STATISTICAL ANALYSIS PLAN

Protocol Number:	SGN35-014
Version:	Version 5; 15 May 2018
Protocol Title:	A randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

A+CHP	brentuximab vedotin (ADCETRIS®), cyclophosphamide, doxorubicin, and prednisone
AE	adverse event
ATA	antitherapeutic antibodies
ALK	anaplastic lymphoma kinase
CHOP	cyclophosphamide, doxorubicin (hydrodoxorubicin), vincristine (Oncovin®), and prednisone
CHP	cyclophosphamide, doxorubicin (hydrodoxorubicin), and prednisone
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete remission
CRF	case report form
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European Quality of Life 5-Dimensional
EMA	European Medicines Agency
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity
HR	hazard ratio
IDMC	Independent Data Monitoring Committee
IRF	independent review facility
IPI	International Prognostic Index
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PR	partial remission
PRO	patient reported outcomes
QLQ-C30	EORTC core quality of life questionnaire
QoL	quality of life
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SCT	stem cell transplant
SPD	sum of the products of diameters
SUV	standard uptake value

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGN35-014, entitled "A randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas". Results of the proposed analyses will become the basis of the clinical study report (CSR) for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the final clinical study report. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the clinical study report.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To compare the progression-free survival (PFS) as determined by an independent review facility (IRF) between the 2 treatment arms

2.2 Secondary Objectives

- To compare the PFS per IRF between the 2 treatment arms for patients with systemic anaplastic large cell lymphoma (sALCL)
- To compare the remission rates per IRF following the completion of study treatment between the 2 treatment arms
- To compare overall survival (OS) between the 2 treatment arms
- To evaluate the safety and tolerability of the 2 treatment arms

2.3 Additional Objectives

- To evaluate medical resource utilization (MRU) and calculate utility values
- To characterize the incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin

3 STUDY ENDPOINTS

3.1 Primary Endpoint

- PFS per IRF

3.2 Secondary Endpoints

3.2.1 Key Secondary Endpoints

- PFS per IRF for patients with sALCL
- Complete remission (CR) rate per IRF following the completion of study treatment

- OS
- Objective response rate (ORR) per IRF following the completion of study treatment

3.2.2 Safety Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events
- Type, incidence, and severity of laboratory abnormalities

3.3 Additional Endpoints

- Incidence of ATA to brentuximab vedotin
- MRU based on the number of medical care encounters
- Quality of Life (QoL) measured by the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) and European Quality of Life 5-Dimensional (EQ-5D) score

4 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trial designed to evaluate the efficacy and safety of including brentuximab vedotin in the treatment of newly-diagnosed, CD30-positive mature T-cell lymphomas. The standard of care in this patient population consists of 6 to 8 cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin [hydrodoxorubicin], vincristine [Oncovin®], prednisone). Patients will be randomized in a 1:1 manner to receive 21-day cycles of treatment in 1 of the following 2 treatment groups:

1. Standard-of-care arm: 6–8 cycles of CHOP; or
2. Experimental arm: 6–8 cycles of brentuximab vedotin plus CHP (A+CHP)

A target of 8 cycles of study treatment will be administered, per investigator decision, based on patient-specific characteristics, including stage of disease and IPI risk score. For patients tolerating study treatment, at least 6 cycles of study treatment should be completed prior to initiating post treatment consolidative stem cell transplant (SCT). Consolidative SCT is defined as SCT following completion of study treatment in the absence of any new anticancer treatment other than stem cell mobilization or conditioning.

Brentuximab vedotin or vincristine will be administered as a placebo-controlled double-dummy and administered to patients in a blinded manner. Placebo replacements for brentuximab vedotin/vincristine will be prepared by the pharmacist at each study site and a pharmacy blind will be enforced.

Approximately 450 patients (~225 patients per treatment arm) will be randomized in this study.

Radiographic disease evaluations, including CT scans of neck, chest, abdomen and pelvis, will be assessed at baseline, after completion of Cycle 4 of study treatment, after completion

of study treatment, at 9, 12, 15, 18, 21, and 24 months after initiation of study treatment, and every 6 months thereafter until disease progression, patient death, or analysis of the primary endpoint, whichever comes first. Patients will be followed for survival until death or study closure, whichever comes first.

