sample size was calculated assuming a 10% drop-out rate.

## 9.5 Treatment

### 9.5.1 Treatments Administered

The Investigator must ensure that the investigational product will be used only in accordance with the protocol.

Subjects randomized to the brentuximab vedotin arm will receive treatment as follows:

- Brentuximab vedotin: 1.8 mg/kg IV infusion (over 30 minutes) on Day 1 of each 21-day cycle
- Rituximab: 375 mg/m<sup>2</sup> IV infusion (per institutional standard of care) on Day 2 (+1) of each 21-day cycle
- Bendamustine: 90 mg/m<sup>2</sup> IV infusion (over 60 minutes) on Day 1 AND Day 2 (+1) of each 21-day cycle

On each treatment day, bendamustine will be the last study drug administered, beginning 30-60 minutes after completion of the brentuximab vedotin or rituximab infusion.

Subjects randomized to the control arm will receive treatment as follows:

- Rituximab: 375 mg/m<sup>2</sup> IV infusion (per institutional standard of care) on Day 1 OR Day 2 (+1) of each 21-day cycle
- Bendamustine: 90 mg/m<sup>2</sup> IV infusion (over 60 minutes) on Day 1 AND Day 2 (+1) of each 21-day cycle

On each treatment day, bendamustine will be the last study drug administered, beginning 30-60 minutes after the completion of the rituximab infusions on days when multiple infusions are performed.

Subjects will receive up to 6 cycles of rituximab and bendamustine with or without brentuximab vedotin. Subjects randomized to brentuximab vedotin who respond to combination treatment and do not experience excessive toxicity may receive additional single-agent brentuximab vedotin (once every 21 days) for up to an additional 10 cycles (up to 16 total cycles of treatment).

#### 9.5.1.1 Required Premedication and Postmedication

Prophylactic premedication with corticosteroids, antihistamines, and acetaminophen will be administered to all subjects within 60 minutes prior to infusion of the first study drug (brentuximab vedotin, rituximab, or bendamustine) each day of treatment. Recommended doses for premedication are:

1. Methylprednisolone 100 mg IV or equivalent (eg, dexamethasone 20 mg IV)
2. Diphenhydramine 25–50 mg IV or equivalent (50 mg is required for Cycles 1 and 2; at the Investigator's discretion, dose may be reduced to 25 mg subsequent to Cycle 2).
3. Acetaminophen per institutional standard



Prophylactic medications can be repeated at 6-hour intervals per Investigator discretion, as long as study medication infusions are ongoing.

For individual subjects who discontinue rituximab and bendamustine and continue on brentuximab vedotin, premedication for single-agent brentuximab vedotin may be reduced or discontinued at the discretion of the Investigator.

The use of transfusions per institutional practice is permitted. The use of white blood cell growth factors (eg, G-CSF) is recommended for all patients. Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the Investigator.

Prophylactic antibiotics should be administered according to institutional standards. The use of the NCCN 2015 guideline for the prevention and treatment of cancer-related infections is recommended. Prophylactic antiemetics should be administered according to institutional standards.

Subjects should be individually evaluated to assess the need for tumor lysis prophylaxis (eg, uric acid correction and hydration/fluid monitoring) prior to the first dose of brentuximab vedotin or rituximab. Subjects should receive prophylaxis as appropriate per the US prescribing information (USPI) or EU Summary of Product Characteristics (SmPC) or institutional standard of care.

#### 9.5.1.2 Brentuximab Vedotin

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

##### 9.5.1.2.1 *Description*

Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake or powder supplied by Seattle Genetics in single-use vials for reconstitution for IV administration. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. See the Pharmacy Manual for further information.

##### 9.5.1.2.2 *Method of Procurement*

Brentuximab vedotin will be provided by the Sponsor.

##### 9.5.1.2.3 *Dose and Administration*

Brentuximab vedotin, 1.8 mg/kg, will be administered on Day 1 of each 21-day cycle (up to 6 cycles of combination treatment) by IV infusion given over approximately 30 minutes. In the absence of infusion-related reactions, the infusion rate for all subjects should be calculated in order to achieve a 30-minute infusion period. Brentuximab vedotin must not be administered as an IV push or bolus. Brentuximab vedotin should not be mixed with other medications.

Brentuximab vedotin will be administered before bendamustine on Day 1 of each treatment cycle.

Dosing is based on subject weight. Doses will be adjusted for subjects who experience a  $\geq 10\%$  change in weight from baseline. An exception to weight-based dosing is made for subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

#### *9.5.1.2.4 Preparation*

Brentuximab vedotin vials are provided via single-use containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate institutional drug disposal procedures.

Brentuximab vedotin should be reconstituted with the appropriate amount of Sterile Water for Injection, United States Pharmacopeia (USP). The vial should be gently swirled until the contents are completely dissolved. The vial must not be shaken. The reconstituted drug product should be inspected visually for any particulate matter and discoloration.

The required volume of reconstituted drug product should be diluted into an infusion bag. The bag should be gently inverted to mix the solution. The bag must not be shaken. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

Detailed drug preparation instructions are provided in the Pharmacy Manual.

#### *9.5.1.2.5 Study Treatment Labeling and Packaging*

Drug product vials may be labeled as brentuximab vedotin, the US adopted name (USAN) and the International Nonproprietary Name (INN), or as SGN-35, the compound code; the 2 names can be used interchangeably.

#### *9.5.1.2.6 Study Treatment Storage and Accountability*

It is forbidden to use investigational drug material for purposes other than as defined in this protocol.

#### Study Treatment Storage

Refrigeration should be set at 2-8°C for storage of vials and solutions containing brentuximab vedotin. The controlled location must be accessible only to the pharmacist, the Investigator, or a duly designated person. Brentuximab vedotin does not contain preservatives; therefore, opened and reconstituted vials of brentuximab vedotin should be used immediately. If not used immediately, the in-use storage should not be longer than 24 hours. It is recommended that brentuximab vedotin vials and solutions be protected from direct sunlight until the time of use. Reconstituted vials and solutions must not be shaken.

## Study Treatment Accountability

Drug accountability instructions are provided in the Pharmacy Manual.

### 9.5.1.3 Rituximab

Rituximab is marketed in the US as Rituxan® by Genentech, Inc. (South San Francisco, CA USA) and in Europe as MabThera by Roche Registration Limited (Welwyn Garden City, Hertfordshire UK). Please refer to the approved USPI or EU SmPC for detailed information.

#### *9.5.1.3.1 Description*

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen.

Rituximab is marketed as Rituxan® in the US and as MabThera® in Europe and is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituxan and MabThera are supplied at concentrations of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials and are formulated in polysorbate 80 (0.7 mg/mL), sodium chloride (9 mg/mL), sodium citrate dihydrate (7.35 mg/mL), and Water for Injection. The pH is 6.5.

#### *9.5.1.3.2 Method of Procurement*

Commercially available rituximab will be provided by the study sites from their usual suppliers or may be provided by the Sponsor.

#### *9.5.1.3.3 Dose and Administration*

Subjects will receive rituximab on Day 2 only (treatment arm) or on Day 1 OR Day 2 (+1; control arm) of each 21-day treatment cycle for a maximum of 6 cycles. Rituximab (375 mg/m<sup>2</sup>) will be administered by IV infusion. Rituximab administration will be performed according to local standard of care.

#### *9.5.1.3.4 Preparation*

Rituximab will be prepared for IV administration according to the USPI or the EU SmPC and local standard of care.

#### *9.5.1.3.5 Storage and Accountability*

Rituximab must be stored, distributed, and disposed of according to institutional practice and the USPI or EU SmPC.

#### 9.5.1.4 Bendamustine

Please refer to the approved USPI or EU SmPC for detailed information on bendamustine hydrochloride.

##### 9.5.1.4.1 *Description*

Bendamustine hydrochloride is provided as a sterile non-pyrogenic white to off-white lyophilized powder in a single-use vial, and it is reconstituted with Sterile Water for Injection, USP. The reconstituted formulation is further diluted according to local standard of care.

##### 9.5.1.4.2 *Method of Procurement*

Bendamustine will be provided by the Sponsor.

##### 9.5.1.4.3 *Dose and Administration*

Bendamustine will be administered at a dose of 90 mg/m<sup>2</sup> by IV infusion given over 60 minutes on Days 1 and 2 (+1 day) of each 21-day cycle for a maximum of 6 cycles.

On days when bendamustine is administered with other study drugs (brentuximab vedotin or rituximab), bendamustine will be the last study drug administered, beginning 30-60 minutes after completion of the brentuximab vedotin or rituximab infusion.

##### 9.5.1.4.4 *Preparation*

Bendamustine will be prepared for IV administration according to the USPI or the EU SmPC and local standard of care. For sites using bendamustine hydrochloride liquid (TREANDA Injection; 45 mg/0.5 mL or 180 mg/2 mL solution): Do not use closed system transfer devices (CSTD), adapters, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS), as TREANDA Injection is incompatible with ABS (refer to US FDA Safety Alerts for Human Medical Products [MedWatch] dated 10 March 2015).

##### 9.5.1.4.5 *Storage and Accountability*

Bendamustine must be stored, distributed, and disposed of according to institutional practice and the USPI or EU SmPC.

#### 9.5.1.5 Management of Adverse Reactions

##### 9.5.1.5.1 *Management of Infusion Reactions*

Infusion-related reactions may occur during the infusion of study treatment. The infusions 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.

Subjects who experience a Grade 3 infusion-related reaction may potentially receive additional treatment at the discretion of the Investigator after discussion with the medical monitor. Treatment should be discontinued for patients who experience Grade 4 infusion-related reactions, unless the reaction can be attributed to a single agent, in which case the single agent must be discontinued.

With the combination of bendamustine and brentuximab vedotin, infusion-related reactions and delayed-type hypersensitivity reactions have been observed. [37] To reduce the risk of infusion reactions, all patients will be premedicated as described in Section 9.5.1.1.

Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occur during the first infusion with time to onset of 30–120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Appropriate medical management (eg, glucocorticoids, epinephrine, bronchodilators, and oxygen) should be instituted for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, rituximab may be temporarily or permanently discontinued. Infusion may be resumed at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor patients with pre-existing cardiac or pulmonary conditions or who experienced prior cardiopulmonary adverse reactions.

If anaphylaxis occurs, study treatment should be immediately and permanently discontinued.

#### *9.5.1.5.2 Management of Suspected PML*

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. See the Investigator's Brochure for further details.

If PML is suspected, hold further brentuximab vedotin and rituximab dosing and undertake a diagnostic work-up including, but not limited to:

- Neurologic examinations, as warranted
- Brain magnetic resonance imaging (MRI)
- PCR analysis for John Cunningham virus (JCV) in cerebrospinal fluid.

If PML is confirmed, permanently discontinue study treatment.

### 9.5.1.5.3 Dose Modifications

#### Brentuximab Vedotin

At the Investigator's discretion, the dose of brentuximab vedotin may be reduced as outlined in [Table 1](#). If toxicity is thought to be due specifically to brentuximab vedotin, the brentuximab vedotin dose may be reduced prior to reducing the dose of bendamustine.

Subjects randomized to brentuximab vedotin who discontinue rituximab and/or bendamustine for any reason may continue to receive brentuximab vedotin per protocol.

Doses reduced for treatment-related toxicity should not be re-escalated. Dose delays of greater than 3 weeks are prohibited without approval of the Medical Monitor.

**Table 1: Recommended dose modifications for brentuximab vedotin-associated toxicity**

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral Neuropathy	Continue at same dose level	Withhold until toxicity resolves to Grade 1 or baseline, then resume treatment at 1.2 mg/kg <sup>a</sup>		Discontinue treatment
Non-hematologic (except peripheral neuropathy)	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is $\leq$ Grade 2 or has returned to baseline, then resume treatment at the same dose level <sup>b</sup> .	Withhold dose until toxicity is $\leq$ Grade 2 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the Investigator <sup>a, b, c</sup> .
Hematologic <sup>d</sup>	Continue at same dose level	Continue at same dose level	Withhold until toxicity resolves to $\leq$ Grade 2 or baseline, then resume treatment at the same dose level <sup>e</sup> . Growth factor support (G-CSF or GM-CSF) should be considered for subsequent cycles. If Grade 4 neutropenia recurs despite growth factor support, consider discontinuation or dose reduction to 1.2 mg/kg.	

G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor.

a Dose reductions below 1.2 mg/kg are not allowed, and toxicities should be managed with dose delays.

b Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.

c Treatment should be discontinued for patients who experience Grade 4 infusion-related reactions.

d Support with blood product transfusions allowed per institutional standard of care.

e Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

f For Grade 3 neuropathy, investigator may withhold dose for 1 cycle and continue other therapy. After resolution to  $\leq$  Grade 1, may resume brentuximab vedotin at 1.2 mg/kg

#### Rituximab

Dose modification of rituximab due to toxicity is allowed per institutional standards and according to the USPI or SmPC at the discretion of the Investigator, including discontinuation of treatment.