Safety assessments will include the incidence and severity of adverse events and changes in clinical laboratory values. Serum concentrations of ATA to brentuximab vedotin will also be measured.

[redacted]

5 ANALYSIS SETS

This section defines each of the analysis sets that will be utilized. The use of each analysis set will be discussed in Section 7.

5.1 Intent-to-Treat (ITT) Analysis Set

The ITT analysis set will include all randomized patients. Patients will be included in the treatment group assigned at randomization regardless of the actual treatment received.

5.2 Safety Analysis Set

The safety analysis set will include all patients who receive any amount of brentuximab vedotin or any component of CHOP. Treatment group will be determined using the actual treatment received, regardless of the randomization treatment assignment. Patients receiving any dose of brentuximab vedotin will be grouped into the experimental group. Patients who do not receive brentuximab vedotin but any dose of any component of CHOP will be grouped into the standard-of-care group.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

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

Unless otherwise specified, all statistical tests will be performed using a two-sided alpha of 0.05. Confidence intervals will be calculated at two-sided 95% level. Multiplicity adjustment for alpha level is discussed in Section 6.8.

Any analysis not described in this plan will be considered exploratory, and will be documented in the CSR as a post hoc analysis or a change to the planned analysis.

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created and attached to the appendix of the CSR.

All statistical Tables, Listings and Figures will be produced using SAS®, version 9.3 or higher. Other statistical software used will be described in the CSR.

6.2 Determination of Sample Size

Approximately 450 patients (~225 patients per treatment arm) will be randomized in this study. The target proportion of patients with a diagnosis of sALCL per central pathology assessment will be 75% (±5%).

[redacted]

6.3 Randomization and Blinding

This is a randomized, double-blind, placebo controlled comparative study that will enroll approximately 450 patients. Patients will be randomized in a 1:1 manner to receive either CHOP or A+CHP. Brentuximab vedotin or vincristine will be dispensed as a placebo-controlled double-dummy and administered to patients in a blinded manner. Placebo replacements for brentuximab vedotin/vincristine will be prepared by the pharmacist at each study site and a pharmacy blind will be enforced.

[redacted]

Randomization will be performed centrally using a system that will assign a unique patient randomization number but will not specify the actual treatment assignment. Randomization procedures are detailed in the Study Manual.

6.4 Data Transformations and Derivations

Age as entered by the Investigative site will be used for all analysis involving age. When only a birth date (and not age) is provided, age in years will be calculated with the SAS INTCK function using informed consent date and birth date.

Study Day will be calculated as Date – First Dose Date + 1 for dates on or after the first dose date. For dates prior to the first dose date, Study Day will be calculated as Date – First Dose Date. For all calculations of Study Day, the First Dose Date will be the earliest date of treatment administration for brentuximab vedotin or any component of multiagent chemotherapy (CHOP or CHP).

Other time variables based on 2 dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

The following unit conversion will be implemented unless otherwise specified:

Months = Days/30.4375

Years =Days/365.25

Baseline values used in all analyses will be the most recent measurement prior to the first dose of study drug (brentuximab vedotin or any component of multiagent chemotherapy (CHOP or CHP).

The end-of-treatment (EOT) date will be the date the EOT visit is performed, or 30 days after the last dose of study drug (other than prednisone) if an EOT visit is not performed.

The date of progression will be the earliest of all radiologic scan dates for the given disease assessment, unless otherwise specified by the IRF Charter.

The date of progression per Investigator will be the earliest of all radiological scan dates or date of biopsy confirming malignancy for the given disease assessment.

6.5 Handling of Dropouts and Missing Data

Missing data will not be imputed, with the exception of AE dates (see Appendix A). Patients with missing values of a variable other than the time-to-event endpoints (PFS and OS) will be excluded from the analysis of that endpoint. Censoring rules will be applied to the estimation of the distribution of the time-to-event endpoints (Section 7.5).