## Bendamustine

With the combination of bendamustine and brentuximab vedotin, an increased incidence of infusion-related reactions and delayed-type hypersensitivity reactions have been observed compared to each agent alone. [37] Thus, all patients require premedication as described in Section 9.5.1.1.

Permanently discontinue bendamustine if CrCL is <40 mL/min; use bendamustine with caution in lesser degrees of renal impairment.

Dose modification of bendamustine due to toxicity is allowed per institutional standards and according to the USPI or SmPC at the discretion of the Investigator. In general, bendamustine administration should be delayed for Grade 4 hematologic toxicity or clinically significant Grade  $\geq 2$  nonhematologic toxicity until sufficient recovery or resolution (Grade  $\leq 1$  or baseline for nonhematologic toxicity; ANC  $\geq 1 \times 10^9/L$  or platelets  $\geq 75 \times 10^9/L$ ). Bendamustine can then be reinitiated at the discretion of the treating physician. Following Grade 4 hematologic toxicity or Grade  $\geq 3$  nonhematologic toxicity, the bendamustine dose should be decreased from 90 mg/m<sup>2</sup> to 70 mg/m<sup>2</sup>, and, if toxicity recurs, the dose can be further decreased to 50 mg/m<sup>2</sup>. Doses lower than 50 mg/m<sup>2</sup> are not allowed.

For patients receiving brentuximab vedotin, if the toxicity is thought to be due specifically to bendamustine, the bendamustine dose may be reduced prior to reducing the dose of brentuximab vedotin.

### **9.5.2 Blinding of Study Medication**

Not applicable; this is an open-label study.

### **9.5.3 Prior and Concomitant Therapy**

Subjects must not receive live vaccines (in particular yellow fever vaccination) or bleomycin while on treatment; subjects requiring these treatments will be discontinued from study. Live vaccines must not be administered within 1 month of starting study treatment.

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

The use of corticosteroids to treat conditions other than DLBCL or follicular NHL grade 3b is permitted per institutional standard. Systemic corticosteroids may be used to keep DLBCL symptoms under control prior to Cycle 1 Day 1 as long as the duration of steroid use is no longer than 14 days.

Routine infectious prophylaxis per the NCCN 2015 guideline for the prevention and treatment of cancer-related infections is recommended.

The use of transfusions per institutional practice is permitted. The use of white blood cell growth factors (eg, G-CSF) is recommended for all patients. Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the Investigator.

Prophylactic antiemetics should be administered according to institutional standard.

Subjects may be eligible for allogenic SCT or ASCT following study treatment. Subjects receiving these treatments should continue in study follow-up.

All subjects who discontinue the study medication should be offered alternative treatment if applicable. Treatment should be given according to normal clinical practice, after a termination visit (see Section 10.3).

### Contraception

Acceptable methods of contraception include: hormonal (birth control pills, injections, implants), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), vasectomy (for males), barrier methods (male and female condoms, diaphragms, and spermicides), bilateral tubal ligation, and complete abstinence. Complete abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

## **9.5.4 Treatment Compliance**

Brentuximab vedotin, rituximab, and bendamustine will be administered by qualified study site staff, and administration information will be recorded in the eCRF.

## **9.5.5 Assignment to Treatment**

After eligibility is determined and within 1 business day of planned first dose of study treatment, subjects will be randomized to treatment by a centralized interactive voice and web recognition system (IXRS). Patients will be stratified at randomization by sAAPI score (0 vs 1 vs 2–3) and disease status after initiation of frontline therapy (refractory or relapse <12 months vs relapse ≥12 months).

## **9.6 Efficacy and Safety Variables**

### **9.6.1 Efficacy and Safety Measurements Assessed**

#### **9.6.1.1 Efficacy Measurements**

#### **Primary Efficacy Criteria:**

The primary efficacy endpoint of this study is ORR.



Subjects will undergo CT/PET (or CT and PET) at baseline, Cycle 2, and Cycle 6 or EOT for patients who do not have an assessment at the end of Cycle 6 or who do not complete 6 cycles of treatment. PET is no longer required after documented postbaseline FDG-negative PET. Disease status will be assessed according to the 2014 Lugano Classification. [38] Detailed response definitions are presented in Appendix 18.6.

### **Secondary Efficacy Criteria:**

Secondary efficacy endpoints will be the following:

- Progression-free survival (PFS)
- Complete response (CR) rate
- Best clinical response
- Duration of response (DOR)
- Overall survival (OS)

See Section 13.6.4 for definitions.

#### **9.6.1.2 Pharmacokinetic/Pharmacodynamic Measurements**

Blood will be collected from subjects assigned to receive brentuximab vedotin (treatment arm) for measurement of ATA to brentuximab vedotin and both brentuximab vedotin and MMAE exposures, and pharmacodynamic (soluble CD30 and other chemokines/cytokines of interest) assessments (Section 11.8). Tumor samples will be collected from all subjects for assessment of CD30 antigen expression, mRNA levels of CD30 and related genes, and COO classification.

#### **9.6.1.3 Safety Measurements**

Safety measurements will include type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities.

## **10. STUDY EVALUATIONS BY VISIT**

A full schedule of study procedures for the screening and treatment periods is provided in [Table 2](#), and a schedule of follow-up assessments is provided in [Table 3](#).

**Table 2: Study Schedule**

		Baseline/ Screening		Enroll- ment	Cycles 1 and 2		Cycle 2 only	Cycles 3-6	Cycle 6 only	Cycles 7+ <sup>g</sup>	EOT visit	Long-term Follow-up	
Visit Window		D -28 to 1	D -7 to 1	D -7 to 1	D1(±1D) to D2	D7- D14	Day 15-21 (+2D)	D1(±1D) to D2	Day 15-21 (+2D)	D1(±1D) to D2	30-37 days post last dose <sup>a</sup>		
Screening/ Baseline and Safety Assessments	Informed consent	X		Eligibility documentation submitted to Sponsor prior to study start; randomization <sup>d</sup>								See Table 3	
	Inclusion/exclusion criteria	X											
	Medical history	X											
	Physical exam (incl. neuro. exam)		X		X	X <sup>o</sup>		X		X	X		
	Tumor specimen/CD30/histology <sup>b,c</sup>	X											
	Height		X										
	Weight		X		X			X		X			
	sAAIPI score <sup>e</sup>	X											
	Electrocardiogram		X		X			X		X			
	HBsAg / HBcAb		X										
	Pregnancy test		X		X			X		X	X		
Treatment	Combination treatment <sup>f</sup>				X			X					
	Single-agent brentuximab vedotin <sup>g</sup>									X			
ATA/PK/PD	PK samples <sup>h</sup> (treatment arm only)				X			X					
	ATA samples <sup>i</sup> (treatment arm only)				X			X			X		
	Pharmacodynamic samples <sup>i</sup>				X			X			X		
Response Assessment	Lymphoma assessment <sup>j</sup>				X			X		X	X		
	CT (chest, neck, abdomen, pelvis) <sup>k</sup>	X					X		X		X <sup>a</sup>		
	PET <sup>k,l</sup>	X					X		X		X <sup>a</sup>		
Safety Assessments	ECOG performance status		X		X <sup>p</sup>	X		X		X	X		
	Serum chemistry		X		X			X		X	X		
	Creatinine clearance <sup>m</sup>		X <sup>n</sup>		X <sup>n</sup>			X <sup>n</sup>					
	Hematology		X		X	X		X		X	X		
	Concomitant medications & AEs	Collect any related to study protocol procedures			Collect from Day 1 (predose) through 30 days post last dose or through EOT visit, whichever is later								

AEs = adverse events; ATA = antitherapeutic antibodies; CT = computed tomography; D = Day; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; sAAIPI = second-line age-adjusted International Prognostic Index.

Note: All Day 1 procedures are before treatment unless otherwise specified.

- a. Response assessments and pregnancy test at EOT not required if performed at last cycle of treatment. EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30-37 days following the patient's last study treatment to ensure that no changes in AE profile have occurred.
- b. Centrally or locally assessed to enable enrollment. Submission of the tumor block or approximately 15 unstained slides from a biopsy of relapsed disease (or initial diagnostic specimen if refractory) is required for subsequent central pathology disease confirmation and further evaluation of additional molecular biomarkers.
- c. Biopsy material will also be collected if available to evaluate changes in molecular biomarkers by different treatments. No additional procedures will be conducted to obtain these research tissues; only available tissue will be used.
- d. Randomization to occur after eligibility is determined and within 1 business day of planned first dose of study treatment. The site will contact the interactive voice and web recognition system (IXRS) for randomization assignment.
- e. ECOG performance status, lactate dehydrogenase (LDH), and disease stage must be recorded on the eCRF; historical values collected within 30 days of determination of the sAAPI are acceptable.
- f. Brentuximab vedotin, rituximab, and bendamustine OR rituximab and bendamustine.
- g. Patients who are responding to combination treatment with brentuximab vedotin and not experiencing excessive toxicity may receive single-agent brentuximab vedotin treatment following combination therapy.
- h. Predose (within 24 hours before the start of the brentuximab vedotin infusion) and postdose (within 30 minutes after the end of the infusion; samples for ADC and MMAE levels only).
- i. Predose (within 24 hours before the start of the first infusion on Day 1).
- j. Consists of the following: physical examination, patient medical history, including a thorough review of the patient's current signs and symptoms, B symptoms, and concomitant medications.
- k. A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as a diagnostic quality CT scan is obtained; PET scans may also be obtained any time during the study if clinically indicated; PET scan not required after documented postbaseline FDG-negative PET scan is obtained.
- l. Obtain until patient experiences progressive disease per Investigator assessment, death, or study closure, whichever comes first.
- m. Calculated using the Cockcroft-Gault formula.
- n. Creatinine clearance must be  $\geq 40$  mL/min and checked Day 1 of each cycle prior to infusion of bendamustine.
- o. At these visits the physical examination may be a brief, targeted examination, at the discretion of the investigator, to identify changes from baseline.
- p. Not required for Cycle 1.

**Table 3: Schedule of Follow-up Assessments**

		Time Point (relative to Cycle 1, Day 1)									Annually after
Visit Window		Month 6 (± 1 week)	Month 9 (± 1 week)	Month 12 (± 1 week)	Month 15 (± 1 week)	Month 18 (± 1 week)	Month 21 (± 1 week)	Month 24 (± 1 week)	Month 30 (± 1 week)	Month 36 (± 1 week)	Month 36 <sup>a</sup> (± 1 week)
Response Assessment	Lymphoma assessment <sup>b</sup>	X	X	X	X	X	X	X	X	X	
	CT (chest, neck, abdomen, pelvis)	X <sup>c,d</sup>		X <sup>c,d</sup>				X <sup>c,d</sup>		X <sup>c,d</sup>	X <sup>c,d</sup>
	PET	X <sup>c,d</sup>		X <sup>c,d</sup>				X <sup>c,d</sup>		X <sup>c,d</sup>	X <sup>c,d</sup>
	Survival status	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>

CT = computed tomography; PET = positron emission tomography.

- a. Long-term response assessments should continue annually after 36 months until death or study closure.
- b. Consists of the following: physical examination, including neurological examination, patient medical history, including a thorough review of the patient's current signs and symptoms, B symptoms, and concomitant medications.
- c. Obtain until patient experiences progressive disease per Investigator assessment, death, or study closure, whichever comes first.
- d. A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as a diagnostic quality CT scan is obtained; PET scans may also be obtained any time during the study if clinically indicated; PET scan not required after documented postbaseline FDG-negative PET scan is obtained.
- e. Once a patient experiences progressive disease per Investigator assessment, survival status should be assessed until death or study closure, whichever comes first. Collect information regarding subsequent anticancer therapies.

## 10.1 Screening (Day -28 to 1)

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

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history, including lymphoma history (Section 11.1)
- Collection / acquisition of tumor specimen for histology and CD30 assessment (Section 11.2)
- sAAIPI score (see Section 11.3)
- Baseline disease assessment (Section 11.9).

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

- Height and weight (Section 11.5)
- Standard 12-lead electrocardiogram (ECG; Section 11.4)
- Physical examination (including neurologic assessment; Section 11.5)
- Serum pregnancy test (women of childbearing potential only)
- ECOG performance status (Section 11.5)
- Clinical laboratory tests (hematology, serum chemistry, CrCL [calculated using the Cockcroft-Gault formula], HBsAg, and HBcAb; Section 11.7).

From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded, as well as any concomitant medications given for the treatment of these AEs.

Within one business day of the planned start of treatment, the study site will contact the IXRS as directed in the study manual. Contact information for the IXRS is provided in the study manual.

## 10.2 Treatment Period

The subject will receive treatment in repeated 21-day cycles of rituximab and bendamustine with or without brentuximab vedotin (Section 9.5.1). In addition, the following procedures will be performed at the indicated time points:

- Cycles 1 and 2, Day 1, pretreatment:
  - For subjects on the treatment arm (brentuximab vedotin) only:  
Pharmacokinetic (PK) and ATA sample collection (within 24 hours before beginning the brentuximab vedotin infusion; Section 11.8)
  - For all subjects:  
Pharmacodynamic sample collection (within 24 hours before beginning study treatment ; Section 11.8)
  - Weight (Section 11.5)
  - Lymphoma assessment (Section 11.6)
  - Standard 12-lead ECG (Section 11.4)
  - Serum pregnancy test (women of childbearing potential only)
  - Physical examination (including neurologic assessment; Section 11.5)
  - ECOG performance status (not required in Cycle 1; Section 11.5)
  - Pre-dose clinical laboratory tests (CrCL [calculated using the Cockcroft-Gault formula], hematology, and serum chemistry; Section 11.7).
- Cycles 1 and 2, Day 1, posttreatment:
  - For subjects on the treatment arm (brentuximab vedotin) only:  
PK sample collection (within 30 minutes after completion of the brentuximab vedotin infusion; Section 11.8).
- Cycles 1 and 2, Day 7-14:
  - Physical examination (Section 11.5)
  - Clinical laboratory tests (hematology; Section 11.7)
  - ECOG performance status (Section 11.5)
- Cycle 2 only, Days 15-21:
  - Disease assessment (Section 11.9).
- Cycles 3 – 6, Day 1, pretreatment:
  - For subjects on the treatment arm (brentuximab vedotin) only:  
PK and ATA sample collection (within 24 hours before beginning the brentuximab vedotin infusion; Section 11.8)

- For all subjects:  
Pharmacodynamic sample collection (within 24 hours before beginning study treatment; Section 11.8)
- Weight (Section 11.5)
- Lymphoma assessment (Section 11.6)
- Standard 12-lead ECG (Section 11.4)
- Serum pregnancy test (women of childbearing potential only)
- Physical examination (including neurologic assessment; Section 11.5)
- ECOG performance status (Section 11.5)
- Pre-dose clinical laboratory tests (CrCL [calculated using the Cockcroft-Gault formula], hematology, and serum chemistry; Section 11.7).
- Cycles 3 – 6, Day 1, posttreatment:
  - For subjects on the treatment arm (brentuximab vedotin) only:  
PK sample collection (within 30 minutes after completion of the brentuximab vedotin infusion; Section 11.8).
- Cycle 6 only, Days 15-21:
  - Disease assessment (Section 11.9).
- Cycles  $\geq 7$ , Day 1, pretreatment:
  - Weight (Section 11.5)
  - Lymphoma assessment (Section 11.6)
  - Standard 12-lead ECG (Section 11.4)
  - Serum pregnancy test (women of childbearing potential only)
  - Physical examination (including neurologic assessment; Section 11.5)
  - ECOG performance status (Section 11.5)
  - Pre-dose clinical laboratory tests (hematology and serum chemistry; Section 11.7).

Any AEs (Section 12.1) and serious adverse events (SAEs; Section 12.1.1), reported or observed, will be reported on the eCRF, and SAEs will be reported as indicated in



Section 12.1.4. Any changes in concomitant medications will be recorded at each visit or as they are reported.

### 10.3 End of Treatment

An EOT visit will be performed 30 – 37 days after the last dose of study treatment (brentuximab vedotin, rituximab, and/or bendamustine). EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30 – 37 days following the patient's last study treatment to ensure that no changes in AE profile have occurred. At the EOT visit, the following assessments/procedures will be performed:

- Pharmacodynamic sample collection (Section 11.8)
- Serum pregnancy test (women of childbearing potential only; not required if performed at the last cycle of treatment)
- Lymphoma assessment (Section 11.6)
- Physical examination (including neurologic assessment; Section 11.5)
- Disease assessment (Section 11.9)
- ECOG performance status (Section 11.5)
- Clinical laboratory tests (hematology and serum chemistry; Section 11.7).

Response assessments and pregnancy test at EOT not required if performed at last cycle of treatment.

Any AEs (Section 12.1) and SAEs (Section 12.1.1), reported or observed, will be reported on the eCRF, and SAEs will be reported as indicated in Section 12.1.4. End-of-treatment evaluations should be obtained before the initiation of non-protocol therapy. If the EOT visit occurs less than 30 days after the last treatment with brentuximab vedotin, the subject will be contacted by telephone 30 to 37 days after the last treatment with brentuximab vedotin to assess any AEs or changes in concomitant medications that may have occurred since the EOT visit.

### 10.4 Follow-Up

At the times indicated in Table 3 until disease progression or study closure, subjects will undergo a follow-up visit. Follow-up visits will include lymphoma assessments (all follow-up visits; Section 11.6) and, at Months 6, 12, 24, 36, and annually thereafter, disease assessments (Section 11.9).

After documented disease progression, the study site will contact the subject to assess survival and disease status (Section 11.10) on the same schedule. In addition, the status of

any AEs of special interest ongoing at the time of last contact will be assessed at follow-up contacts. Follow-up will continue until death or until the study is closed.

#### **10.5 End of Study/End of Follow-up**

The date the subject met criteria for study discontinuation and the reason for study discontinuation will be collected.

## **11. METHODS OF ASSESSMENT**

### **11.1 Medical History**

A full medical history, including demographic information and history of DLBCL or follicular NHL grade 3b and prior treatments, will be performed at screening. Any AEs (Section 12.1) occurring after screening and before the first dose of study drug will be included as medical history.

### **11.2 Histology / CD30 Assessment**

Histologically confirmed DLBCL or follicular NHL grade 3b must be determined by local pathology assessment. CD30 expression will be determined by local or central laboratory visual assessment using IHC (anti-CD30 BerH2 antibody) to determine eligibility.

If adequate tissue is not available or if disease has relapsed and the patient has not had a biopsy since the relapse was documented, a new biopsy must be obtained. A new biopsy is not required for patients with refractory disease, provided a biopsy was obtained prior to the initiation of the most recent therapy.

Submission of the tumor block or approximately 15 unstained slides from a biopsy of relapsed disease (or initial diagnostic specimen if refractory) is required for subsequent central pathology disease confirmation and further evaluation CD30 expression, and additional molecular biomarkers.

Biopsy material will also be collected from patients who provided consent if available from biopsies performed anytime while the subject is on study to evaluate changes in molecular biomarkers by different treatments. The tumor tissue will be used to conduct exploratory correlative studies. Tumor based molecular biomarkers may include, but are not limited to COO, prognostic markers for lymphoma, and CD30 pathway related markers. These will be conducted on the following tissues if available:

- Leftover unstained slides or tumor tissue from a diagnostic biopsy will be obtained at baseline if available
- Unstained slides or leftover tissue from a core biopsy obtained as part of standard-of-care clinical intervention while a patient is participating in the study (e.g., for treatment failure at any time)

No additional procedures will be conducted to obtain these research tissues, and thus no additional patient risk is introduced with these optional exploratory correlative studies.

### **Biospecimen Samples for Future Research**

In the United States, remaining de-identified unused blood and tissue will be retained by Seattle Genetics and used for future research for patients who provide consent. The planned

future research includes, but is not limited to, the identification of targets for novel ADCs, the biology of ADC sensitivity and resistance mechanisms, and the identification of predictive pharmacodynamic biomarkers of response to ADCs. Blood and tissue samples donated for future research will be retained for 25 years. Outside the US or if additional consent is not granted, any blood and tissue samples remaining after all study testing is completed will be destroyed following study closure.

### **11.3 Second-line Age-adjusted International Prognostic Index**

The sAAIPI is a score of 0, 1, 2, or 3, determined by adding 1 for each of the following risk factors present (see Appendix 18.5):

- ECOG  $\geq 2$
- LDH > ULN
- Stage III or IV disease.

ECOG performance status, LDH, and disease stage must be recorded on the eCRF; historical values collected within 30 days of determination of the sAAIPI are acceptable.

### **11.4 Electrocardiograms**

ECG recordings will be obtained. A copy of all ECGs will be retained on site.

For the purposes of screening, the Investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically acceptable for inclusion, if abnormal.

ECGs may be repeated for quality reasons, and additional ECGs may be collected by the Investigator for safety reasons. Any posttreatment clinically relevant abnormal ECG findings will be reported as AEs.

### **11.5 Physical Examination, ECOG Performance Status, and Weight**

Physical examinations will be performed at the time points indicated in Table 2 and include assessments of the following body parts/systems: HEENT (head, ears, eyes, nose, and throat), neck, cardiovascular and respiratory systems, lymph nodes, abdomen, extremities, skin, and neurological.

At the Day 7-14 visits in Cycles 1 and 2, the physical examination may be a brief, targeted examination, at the discretion of the investigator, to identify changes from baseline.

ECOG performance status (Appendix 18.3) will be assessed at the time points indicated in Table 2 and recorded on the eCRF.

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

## 11.6 Lymphoma Assessment

The lymphoma assessment includes physical examination (see Section 11.5), patient medical history (including a thorough review of the patient's current signs and symptoms), B symptoms, and concomitant medications.

In the absence of radiological examination (Section 11.9), disease progression can be determined based on lymphoma assessment alone.

## 11.7 Clinical Laboratory Tests

Blood samples will be taken for central and local laboratory analyses. Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions. Hematology and serum chemistry assessments will be performed by the central laboratory to evaluate safety at the times indicated in Table 2. The following parameters will be determined:

**Hematology:** White blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell count, platelet count, and hemoglobin/hematocrit.

**Serum chemistry:** Albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, LDH, phosphorus, potassium, sodium, total bilirubin, uric acid, lipase, amylase, glucose, and hemoglobin A1c (HbA1c; at screening only).

**Creatinine clearance** will be calculated using the Cockcroft-Gault [39] formula:

Male subjects	$\text{Creatinine clearance (mL/min)} = \frac{[140 - \text{Age (years)}] \times \text{body weight (kg)}}{72 \times \text{serum creatinine}}$
Female subjects	$\text{Creatinine clearance (mL/min)} = 0.85 \times \frac{[140 - \text{Age (years)}] \times \text{body weight (kg)}}{72 \times \text{serum creatinine}}$

Pregnancy will be determined as indicated in Table 2 by serum  $\beta$ -hCG for females of childbearing potential.

Baseline screening for hepatitis B infection by HBsAg and HBcAb.

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

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

## 11.8 Pharmacokinetic, Pharmacodynamic, and Immunogenicity Samples

Blood will be collected from subjects assigned to receive brentuximab vedotin (treatment arm) for measurement of ATA to brentuximab vedotin and both brentuximab vedotin and

MMAE exposures. PK samples will be collected during Cycles 1 – 6 within 24 hours before the start of the Day 1 brentuximab vedotin infusion (predose) and within 30 minutes after the end of the Day 1 brentuximab vedotin infusion (postdose). Samples for ATA will be collected within 24 hours before the brentuximab vedotin infusion on Day 1 of each cycle (Cycles 1 – 6) and at EOT.

Blood will be collected for pharmacodynamic assessments from all subjects. Potential pharmacodynamics biomarkers include but are not limited to soluble CD30, inflammatory cytokines, and circulating tumour DNA. Samples for pharmacodynamic studies will be collected from patients on both treatment arms within 24 hours before the first infusion on Day 1 of each cycle (Cycles 1 – 6) and at EOT.

Sample handling and shipping information will be provided in the study manual.

### **11.9 Imaging/Response Assessment**

Response will be assessed according to the 2014 Lugano Classification [38] as outlined in Section 13.6.4.1 and Appendix 18.6. Imaging studies will be performed at the time points indicated in Table 2 and Table 3. Imaging will include: (1) diagnostic quality CT of neck, chest, abdomen, and pelvis and (2) PET. A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as a diagnostic quality CT scan is obtained. PET scans may also be obtained any time during the study if clinically indicated. Additional PET scan is not required if a documented postbaseline FDG-negative PET scan has been obtained. Specific imaging requirements will be outlined in a separate manual. For PET scans performed while patients are receiving study therapy, Deauville scores of 1, 2, and 3 will be regarded as negative, indicative of complete metabolic response (CMR), while scores of 4 and 5 will be regarded as positive.

In the absence of radiological examination, disease progression can be determined based on lymphoma assessment (Section 11.6) alone.

### **11.10 Long-term and Survival Status Follow-up**

At the times indicated in Table 3, lymphoma assessment and imaging will be performed until disease progression (for subjects who discontinued treatment for reasons other than disease progression); after disease progression, follow-up contact may be limited to telephone contact. Follow-up data will include survival status, disease status, and poststudy treatment for lymphoma. In addition, the status of any AEs will be assessed as specified in Section 12.1.3.

## **12. SAFETY MEASUREMENTS AND VARIABLES**

### **12.1 Adverse Events**

#### **12.1.1 Definitions**

##### **Adverse Events**

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a subject 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 eCRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded.
- 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 postdose) through the end of the safety reporting period (see Section [12.1.3](#)). Complications that occur in association with any procedure (eg, biopsy) should be recorded as 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 an 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 (eg, 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 AE 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 serious AEs 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 NCI CTCAE, Version 4.03 (Appendix 18.4). These criteria are provided in the study manual.

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 SAEs).

## Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study drug (brentuximab vedotin, rituximab, or bendamustine) should be evaluated by the Investigator using the following criteria:



Related:	<p>There is evidence to suggest a causal relationship between the drug and the AE, such as:</p> <ul style="list-style-type: none"> <li>• An event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)</li> <li>• An event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture)</li> </ul>
Unrelated:	<p>Another cause of the AE is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible</p>

### **12.1.2 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 eCRF and/or SAE form, as appropriate.

#### **Eliciting Adverse Events**

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

#### **Recording Adverse Events**

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

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

#### **Diagnosis vs Signs or Symptoms**

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

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

The following should be considered when recording SAEs:

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

## **Progression of the Underlying Cancer**

Do not use the term ‘disease progression’ when reporting an AE because it is too general. Instead, report the specific disease (clinical) manifestation of the progression (eg, ‘malignant pleural effusion’, ‘spinal bone metastases’, ‘lymphadenopathy from underlying non-Hodgkin lymphoma’, ‘brain metastases’).

## **Pregnancy**

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

All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the eCRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events and Pre-Existing Conditions eCRF.

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

### **12.1.3 Reporting Periods for Adverse Events and Serious Adverse Events**

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through 30 days after the last dose of study treatment (brentuximab vedotin, rituximab, and/or

bendamustine). However, all study protocol-related AEs are to be collected from the time of informed consent.

All SAEs that occur after the end of safety reporting period (ie, more than 30 days after the last dose of study treatment) and are considered 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, or study closure. All non-serious AEs will be followed through the safety reporting period. Ongoing non-serious AEs of interest (including but not limited to neuropathy) may be followed until resolution, return to baseline, or study closure.

#### **12.1.4 Serious Adverse Events Require Immediate Reporting**

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

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

- Patient number
- Date of event onset
- Description of the event
- Study treatment, if known

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

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

#### **12.1.5 Sponsor Safety Reporting Requirements**

According to the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's final guidance Safety Reporting Requirements for INDs and BA/BE Studies (December 2012), 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 FDA as individual IND safety reports.

In this study, the SAEs that do not require individual IND safety reports are disease progression events.

These anticipated SAEs will be reviewed periodically by Seattle Genetics' Drug Safety Department. If, upon review, an SAE is occurring at a higher rate than that which would be

expected for the study population, then an IND safety report for the SAE will be submitted to the FDA.

These safety reporting requirements apply only to the process by which the Sponsor reports SAEs to the FDA. Investigators are required to report all SAEs, including anticipated SAEs, to the Sponsor.

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

### **13. DATA MANAGEMENT AND STATISTICAL ANALYSIS**

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

#### **13.1 Data Management**

An eCRF will be used for the current study and a data management plan will be prepared by the CRO PRA Health Sciences.

Previous and concomitant medications will be coded using the latest available World Health Organization (WHO) Drug Reference Dictionary. Coexistent diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between Seattle Genetics, Inc., and the PRA Health Sciences project team.

#### **13.2 Sample Size Estimation**

Approximately 110 patients will be randomized in a 1:1 manner to each treatment arm (approximately 55 patients per treatment arm).

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

#### **13.3 Statistical Analysis Plan**

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

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

### **13.4 Randomization**

Patients will be randomized in a 1:1 manner to receive rituximab plus bendamustine with or without brentuximab vedotin stratified by sAAIPI score (0 vs 1 vs 2–3) and duration of remission after initiation of frontline therapy (refractory or relapse <12 months vs relapse ≥12 months). Randomization will be performed by an IXRS.

### **13.5 Analysis Populations**

#### **13.5.1 Intent-to-Treat Population**

The intent-to-treat (ITT) Population will include all subjects who are randomized. Subjects will be grouped according to their randomized treatment group assignment regardless of the treatment they actually received.

#### **13.5.2 Safety Population**

The safety population will include all subjects who are enrolled and received at least 1 dose of study treatment (brentuximab vedotin, rituximab, or bendamustine).

#### **13.5.3 Efficacy Evaluable Population**

The efficacy evaluable population will include all subjects who received at least 2 cycles of combination treatment at the recommended dose level and had a baseline tumor assessment and at least 1 postbaseline tumor assessment, or who had documented disease progression at any time after the first dose of combination therapy at the recommended dose level.

#### **13.5.4 Per-Protocol Population**

A per-protocol population may be defined in the SAP.

### **13.6 Statistical Methods**

#### **13.6.1 Missing Data**

Missing data will not be imputed, with the exception of missing or partial dates; imputation rules for missing or partial dates will be specified in the SAP.

Time-to-event data will be censored as outlined in Section [13.6.4.2](#). All other missing data will be treated as missing.

### 13.6.2 Demographic and Baseline Data

Demographic and baseline data will be summarized descriptively by treatment arm. For continuous variables, descriptive statistics will include the mean, standard deviation (or standard error), median, range, and interquartile range. For categorical variables, descriptive statistics will include the number and percent. All demographic and baseline data will be listed.

### 13.6.3 Subject Disposition

The number and percent of subjects who complete combination treatment (6 cycles), who discontinue early, and the reasons for discontinuation will be summarized. Disposition by the number of cycles of treatment will be summarized by treatment arm.

### 13.6.4 Efficacy

#### 13.6.4.1 Response to Treatment

Subjects will be assigned a response status based on imaging and lymphoma assessments at each visit as indicated in [Table 2](#) and [Table 3](#). The response criteria are based upon the 2014 Lugano Classification [38] and are summarized in Appendix [18.6](#).

ORR will be analyzed based on the ITT population. ORR is defined as the proportion of patients who achieve a CR (including CMR) or PR (including partial metabolic response, or PMR) as best response to combination therapy on study. The final analysis of ORR between the 2 treatment arms, which is planned to occur after all patients have completed combination therapy or discontinued therapy, will be compared and tested at a 1-sided 0.05 alpha level using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata. A statistically significant improvement of 22%, assuming a 50% ORR in the control arm and 72% in the brentuximab vedotin arm, would be considered clinically meaningful.

If fewer than 5 subjects have sAAPI score of 0 or 1, then these groups will be combined for analyses. If fewer than 5 subjects have sAAPI score of 2-3, then this group will be combined with sAAPI score of 1 for analyses.

#### 13.6.4.2 Secondary Efficacy Endpoints

Time-to-event variables (DOR, PFS, and OS) will be summarized descriptively using the Kaplan-Meier estimate. Additional details will be provided in the SAP. Secondary endpoints will be assessed in the ITT population (except as indicated below).

CR Rate and Best Clinical Response: Response (CR/CMR, PR/PMR, ORR [CR/CMR+PR/PMR], stable disease [SD] or no metabolic response [NMR], and PD/progressive metabolic disease [PMD]) will be summarized descriptively by treatment arm. CR rate will be summarized with 95% confidence intervals. Best clinical response is

defined as the best response (ordered from best to worst as CR/CMR, PR/PMR, SD/NMR, or PD/PMD) observed during the treatment period.

**DOR (for PR/CR and CR):** DOR is defined as the time from first observation of response (PR/PMR+CR/CMR or CR/CMR) to disease progression/relapse, receipt of subsequent lymphoma chemotherapy other than the components of the study treatment regimen (excludes post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, and consolidative autologous or allogeneic SCT), or death from any cause, whichever occurs first. Durations will be assessed in the ITT population with a PR or CR and calculated separately for subjects with CR/CMR and those with PR/PMR+CR/CMR combined. For subjects with a remission without subsequent disease progression/relapse or death on study, DOR will be censored at the time of the last disease assessment demonstrating a lack of disease progression/relapse. If more than one date of progression is available, the earliest date will be used to determine DOR. Full censoring rules will be provided in the SAP. Subjects who receive SCT in remission will continue to be followed for DOR.

**Progression-free Survival:** PFS is defined as the time from randomization to first documentation of disease progression/relapse, death due to any cause, or receipt of subsequent lymphoma chemotherapy other than the components of the study treatment regimen (excludes post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, and consolidative autologous or allogeneic SCT), whichever occurs first. For subjects without disease progression/relapse or death on study, PFS will be censored at the time of the last on-study disease assessment demonstrating a lack of disease progression/relapse. If more than one date of progression is available, the earliest date will be used to determine PFS. Full censoring rules will be provided in the SAP. Subjects who receive SCT in remission will continue to be followed for PFS.

**Overall Survival:** OS is defined as the time from randomization to death due to any cause. For subjects not known to have died at the conclusion of the study, OS will be censored at the time the subject was last known to be alive (including follow-up data).

### **13.6.5 Pharmacokinetics and Pharmacodynamics**

Pharmacokinetic (brentuximab vedotin ADC and MMAE) and ATA to brentuximab vedotin results will be summarized. Pharmacodynamic results (eg, CD30 expression, mRNA levels of CD30 and related genes, COO classification, and soluble CD30 and other chemokines/cytokines of interest) will be summarized by study arm.

### **13.6.6 Safety**

Safety data will be summarized for the safety population.

Exposure to treatment will be summarized separately for brentuximab vedotin, rituximab, and bendamustine. Summaries will include the duration of treatment, number of doses



received, number of cycles received, number of doses interrupted and the reasons for dose interruption, the number of subjects with dose decreases for toxicity, the cumulative dose, and the relative dose intensity.

All AEs reported after initiation of treatment and pre-existing conditions that worsen after initiation of treatment will be considered treatment-emergent AEs (TEAEs). All AEs will be coded by system organ class, MedDRA preferred term, and severity grade using NCI CTCAE (Version 4.03; Appendix 18.4). All recorded AEs will be included in the data listings.

The number and percent of subjects reporting all TEAEs, treatment-related AEs, SAEs, and deaths; TEAEs according to worst CTCAE grade; and AEs leading to treatment discontinuation will be summarized by preferred term and, where appropriate, system organ class. Deaths, SAEs, and AEs leading to treatment discontinuation will also be listed.

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by scheduled visit. Where appropriate, laboratory results will be graded according to CTCAE (Version 4.03), and shift tables from baseline to worst observed posttreatment grade will be presented.

All medications received during the treatment period will be considered as concomitant medications and will be coded by WHO medical dictionary and summarized.

#### **13.6.7 Additional Data**

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

#### **13.6.8 Interim Analysis**

[REDACTED]

[REDACTED]

#### **13.6.9 Independent Data Monitoring Committee**

The IDMC will consist of individuals external to Seattle Genetics, Inc. and PRA Health Sciences chosen for their expertise in oncology. Members of the IDMC will include, at a minimum, physicians and appropriate statistical representation. The primary role of this IDMC will be to monitor safety data and review the results of the futility analysis.

The IDMC will review unblinded safety data after the first 20 patients have completed 2 cycles of therapy and then every 6 months thereafter and as needed. The IDMC may recommend changes such as, but not limited to, lowering the starting dose level of bendamustine to 70 mg/m<sup>2</sup> in the case of unacceptable toxicity at the proposed starting dose. In addition, the IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Seattle Genetics, Inc. senior management at any time during the conduct of the study.

The safety analysis will evaluate the overall safety of the treatment regimens including, but not limited to, the following parameters:

- Type, incidence, severity, seriousness, and relatedness of AEs
- Incidence of Grade  $\geq 3$  neuropathy
- Type, incidence, and severity of laboratory abnormalities
- Incidence and severity of infusion-related and hypersensitivity reactions.

Details of the safety reviews will be provided in the IDMC charter.

In addition, a formal interim analysis for futility will be performed after 50% of patients have completed the Cycle 2 response assessment (Section 13.6.8). The primary efficacy endpoint (ORR) will be used to assess futility. The IDMC will provide recommendations to the Sponsor's Data Review Board as to appropriate study direction.

## **14. MONITORING PROCEDURES (QUALITY ASSURANCE)**

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, in order to fulfill these obligations and to maintain current of study progress, the Sponsor's monitors or representatives will visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted in order to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

### **14.1 Routine Monitoring**

Sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

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

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

### **14.2 Inspections and Auditing Procedures**

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

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

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

## **15. STUDY MANAGEMENT AND MATERIALS**

### **15.1 Electronic Case Report Forms**

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

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

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

### **15.2 Data Collection**

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

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

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

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

Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialed and dated on the day the change is made by the Investigator or

designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

### **15.3 Source Documents Maintenance**

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

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

### **15.4 Record Maintenance**

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

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

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

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

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

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

## **15.5 Confidentiality**

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

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

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

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

## **16. ADMINISTRATION PROCEDURES**

### **16.1 Regulatory Approval**

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

### **16.2 Protocol Amendments**

In accordance with ICH Topic E6 (R1) Guideline for GCP, the Investigator should not implement any deviation from or changes to the protocol without agreement by the Sponsor and documented approval from the IRB/IEC of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor[s] or change of telephone number[s]).

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

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

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

### **16.3 Protocol Adherence and Deviations**

The protocol must be read thoroughly, and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-Investigator.

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

#### **16.4 Study Documentation, Privacy, and Records Retention**

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

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

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

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

#### **16.5 Publication Policy**

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

#### **16.6 Clinical Study Report**

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



## **16.7 Contractual and Financial Details**

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

## **16.8 Insurance, Indemnity, and Compensation**

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

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

## **16.9 Discontinuation of the Study**

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

## **16.10 Study Center File Management**

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

1. Investigator's Brochure;
2. Current, signed version of the protocol and any previous versions of the protocol;
3. Protocol amendments (if applicable);
4. Operations Manual (if applicable);
5. Current informed consent form (blank) and any previous versions of the informed consent form;
6. Curricula Vitae of Investigator(s) and sub-Investigator (s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug [IND] regulations), signed by all Principal Investigators. The names of any sub-Investigators must appear on this form. Investigators must also complete all regulatory documentation as required by ICH GCP and by local or national regulations;

7. Documentation of IRB/IEC approval of the protocol, the informed consent form, any protocol amendments, and any informed consent form revisions;
8. All correspondence between the Investigator, IRB/IEC, and the Sponsor/CRO relating to study conduct;
9. Laboratory certification(s);
10. Monitoring log;
11. Study drug invoices;
12. Signature list of all staff completing eCRFs; and
13. Signature list of all staff completing drug accountability summaries.

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## **18.APPENDICES**

### **18.1 Appendix 1: Declaration of Helsinki**

#### **WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:  
29th WMA General Assembly, Tokyo, Japan, October 1975  
35th WMA General Assembly, Venice, Italy, October 1983  
41st WMA General Assembly, Hong Kong, September 1989  
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996  
52nd WMA General Assembly, Edinburgh, Scotland, October 2000  
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)  
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)  
59th WMA General Assembly, Seoul, October 2008  
64th WMA General Assembly, Fortaleza, Brazil, October 2013

#### **A. Preamble**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

#### **General Principles**

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.



### **Risks, Burdens and Benefits**

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

### **Vulnerable Groups and Individuals**

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

### **Scientific Requirements and Research Protocols**

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
  - The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The

protocol should include information regarding funding, Sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

- In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

### **Research Ethics Committees**

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

### **Privacy and Confidentiality**

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

### **Informed Consent**

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek

informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

### **Use of Placebo**

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
- and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
- Extreme care must be taken to avoid abuse of this option.

### **Post-Trial Provisions**

34. In advance of a clinical trial, Sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

### **Research Registration and Publication and Dissemination of Results**

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

### **Unproven Interventions in Clinical Practice**

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert

advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

## 18.2 Appendix 2: Elements of Informed Consent

### **ELEMENTS OF INFORMED CONSENT**

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- That the study involves research.
- The purpose of the study.
- The study treatment(s) and the probability for random assignment to each treatment.
- The study procedures to be followed including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the study that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of study-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the study.
- The anticipated expenses, if any, to the subject for participating in the study.
- That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

- The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- The expected duration of the subject's participation in the study.
- The approximate number of subjects involved in the study.

### 18.3 **Appendix 3: Eastern Cooperative Oncology Group Performance Status**

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



#### **18.4 Appendix 4: Common Terminology Criteria for Adverse Events (CTCAE; v 4.03)**

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

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

## 18.5            **Appendix 5: Second-line Age-adjusted International Prognostic Index**

Add 1 for each of the following risk factors present:

- ECOG  $\geq 2$
- LDH > ULN
- Stage III or IV disease

A score of 0 (no risk factors present) indicates low risk, 1 (any 1 risk factor present), indicates low-intermediate risk, 2 (any 2 risk factors present), indicates high-intermediate risk, and 3 (all 3 risk factors present), indicates high risk.

From: Hamlin PA, Zelenetz AD, Kewalramani T, et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. Blood 102 (6): 1989-96, 2003.

## 18.6 Appendix 6: Response Assessment – The Lugano Classification

Response and Site	PET-CT–Based Response	CT-Based Response
<b>Complete Response</b>	<b>Complete metabolic response</b>	<b>Complete radiologic response (all of the following)</b>
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer’s ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to $\leq 1.5$ 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
<b>Partial Response</b>	<b>Partial metabolic response</b>	<b>Partial remission (all of the following)</b>
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease	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
<b>No Response or Stable Disease</b>	<b>No metabolic response</b>	<b>Stable disease</b>
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

*continued*

## Appendix 6: Response Definitions (continued)

<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 $\leq 2$ cm 1.0 cm for lesions $> 2$ cm In the setting of splenomegaly, the splenic length must increase by $> 50\%$ of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to $> 16$ cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node $> 1.5$ cm in any axis A new extranodal site $> 1.0$ cm in any axis; if $< 1.0$ cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

\* 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 (eg, 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 (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

† 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 (see Barrington SF, Mikhael NG, Kostakoglu L, et al. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 32(27): 3048-58, 2014). From 38. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma:

The Lugano Classification. J Clin Oncol 32(27): 3059-67, 2014.

## 18.7 Appendix 7: Futility Boundaries for the Interim Analysis

[REDACTED]

[REDACTED]

[REDACTED]

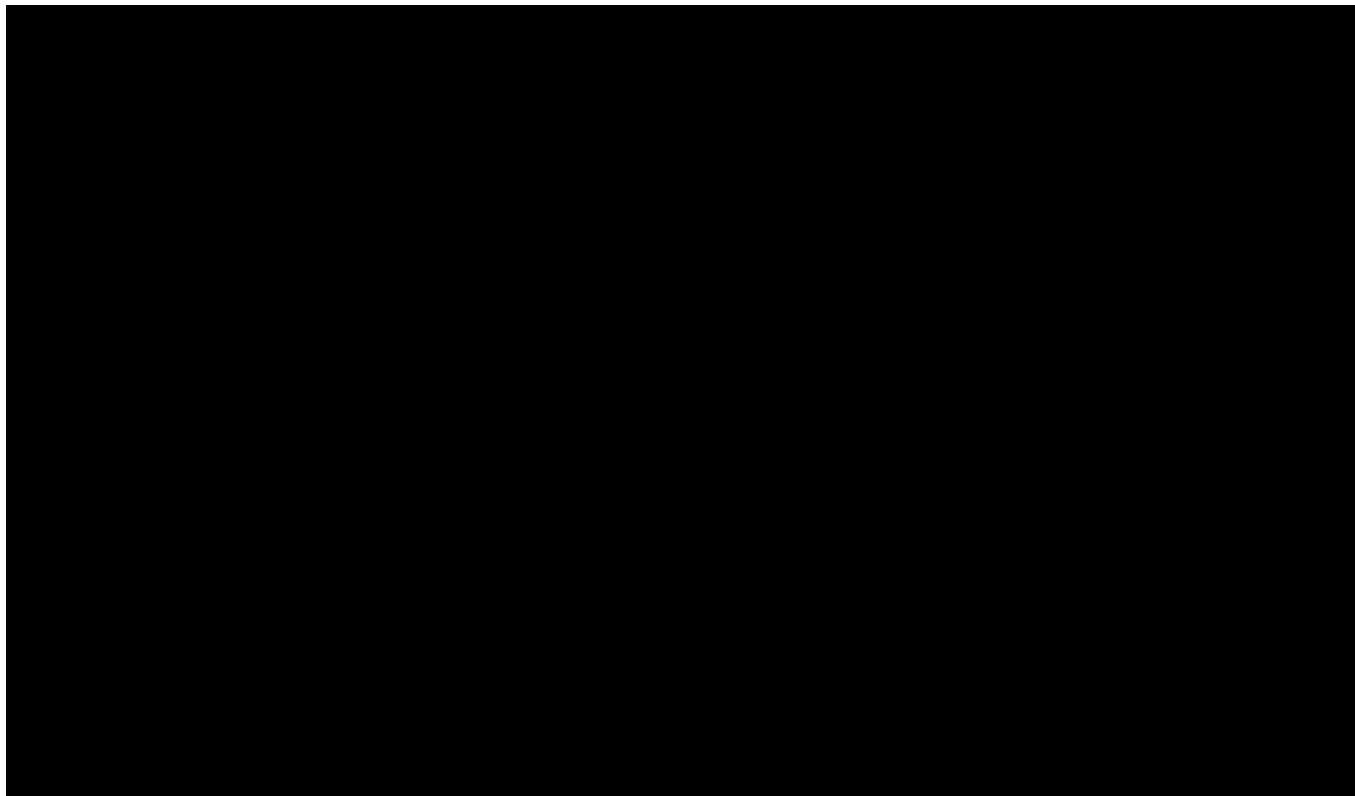
[REDACTED]

[REDACTED]

---

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]	[REDACTED]
■			

---



## 18.8 Appendix 8: Summary of Changes in V02

### RATIONALE:

The protocol was updated to add the EudraCT number to the cover page.

### SUMMARY OF CHANGES:

Section: Cover page:

Replace:

**Protocol Number:** SGN35-023

**IND number:** 71634

**Study Phase:** 2

With:

**Protocol Number:** SGN35-023

**IND number:** 71634

**Study Phase:** 2

**EudraCT Number:** 2015-001671-51

Section: Global

Replace:

Version ~~01~~ Date ~~01 June 2015~~

With:

Version **02**, Date **17 June 2015**



## 18.9 Appendix 9: Summary of Changes in V03

### RATIONALE:

The protocol was amended for the following reasons:

- To provide additional detail in the study objective and endpoints.
- To exclude patients unable to give consent by removing the option for a legally acceptable representative to consent.
- Revise the entry criteria to
  - Increase the required platelet count for study entry to  $\geq 75,000/\mu\text{L}$
  - Require females of childbearing potential and males who have partners of childbearing potential to use 2 effective contraceptive methods and to specify which methods are considered effective
  - Exclude subjects with
    - major surgery less than 30 days prior to first dose of study drug
    - live vaccines within 1 month of first dose of study drug
    - current severe immunodeficiency
    - history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection
    - concomitant use of bleomycin.
- Require study discontinuation in the case of pregnancy.
  - Require pretreatment assessment for hepatitis B (HBsAg and HBcAb).
  - Require electrocardiogram assessment at each cycle.
  - Require pregnancy testing (for women of childbearing potential only) at each cycle and require that pregnancy testing be by serum  $\beta$ -hCG
- Clearly specify the requirement for physical examinations and require physical examination to include neurological examination at all time points where physical examination is required, including where it is required as part of the lymphoma assessment.
- To clarify that sampling for brentuximab and MMAE exposure was only required for subjects on the treatment arm (brentuximab vedotin) and to extend this sampling to all combination treatment cycles (up to Cycle 6).
- To limit ATA sampling to the treatment arm (brentuximab vedotin).
- Clarify that safety reporting is required in all regions of study conducted as required by local and international standards.
- To update the reference to the NCCN guideline for the prevention and treatment of cancer-related infections.
- To require physical examination at screening.

- To correct an error in the Table of Events (extraneous footnote), add physical examination, add clarification regarding CT and PET, and make updates consistent with the other changes contained in this amendment.
- To provide additional details regarding the collection, handling, and storage of biological samples.
- To add glucose to the required battery of clinical laboratory tests.
- To update and add additional details regarding safety reporting contacts.
  - To specify that subjects may become eligible for transplant (allogenic HCT or ASCT) on study.
- To make minor editorial and formatting corrections.

#### **SUMMARY OF CHANGES:**

Section: Synopsis, Objectives, Primary Objective, page 4

Replace:

- To compare the objective response rate (ORR) ~~between the 2 arms~~

With:

- To compare the objective response rate (ORR) **among subjects with relapsed or refractory CD30-positive diffuse large B-cell lymphoma (DLBCL) receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)**

Section: Synopsis, Objectives, Secondary Objectives, page 4

Replace:

- To compare progression-free survival (PFS) ~~between the 2 arms~~
- To compare the complete remission (CR) rate between the 2 arms
- To compare duration of response (DOR) between the 2 arms
- To compare overall survival (OS) between the 2 arms
- To evaluate the safety and tolerability of the 2 arms

With:

- To compare progression-free survival (PFS) **among subjects with relapsed or refractory CD30-positive DLBCL receiving rituximab and bendamustine plus**

**brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)**

- To compare the complete remission (CR) rate between the 2 arms **of the study**
- To compare duration of response (DOR) between the 2 arms **of the study**
- To compare overall survival (OS) between the 2 arms **of the study**
- To evaluate the safety and tolerability of the 2 arms **of the study**

Section: Synopsis, Objectives, Exploratory Objectives, page 4; 8.3, Exploratory Objectives, page 24

Add:

- To characterize the incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin **among subjects with relapsed or refractory CD30-positive DLBCL receiving rituximab and bendamustine plus brentuximab vedotin**

Section: Synopsis, Study Design and Methodology, page 4

Add:

...for the treatment of patients with relapsed or refractory CD30-positive diffuse large B-cell lymphoma (DLBCL) **and follicular NHL grade 3b** after failure of second-line ...

Section: Synopsis, Inclusion Criteria, page 5; 9.4.1, Inclusion Criteria, page 28-29;

Criterion 6b:

Replace:

- b. Platelet count  $\geq 50,000/\mu\text{L}$  (unless documented bone marrow involvement)

With:

- b. Platelet count  $\geq 75,000/\mu\text{L}$  (unless documented bone marrow involvement)

Criterion 7:

Replace:

7. Females of childbearing potential must have a negative serum ~~or urine~~ beta human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test result within 7 days prior to the first dose of study drug.

With:

7. Females of childbearing potential must have a negative serum beta human chorionic gonadotropin ( $\beta$ -hCG) pregnancy test result within 7 days prior to the first dose of study drug.

Criterion 8:

8. Females of childbearing potential and males who have partners of childbearing potential must agree ~~to use an effective contraceptive method~~ during the study and for 6 months following the last dose of brentuximab vedotin or 12 months following the last dose of rituximab, whichever is later.

With:

8. Females of childbearing potential and males who have partners of childbearing potential must agree **to use 2 effective contraceptive methods** during the study and for 6 months following the last dose of brentuximab vedotin or 12 months following the last dose of rituximab, whichever is later.

Criterion 9:

Replace:

9. Patients ~~or their legally authorized representative~~ must provide written informed consent.

With:

9. Patients must **be willing and able** to provide written informed consent.

Section: Synopsis, Exclusion Criterion, page 6; 9.4.2, Exclusion Criteria, page 29-30

Criterion 5:

Add:

5. Chemotherapy, radiotherapy, biologics, and/or other antitumor treatment with immunotherapy that is not completed 4 weeks prior to first dose of study drug. **Concomitant use of other systemic antineoplastic agents (including bleomycin) while on study is excluded.**

New criteria:

18. **Major surgery less than 30 days prior to first dose of study drug. Major surgery is any invasive operative procedure in which a more extensive resection is performed, eg, a body cavity is entered, organs are removed, or normal anatomy is altered.**
19. **Live vaccines (in particular yellow fever vaccination) within 1 month prior to the first dose of study drug.**
20. **Current severe immunodeficiency, or history of recurring or chronic infections, or with underlying conditions which may further predispose patients to serious infection.**

Section: Synopsis, Study Evaluations, Primary Efficacy Criteria, page 7;

Replace:

The primary efficacy endpoint of this study is ORR

With:

The primary efficacy endpoint of this study is **objective response rate (ORR) as assessed by the 2014 Lugano Classification.**

Section: Synopsis, Study Evaluations, Secondary Efficacy Criteria, page 7; 8.4.2, Secondary Endpoints, page 25; 9.6.1.1, Efficacy Measurements, page 41

Replace:

- PFS
- CR rate

...

- DOR
- OS

With:

- **Progression-free survival (PFS)**
- **Complete response (CR) rate**

...

- **Duration of response (DOR)**
- **Overall survival (OS)**

Section: Synopsis, Study Evaluations, Pharmacokinetic/Pharmacodynamic Measurements, page 7; 8.4.3, Pharmacokinetic / Pharmacodynamic Measurements, page 25; 9.6.1.2, Pharmacokinetic/Pharmacodynamic Measurements, page 41

Replace:

Blood will be collected for ATA to brentuximab vedotin, brentuximab vedotin and MMAE exposures, and pharmacodynamic (soluble CD30 and other chemokines/cytokines of interest) assessments. Tumor samples will be collected for assessment of CD30 antigen expression, mRNA levels of CD30 and related genes, and cell of origin classification.

With:

Blood will be collected **from subjects assigned to receive brentuximab vedotin (treatment arm) for measurement of** ATA to brentuximab vedotin; **and both** brentuximab vedotin and MMAE exposures; ~~and~~.

**Blood will be collected from all subjects for** pharmacodynamic (soluble CD30 and other chemokines/cytokines of interest) assessments. Tumor samples will be collected **from all subjects** for assessment of CD30 antigen expression, mRNA levels of CD30 and related genes, and cell of origin classification.

Section: 4, List of Abbreviations and Definition of Terms, page 15

Add:

**PMD                      Progressive metabolic disease**

Section: 5.3, Subject Information and Consent, page 17-18

Delete:

The Investigator will explain the benefits and risks of participation in the study to each subject ~~or the subject's legally acceptable representative~~ and obtain written informed consent...

Each subject's original consent form, personally signed and dated by the subject ~~or by the subject's legally acceptable representative~~, and by the person who conducted the informed consent discussion, will be retained by the Investigator.

Change:

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. ~~In this instance approval should always be given by the IRB/IEC and existing subjects should be informed of the changes and re-consented.~~ This is documented in the same way as previously described.

To:

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

Section: 6, Investigators and Study Administrative Structure, page 19

Replace:

Contact information for the central pathologist will be provided in the study manual.

With:

**Ventana Medical Systems, Inc.  
1910 E. Innovation Park Drive  
Tucson, Arizona 85755 USA  
+1 (520) 887 2155  
(800) 227 2155**

Section: 8.1, Primary Study Objective, page 24

Replace:

- To compare the ORR ~~between the 2 arms~~

With:

- To compare the **objective response rate (ORR) among subjects with relapsed or refractory CD30-positive DLBCL receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)**

Section: 8.2, Secondary Study Objective, page 24

Replace:

- To compare PFS ~~between the 2 arms~~
- To compare the CR rate between the 2 arms
- To compare duration of response (DOR) between the 2 arms

- To compare OS between the 2 arms
- To evaluate the safety and tolerability of the 2 arms

With:

- To compare **progression-free survival (PFS) among subjects with relapsed or refractory CD30-positive DLBCL receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)**
- To compare the **complete remission (CR) rate between the 2 arms of the study**
- To compare duration of response (DOR) between the 2 arms **of the study**
- To compare **overall survival (OS) between the 2 arms of the study**
- To evaluate the safety and tolerability of the 2 arms **of the study**

Section: 8.4.1, Primary Endpoint, page 25

Replace:

The primary efficacy endpoint of this study is ORR

With:

The primary efficacy endpoint of this study is **objective response rate (ORR) as assessed by the 2014 Lugano Classification. [38, Appendix 18.6]**

Section: 9.1, Overall Study Design and Plan, page 26

Add:

for the treatment of patients with relapsed or refractory **CD30-positive DLBCL and grade 3b follicular lymphoma** after failure of second-line salvage

Add

**Once stained for CD30 expression by the central pathology laboratory, slides may be retained to support future research efforts by the sponsor.**



Section: 9.4.3.1, Discontinuation of Study Drug, page 31:

Add:

**Study drug must be discontinued in the case of pregnancy.**

Section: 9.5.1.1, Required Premedication and Postmedication, page 33

Replace:

...NCCN ~~2012~~ guideline for the prevention and treatment of cancer-related infections is recommended...

With:

...NCCN **2015** guideline for the prevention and treatment of cancer-related infections is recommended...

Section: 9.5.1.3.3 Dose and Administration, page 35

Add:

Subjects will receive rituximab on Day 2 only (treatment arm) or on Day 1 OR Day 2 (+1; control arm) of each 21-day treatment cycle for a maximum of 6 cycles.

Section: 9.5.3, Prior and Concomitant Therapy, page 39-40

Add:

**Subjects must not receive live vaccines (in particular yellow fever vaccination) or bleomycin while on treatment; subjects requiring these treatments will be discontinued from study. Live vaccines must not be administered within 1 month of starting study treatment.**

Replace:

...NCCN ~~2012~~ guideline for the prevention and treatment of cancer-related infections is recommended...

With:

...NCCN **2015** guideline for the prevention and treatment of cancer-related infections is recommended...

Add:

**Subjects may be eligible for allogenic SCT or ASCT following study treatment. Subjects receiving these treatments should continue in study follow-up.**

Add:

**Contraception**

**Acceptable methods of contraception include: hormonal (birth control pills, injections, implants), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), vasectomy (for males), barrier methods (male and female condoms, diaphragms, and spermicides), bilateral tubal ligation, and complete abstinence. Complete abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).**

Section: Table 2: Study Schedule, page 43-44

Add (new row):

**Physical Examination (incl. neuro exam)** (with indicators at Screening/Baseline [Day -7 to 1], Day 1 of each cycle, and EOT)

Add to the row labeled Electrocardiogram:  
(indicators at Day 1 of each cycle).

Add (new row):

**HBsAg / HBcAb** (with indicator at Screening/Baseline [Day -7 to 1]).

Add to the row labeled Pregnancy test:  
(indicators at Day 1 of each cycle).

Add (to title of row previously called PK samples<sup>h</sup>):

PK samples<sup>h</sup> (**treatment arm only**)

and add additional indicator at Cycles 2-6 [D1(±1D) to D2].

Change the row labeled ATA/pharmacodynamic samples<sup>i</sup> to 2 rows, labeled  
**ATA/ samples<sup>i</sup> (treatment arm only)**  
and **Pharmacodynamic samples<sup>i</sup>**  
(indicators at Day 1 of Cycles 1 – 6 and at EOT for both rows).

Add to the list of abbreviations:

**HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody;**

Add:

**Note: All Day 1 procedures are before treatment unless otherwise specified.**

Delete:

Footnote a: ~~Long term response assessments should continue annually after 24 months until death or study closure.~~

Add:

To footnote b: Locally assessed to enable enrollment. **Submission of the tumor block or approximately 15 unstained slides from a biopsy of relapsed disease obtained within 1 year prior to screening (or initial diagnostic specimen if refractory) is required for subsequent central pathology disease confirmation and further evaluation of additional molecular biomarkers.**

Add:

New footnote c (for “Optional tumor specimen”): **Biopsy material will also be collected if available to evaluate changes in molecular biomarkers by different treatments. No additional procedures will be conducted to obtain these research tissues; only available tissue will be used.**

Change (footnotes h and i):

- h. Predose (within 24 hours before the start of the brentuximab vedotin infusion) and within 30 minutes after the end of the infusion (samples for ADC and MMAE levels only).
- i Predose (within 24 hours before the start of the infusion).

To:

- h. Predose (within 24 hours before the start of the brentuximab vedotin infusion) and **postdose** (within 30 minutes after the end of the infusion; samples for ADC and MMAE levels only).
- i Predose (within 24 hours before the start of the **first** infusion on **Day 1**).

Add:

New footnote k (for “CT (chest, neck, abdomen, pelvis)”): **A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as a diagnostic quality CT scan is obtained; PET scans may also be obtained any time during the study if clinically indicated; PET scan not required after documented postbaseline FDG-negative PET scan is obtained.**

Revise footnote indicators to accommodate changes.

Section: Table 3: Study Schedule, page 45

Add (to footnote b):

Consists of the following: physical examination, **including neurological examination**, patient medical history,...

Section: 10.1, Screening (Day -28 to 1), page 46

Add:

**HBsAg and HBcAb;**

Section: 10.1, Screening (Day -28 to 1), page 46; 10.3, End of Treatment, page 48:

Delete:

- Serum ~~or urine~~ pregnancy test...

Section: 10.1, Screening (Day -28 to 1), page 46; 10.2, Treatment Period (Cycle 1, Day 1 pretreatment, Cycles 2 – 6, Day 1 pretreatment, Cycles  $\geq 7$ , Day 1 pretreatment), page 47-48; 10.3, End of Treatment, page 48:

Add:

- **Physical examination (including neurologic assessment; Section 11.5)**

Section: 10.2, Treatment Period, page 47-48;

Under Cycle 1;

Replace

- Pharmacokinetic (PK) sample collection (within 24 hours before beginning the brentuximab vedotin infusion; Section 11.8)

With:

- **For subjects on the treatment arm (brentuximab vedotin) only:  
Pharmacokinetic (PK) and ATA sample collection (within 24 hours before beginning the brentuximab vedotin infusion; Section 11.8)**
- **For all subjects:  
Pharmacodynamic sample collection (within 24 hours before beginning the brentuximab vedotin infusion; Section 11.8)**

Under Cycle 1, Day 1, posttreatment;

Add:

- **For subjects on the treatment arm (brentuximab vedotin) only:**  
PK sample collection (within 30 minutes after completion of the brentuximab vedotin infusion; Section 11.8).

Under Cycle 1, pretreatment; Cycles 2 – 6, Day 1, pretreatment; Cycles  $\geq 7$ , Day 1, pretreatment;

Add:

- **Standard 12-lead ECG (Section 11.4)**
- **Serum pregnancy test (women of childbearing potential only)**

Under Cycles 2 – 6, Day 1, pretreatment;

Add:

- **For subjects on the treatment arm (brentuximab vedotin) only:**  
**PK and ATA sample collection (within 24 hours before beginning the brentuximab vedotin infusion; Section 11.8)**
- **For all subjects:**  
**Pharmacodynamic sample collection (within 24 hours before beginning the brentuximab vedotin infusion; Section 11.8)**

Add (new top level bullet):

- **Cycles 2 – 6, Day 1, posttreatment:**
  - **For subjects on the treatment arm (brentuximab vedotin) only:**  
**PK sample collection (within 30 minutes after completion of the brentuximab vedotin infusion; Section 11.8).**

Section: 11.2, Histology / CD30 Assessment, page 50

Add:

...Submission of the tumor block or approximately 15 unstained slides from a biopsy of relapsed disease **obtained within 1 year prior to screening** (or **initial** diagnostic specimen if refractory) is required for subsequent central pathology disease confirmation and further evaluation of additional molecular biomarkers.

~~Optional diagnostic biopsies~~ **Biopsy material** will also be collected if available **from biopsies performed anytime while the subject is on study** to evaluate changes ~~of~~ **in** molecular biomarkers by different treatments. **The tumor tissue will be used to conduct exploratory correlative studies.** Tumor based molecular biomarkers may include, but are not limited to

COO, prognostic markers for DLBCL and CD30 pathway related markers. **These will be conducted on the following tissues if available:**

- **Leftover unstained slides or tumor tissue from a diagnostic biopsy will be obtained at baseline if available**
- **Unstained slides or leftover tissue from a core biopsy obtained as part of standard-of-care clinical intervention while a patient is participating in the study (e.g., for treatment failure at any time)**

**No additional procedures will be conducted to obtain these research tissues, and thus no additional patient risk is introduced with these optional exploratory correlative studies.**

#### **Biospecimen Samples for Future Research**

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

Section: 11.5, ECOG Performance Status and Weight, page 51:

Change Section Heading to:

**Physical Examination, ECOG Performance Status, and Weight**

Add:

**Physical examinations will be performed at the time points indicated in Table 2 and include assessments of the following body parts/systems: HEENT (head, ears, eyes, nose, and throat), neck, cardiovascular and respiratory systems, lymph nodes, abdomen, extremities, skin, and neurological.**

Change:

Body weight (kg) will be measured and recorded at each study cycle visit.

To:

Body weight (kg) will be measured and recorded at **Day 1** of each study cycle visit.

Section: 11.6, Lymphoma Assessment, page 51:

Add:

The lymphoma assessment includes physical examination (**see Section 11.5**), patient medical history...

Section: 11.7, Clinical Laboratory Tests, page 52

Replace:

~~Clinical~~ chemistry:

With:

**Serum** chemistry:

Add:

**glucose**

Replace:

Pregnancy will be determined ~~at screening and EOT by either urine or serum~~ for females of childbearing potential.

With:

Pregnancy will be determined **as indicated in Table 2** by serum **β-hCG** for females of childbearing potential.

**Baseline screening for hepatitis B infection by HBsAg and HBcAb.**

Section: 11.8 Pharmacokinetic, Pharmacodynamic, and Immunogenicity Samples, page 52

Change:

Blood will be collected for PK, immunogenicity, and pharmacodynamic assessments. Potential pharmacodynamics markers include but not limited to sCD30 and inflammatory cytokines. It may also include circulating tumour DNA biomarkers. For subjects assigned to receive brentuximab vedotin, samples for PK analysis will be collected during Cycle 1 within 24 hours before the start of the Day 1 brentuximab vedotin infusion and within 30 minutes after the end of the Day 1 brentuximab vedotin infusion.

Samples for pharmacodynamics and ATA will be collected from patients on both treatment arms within 24 hours before the infusion on Day 1 of each cycle (Cycles 1 – 6) and at EOT. Sample handling and shipping information will be provided in the study manual.

To:

**Blood will be collected from subjects assigned to receive brentuximab vedotin (treatment arm) for measurement of ATA to brentuximab vedotin and both brentuximab vedotin and MMAE exposures only from subjects on the treatment arm (brentuximab vedotin). PK samples will be collected during Cycles 1 – 6 within 24 hours before the start of the Day 1 brentuximab vedotin infusion (predose) and within 30 minutes after the end of the Day 1 brentuximab vedotin infusion (postdose). Samples for ATA will be collected within 24 hours before the brentuximab vedotin infusion on Day 1 of each cycle (Cycles 1 – 6) and at EOT.**

**Blood will be collected for pharmacodynamic assessments from all subjects. Potential pharmacodynamics biomarkers include but are not limited to soluble CD30, inflammatory cytokines, and circulating tumour DNA. Samples for pharmacodynamic studies will be collected from patients on both treatment arms within 24 hours before the first infusion on Day 1 of each cycle (Cycles 1 – 6) and at EOT.**

**Sample handling and shipping information will be provided in the study manual.**

Section: 12.1.4, Serious Adverse Events Require Immediate Reporting, page 58

Change:

The completed SAE form and SAE Fax Cover Sheet are to be faxed to the Sponsor's Drug Safety Department at **(425) 527-4308** or **1-866-333-6227 (toll free US only)** or within 24 hours.

To:

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

Section: 12.1.5, Sponsor Safety Reporting Requirements, page 58-59:

Delete (from the section title):

~~in the United States~~

Delete:

These safety reporting requirements apply only to the process by which the Sponsor reports SAEs to the FDA. Investigators are required to report all SAEs, including anticipated SAEs, to the Sponsor. ~~In addition, the Sponsor will report all SAEs to international authorities as required per local regulatory reporting requirements.~~

Add:

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

Section: 13.6.4.2, Secondary Efficacy Endpoints, page 62-63;

Add:

**CR Rate and Best Clinical Response:** Response (CR/CMR, PR/PMR, ORR [CR/CMR+PR/PMR], stable disease [SD] **or no metabolic response [NMR]**, and **PD/progressive metabolic disease [PMD]**) will be summarized descriptively by treatment arm. CR rate will be summarized with 95% confidence intervals. **Best clinical response is**



defined as the best response (ordered from best to worst as CR/CMR, PR/PMR, SD/NMR, or PD/PMD) observed during the treatment period.

Add:

**...Subjects who receive SCT in remission will continue to be followed for DOR.**

**...Subjects who receive SCT in remission will continue to be followed for PFS.**

Section: 13.6.5, Pharmacokinetics and Pharmacodynamics, page 63;

Change:

Pharmacokinetic (brentuximab vedotin ADC and MMAE), ATA to brentuximab vedotin, and pharmacodynamic (CD30 expression, mRNA levels of CD30 and related genes, COO classification, and soluble CD30 and other chemokines/cytokines of interest) results will be summarized by treatment arm.

To:

**Pharmacokinetic (brentuximab vedotin ADC and MMAE) and ATA to brentuximab vedotin results will be summarized. Pharmacodynamic results, (eg, CD30 expression, mRNA levels of CD30 and related genes, COO classification, and soluble CD30 and other chemokines/cytokines of interest) results will be summarized by study arm.**

Section: 15.4, Record Maintenance, page 68:

Delete:

The Investigator shall take responsibility for maintaining adequate and accurate ~~hard-copy~~ source documents of all observations and data generated during this study.

Section: Global

Replace:

~~study~~ arm

With:

**treatment** arm

Replace:

Version 02, Date ~~17 June 2015~~

With:

Version 03, Date **10 November 2015**

## 18.10 Appendix 10: Summary of Changes in V04

### RATIONALE:

The protocol was amended to

- Clarify that the objectives of the study were to investigate the effects of study treatment both in patients with DLCBL and those with follicular NHL grade 3b
- Allow a second dose reduction of bendamustine (to 50 mg/m<sup>2</sup>)
- Recommend prophylactic growth factor support and clarified that transfusions and intrathecal prophylactic treatment for cerebral/meningeal disease are permitted
- Correct an error regarding timing of posttreatment assessments: The timing of all posttreatment assessments is relative to Cycle 1 Day 1 (not the end of treatment)
- Add an additional safety assessment visit during the second week of Cycles 1 and 2
- To change the definition of PFS and OS to begin at randomization (rather than date of first treatment) and to include subsequent treatment for lymphoma (other than post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, and consolidative autologous or allogeneic SCT) as an event in the progression analyses to reflect current statistical planning
- Remove the requirement that biopsy samples be obtained within than 1 year before screening
- Clarify that tumor samples are only to be collected from archival samples; no tumor biopsies are required to be performed for this study
- Make minor editorial and formatting changes throughout the protocol

### SUMMARY OF CHANGES:

*Note: Editorial and formatting changes are not included below.*

Section: Synopsis, Objectives, Primary Objective, page 4

Add:

- To compare the objective response rate (ORR) among subjects with relapsed or refractory CD30 positive diffuse large B-cell lymphoma (DLBCL) **or follicular non-Hodgkin lymphoma (NHL) grade 3b** receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)

Section: Synopsis, Objectives, Secondary Objectives, page 4; 8.2, Secondary Study Objectives, page 24

Add:

- To compare progression-free survival (PFS) among subjects with relapsed or refractory CD30-positive DLBCL **or follicular NHL grade 3b** receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)

Section: Synopsis, Objectives, Exploratory Objectives, page 4; 8.3, Exploratory Objectives, page 24

Add:

- To characterize the incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin among subjects with relapsed or refractory CD30-positive DLBCL **or follicular NHL grade 3b** receiving rituximab and bendamustine plus brentuximab vedotin

Section: Synopsis, Study Design and Methodology, page 4

Change:

...brentuximab vedotin in combination with rituximab and bendamustine for the treatment of patients with relapsed or refractory CD30-positive ~~diffuse large B-cell lymphoma (DLBCL)~~ and ~~grade 3b~~ follicular lymphoma **grade 3b** after failure...

Section: Synopsis, Study Design And Methodology, page 5; 9.1, Overall Study Design and Plan, page 26

Add:

DLBCL **or follicular NHL grade 3b** will be histologically...

Section: Synopsis, Study Population and Main Criteria for Inclusion/Exclusion, page 5

Delete:

1. Patients with histologically confirmed CD30-positive DLBCL or follicular ~~non-Hodgkin lymphoma (NHL)~~ grade 3b, defined as any detectable CD30 expression on tumor cells based on local pathologic assessment.

Section: Synopsis, Number of Subjects, page 6

Add:

Approximately 110 patients with relapsed or refractory DLBCL **or follicular NHL grade 3b** will be enrolled in the study (approximately 55 patients in each treatment arm).

Section: Synopsis, Primary Efficacy Criteria, page 7; Figure 1, footnote d, page 27

Replace:

...the ~~end~~ of combination treatment...

With:

...the **start** of combination treatment (**Cycle 1 Day 1**)...

Section: 4, List of Abbreviations and Definition of Terms, page 14-15

Delete:

~~ASCO — American Society of Clinical Oncology~~

Add:

**NMR      No metabolic response**

Section: 7.1, Disease Review (second paragraph), page 21

Add:

**...Follicular NHL grade 3b, an aggressive follicular lymphoma, is often treated under the same guidelines. [31]**

Section: 7.3, Clinical Study Rationale, page 22

Add:

In the relapsed or refractory setting, DLBCL **and follicular NHL grade 3b** patients who...

Section: 8.3, Primary Study Objectives, page 24

Add:

- To compare the objective response rate (ORR) among subjects with relapsed or refractory CD30 positive DLBCL **or follicular NHL grade 3b** receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)

Section: 8.4.3, Pharmacokinetic / Pharmacodynamic Measurements, page 25

Add:

Tumor samples **from prior biopsies/aspirates** will be collected from all subjects for assessment

Section: 9.1, Overall Study Design and Plan, page 26

Change:

...CD30-positive DLBCL ~~and or grade 3b~~ follicular lymphoma **grade 3b** after failure of second-line **salvage** therapy or greater...

Section: 9.5.1.1, Required Premedication and Postmedication, page 33

Add:

**The use of transfusions per institutional practice is permitted. The use of white blood cell growth factors (eg, G-CSF) is recommended for all patients. Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the Investigator.**

Section: 9.5.1.3.1, Description, pages 35

Add:

**Rituximab is marketed as Rituxan® in the US and as MabThera® in Europe** and is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituxan ~~is~~ **and Mabthera** are supplied at a concentrations of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. ~~The product is and are~~ formulated in polysorbate 80 (0.7 mg/mL), sodium chloride (9 mg/mL), sodium citrate dihydrate (7.35 mg/mL), and Water for Injection. The pH is 6.5.

Section: 9.5.1.5.3, Dose Modifications, pages 38-39

Delete:

~~Common toxicities including myelosuppression, nausea, gastrointestinal toxicity, fatigue, pyrexia, headache, weight decrease, dyspnea, rash, and stomatitis should be managed according to institutional standards or accepted guidelines (eg, American Society of Clinical Oncology [ASCO] guidelines for the use of white blood cell growth factors [38]). Growth factor support may be administered as needed according to institutional standard of care.~~

Replace:

Following Grade 4 hematologic toxicity or Grade  $\geq 3$  nonhematologic toxicity, the bendamustine dose should be decreased from 90 mg/m<sup>2</sup> to 70 mg/m<sup>2</sup>. Doses lower than 70 mg/m<sup>2</sup> are not allowed.

With:

Following Grade 4 hematologic toxicity or Grade  $\geq 3$  nonhematologic toxicity, the bendamustine dose should be decreased from 90 mg/m<sup>2</sup> to 70 mg/m<sup>2</sup> **and, if toxicity recurs, the dose can be further decreased to 50 mg/m<sup>2</sup>**. Doses lower than 50 mg/m<sup>2</sup> are not allowed.

Delete:

~~If toxicity recurs following dose reduction, bendamustine should be discontinued.~~

Section: 9.5.3, Prior and Concomitant Therapy, page 39-40

Add:

... other than DLBCL **or follicular NHL grade 3b** is permitted...

Replace:

~~The use of transfusions, platelet and/or colony stimulating factors per institutional practice is permitted. In addition, the ASCO guideline for the use of white blood cell growth factors is recommended for the management of neutropenia and febrile neutropenia. [38] Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the Investigator.~~

With

The use of transfusions per institutional practice is permitted. **The use of white blood cell growth factors (eg, G-CSF) is recommended for all patients. Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the Investigator.**

Section: Table 2: Study Schedule, pages 43-44

Modify table structure to include a single spanner head for Cycles 1 and 2, including a new column for D7-D14, with indicators for physical examination, ECOG performance status, and hematology. Add a column for Cycle 2 only, Day 15-21 (+2D), with indicators for CT and PET. Update 2 following columns to indicate Cycles 3-6 and Cycle 6 only, respectively.

Delete:

From footnote b: ...15 unstained slides from a biopsy of relapsed disease ~~obtained within 1 year prior to screening~~ (or initial diagnostic specimen if refractory)...

Add:

New footnotes, o and p, for the physical examination on Days 7-14 of Cycles 1 and 2:

- o. At these visits the physical examination may be a brief, targeted examination, at the discretion of the investigator, to identify changes from baseline.**
- p. Not required for Cycle 1.**

Section: 10.1, Screening (Day -28 to 1), page 46

Replace:

- Medical history, including ~~DLCBL~~ history...

With:

- Medical history, including **lymphoma** history...

Section: 10.2, Treatment Period, pages 46-49

Update section Structure to reflect changes to structure of Table 2,

Add:

- Cycles 1 **and 2**, Day 1, pretreatment:
  - ...
  - Pharmacodynamic sample collection (within 24 hours before beginning ~~the brentuximab vedotin infusion;~~ **study treatment;**
  - ...
  - **ECOG performance status (not required in Cycle 1; Section 11.5)**
  - ...

- Cycles 1 and 2, Day 1, posttreatment:

...

- Cycles 1 and 2, Day 7-14:
  - Physical examination (Section 11.5)
  - Clinical laboratory tests (hematology; Section 11.7).
  - ECOG performance status (Section 11.5)

...

- Cycle 2 only, Days 15-21:
  - Disease assessment (Section 11.9).
- ~~Cycles 2~~ Cycles 3 – 6, Day 1, pretreatment:
  - Pharmacodynamic sample collection (within 24 hours before beginning the ~~brentuximab vedotin infusion;~~ **study treatment;**

...

- ~~Cycles 2~~ Cycles 3 – 6, Day 1, posttreatment:

...

- ~~Cycles 2 and 6 only~~ Cycle 6 only, Days 15-21:

Section: 10.3, End of Treatment, page 49

Add:

An EOT visit will be performed 30 – 37 days after the last dose of study treatment (brentuximab vedotin, rituximab, and/or bendamustine). **EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30 – 37 days following the patient’s last study treatment to ensure that no changes in AE profile have occurred.** At the EOT visit, the following assessments/procedures will be performed:

...

- Pharmacodynamic sample collection (Section 11.8)

...

**Response assessments and pregnancy test at EOT not required if performed at last cycle of treatment.**



Section: 11.1, Medical History, page 51

Add:

...history of DLBCL **or follicular NHL grade 3b** and prior treatments...

Section: 11.2, Histology / CD30 Assessment, page 51

Change:

Histologically confirmed DLBCL **or follicular NHL grade 3b** and prior treatments  
...15 unstained slides from a biopsy of relapsed disease ~~obtained within 1 year prior to screening~~ (or initial diagnostic specimen if refractory)...

Biopsy material will also be collected **from patients who provided consent** if available...  
markers for ~~DLBCL~~ **lymphoma**,...

Section: 11.5, Physical Examination, ECOG Performance Status, and Weight, page 52

Add:

**At the Day 7-14 visits in Cycles 1 and 2, the physical examination may be a brief, targeted examination, at the discretion of the investigator, to identify changes from baseline.**

Section: 11.10, Long-term and Survival Status Follow-up, page 54

Change:

...and poststudy treatment for ~~DLBCL~~ **lymphoma** and CD30 pathway...

Section: 12.1.4, Serious Adverse Events Require Immediate Reporting, page 59

Add:

...Cover Sheet are to be faxed **or emailed** to the Drug Safety Department ...

Section: 13.6.4.2, Secondary Efficacy Endpoints, page 64

Add:

DOR (for PR/CR and CR): DOR is defined as the time from first observation of response (PR/PMR+CR/CMR or CR/CMR) to disease progression/relapse, **receipt of subsequent lymphoma chemotherapy other than the components of the study treatment regimen (excludes post-treatment consolidative radiotherapy, post-treatment chemotherapy for**

**the purpose of mobilizing peripheral blood stem cells, and consolidative autologous or allogeneic SCT),** or death from any cause, whichever occurs first. Durations will be assessed in the ITT population with a PR or CR and calculated separately for subjects with CR/CMR and those with PR/PMR+CR/CMR combined. For subjects with a remission without subsequent disease progression/relapse or death on study, DOR will be censored at the time of the last disease assessment demonstrating a lack of disease progression/relapse. **If more than one date of progression is available, the earliest date will be used to determine PFS. Full censoring rules will be provided in the SAP.** Subjects who receive SCT in remission will continue to be followed for DOR.

Replace:

Progression-free Survival: PFS is defined as the time from ~~first dose of study medication~~ to first documentation of disease progression/relapse, or to death due to any cause, whichever occurs first. For subjects without disease progression/relapse or death on study, PFS will be censored at the time of the last on-study disease assessment demonstrating a lack of disease progression/relapse. If more than one date of progression is available, the earliest date will be used to determine PFS. Subjects who receive SCT in remission will continue to be followed for PFS.

With:

Progression-free Survival: PFS is defined as the time from **randomization** to first documentation of disease progression/relapse, or to death due to any cause, **or receipt of subsequent lymphoma chemotherapy other than the components of the study treatment regimen (excludes post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, and consolidative autologous or allogeneic SCT),** whichever occurs first. For subjects without disease progression/relapse or death on study, PFS will be censored at the time of the last on-study disease assessment demonstrating a lack of disease progression/relapse. If more than one date of progression is available, the earliest date will be used to determine PFS. **Full censoring rules will be provided in the SAP.** Subjects who receive SCT in remission will continue to be followed for PFS.

Replace:

Overall Survival: OS is defined as the time from ~~first dose of study medication~~ to death due to any cause. For subjects not known to have died at the conclusion of the study, OS will be censored at the time the subject was last known to be alive (including follow-up data).

With:

Overall Survival: OS is defined as the time from **randomization** to death due to any cause. For subjects not known to have died at the conclusion of the study, OS will be censored at the time the subject was last known to be alive (including follow-up data).

Section: 17, Reference List, page 78

Delete:

~~38. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 24(19): 3187-3205, 2006.~~

Update subsequent reference number and as appropriate in report body.

Section: Global

Replace:

Version ~~03~~, Date ~~10 November 2015~~

With:

Version **04**, Date **19 February 2016**

## 18.11 Appendix 11: Summary of Changes in V05

### RATIONALE:

The protocol was amended to

- Reflect that Teva Pharmaceuticals is discontinuing distribution of the bendamustine hydrochloride liquid formulation TREANDA, which was being used at all US sites in this study. Investigators may continue to dispense TREANDA until its expiration date, as described in previous versions of the protocol and in the pharmacy manual. When acquiring new supplies, sites are to acquire bendamustine hydrochloride lyophilized powder.
- Allow the assessment of CD30 for eligibility assessment to be performed either by local or central laboratory
- Clarify that a new biopsy may be required for subjects with relapsed disease if one has not been obtained since relapse
- To correct an inconsistency between the schedule of follow-up assessments and the text description of follow-up events
- Make minor editorial and formatting changes throughout the protocol

### SUMMARY OF CHANGES:

*Note: Editorial and formatting changes are not included below.*

Section: Synopsis, Study Design and Methodology, page 5; 9.1, Overall Study Design and Plan, page 26

Change:

DLBCL or follicular NHL grade 3b will be histologically determined by local pathology assessment, and CD30 expression will be ~~locally~~ determined by **local or central laboratory** visual assessment of any detectable level of CD30 on tumor cells by immunohistochemistry (IHC; using anti-CD30 BerH2 antibody) to determine eligibility for enrollment. Tissue will be sent to a central laboratory for **disease confirmation and retrospective** evaluation of biomarkers including...

Section: Synopsis, Inclusion Criteria, page 5; 9.4.1, Inclusion Criteria, page 28

Add (Inclusion Criterion 1):

- Patients with histologically confirmed CD30-positive DLBCL or follicular NHL grade 3b, defined as any detectable CD30 expression on tumor cells based on local **or central** pathologic assessment.

Section: 9.5.1.4, Bendamustine, page 36

Replace:

~~Bendamustine hydrochloride is marketed in the US as TREANDA® by Cephalon, Inc., (Frazer, PA USA) and in the EU as Levact by Napp Pharmaceuticals, Ltd, Cambridge, Cambridgeshire UK. Please refer to the approved USPI or EU SmPC for detailed information.~~

*9.5.1.4.1 Description*

~~In the US, bendamustine hydrochloride is provided as a liquid, 90 mg/mL formulation. In the EU, it is provided as a sterile non-pyrogenic white to off-white lyophilized powder in a single-use vial, and it is reconstituted with Sterile Water for Injection, USP. Both the liquid and reconstituted formulations are further diluted according to local standard of care.~~

With:

Please refer to the approved USPI or EU SmPC for detailed information on **bendamustine hydrochloride**.

*9.5.1.4.1 Description*

**Bendamustine hydrochloride** is provided as a sterile non-pyrogenic white to off-white lyophilized powder in a single-use vial, and it is reconstituted with Sterile Water for Injection, USP. **The** reconstituted formulation **is** further diluted according to local standard of care.

Section: Table 2: Study Schedule, page 43

Add (footnote b):

- **Centrally or** locally assessed to enable enrollment. Submission of the tumor block...

Section: Table 3: Schedule of Follow-up Events, page 44

Add indicator ('X') to "Lymphoma assessment" row under Month 30

Section: 11.2, Histology / CD30 Assessment, page 4

Add:

- Histologically confirmed DLBCL or follicular NHL grade 3b must be determined by local pathology assessment. **CD30 expression will be determined by local or central laboratory visual assessment using IHC (anti-CD30 BerH2 antibody) to determine eligibility.**

**If adequate tissue is not available or if disease has relapsed and the patient has**

**not had a biopsy since the relapse was documented, a new biopsy must be obtained. A new biopsy is not required for patients with refractory disease, provided a biopsy was obtained prior to the initiation of the most recent therapy.**

Submission of the tumor block or approximately 15 unstained slides from a biopsy of relapsed disease (or initial diagnostic specimen if refractory) is required for subsequent central pathology disease confirmation and further evaluation **CD30 expression, and**~~of~~ additional molecular biomarkers.

Section: Global

Replace:

Version ~~04~~, Date ~~19 February 2016~~

With:

Version **05**, Date **13 July 2016**