[redacted]

6.7 Multicenter Studies

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

[redacted]

6.9 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints (see Section 7). Subgroups may include but are not limited to the following:

- Age (18–64 years, ≥65 years old)
- Age (<60 years, ≥60 years old)
- Gender (Male, Female)
- Race
- Geographic region
- Categorized weight at baseline (<70, 70–<100, and 100+ kg)
- Prior cutaneous ALCL (yes, no)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, or 2)
- Disease indication (histologic subtype)
- Anaplastic lymphoma kinase (ALK) status (positive, negative) in sALCL patients
- Disease stage (Stage I, Stage II, Stage III, Stage IV)
- International prognostic index (IPI) Score (0, 1, 2, 3, 4, 5);

- For all patients
- For ALK+ sALCL patients
- For ALK- sALCL patients

- [redacted]

- Malignant cutaneous lesions at baseline (yes, no)
- Bone marrow involvement at baseline (yes, no)
- Patients with central pathology-confirmed histologic subtype
- Patients with central pathology-confirmed CD30 expression
- Patients with and without consolidative autologous or allogeneic SCT
- Cycles of study treatment received (≤6 cycles, >6 cycles)

6.10 Covariates

This is a phase 3 study. Stratified analyses specified in Section 7 will include adjustment for the stratification factors as recorded at randomization. Covariates may be considered for adjustment in exploratory regression analyses.

[redacted]

[redacted]

7 PLANNED ANALYSES

7.1 Disposition

Patient enrollment and disposition will be summarized by treatment group and total using the ITT analysis set. The table will present the number and percentage of patients who were randomized, received study drug, received treatment per randomization assignment, and participated in follow-up visits. The number and percentage of patients who discontinued treatment will be summarized by the reason for treatment discontinuation. The number and percentage of patients who discontinued the study will be summarized by the primary reason for study discontinuation.

Number of patients who signed informed consent and number of patients in each analysis set will be summarized by treatment group and total.

The number of patients enrolled in each country and at each site will be summarized by treatment group and total.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, gender, ethnicity, race, baseline height, weight, body mass index, and ECOG score will be summarized by treatment group and total using the ITT analysis set. Disease-specific characteristics, including time from diagnosis, ALK status, and IPI score will be summarized by treatment group and total using the ITT analysis set. Demographics, baseline characteristics and disease-specific characteristics will also be summarized by treatment group within the subgroup of patients receiving ≤6 cycles of study treatment and the subgroup of patients receiving >6 cycles of study treatment. Previous cancer-related treatments for primary cutaneous ALCL patients who transformed to sALCL will be summarized by treatment group and total. A comparison of the stratification factors as recorded at randomization and as recorded in the CRF at baseline will be presented.

7.3 Protocol Deviations

Important protocol deviations (defined as protocol violations by Seattle Genetics) are those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the subject's rights, safety, or welfare. Important protocol deviations also include exemptions to the study inclusion/exclusion criteria and will be summarized by category by treatment group and total. A list of patients with important protocol deviations will be presented.

7.4 Treatment Administration

Treatment administration will be summarized by treatment agent, treatment group and total using the safety analysis set. Summary statistics for duration of therapy (weeks) and the number of

cycles per patient will be presented, as well as the number and percentage of patients who were treated at each cycle and completed each cycle. Cumulative dose (mg), intended dose intensity (IDI), absolute dose intensity (ADI) and relative dose intensity (RDI) will be described. The number and percentage of patients whose dose was ever modified will be summarized by modification type, cycle and overall (i.e. overall drug administrations for a patient).

Duration of treatment for IV-administered treatments is defined as time from the first study dose to 21 days after the last study dose [(last dose date +21) – first dose date]. If death occurs less than 21 days after the last study dose, duration of treatment is defined as [date of death – first dose date +1].

Duration of treatment for prednisone is defined as the time from first study dose to 21 days after the Day 1 dose date of the last cycle [(last cycle Day 1 date +21) – first dose date]. If death occurs less than 21 days after the Day 1 dose date of the last cycle, duration of treatment for prednisone is defined as [date of death – first dose date +1].

IDI is defined as is the intended dose of drug (e.g. mg/kg) per unit of time. For example, for brentuximab vedotin this is (1.8 mg/kg)/3 weeks=0.6. For vincristine only, IDI is defined as 2 mg per 3 weeks=0.667 mg per week. For prednisone, IDI is defined as 500 mg/3weeks=166.67 mg/week.

ADI is defined as the actual dose (e.g. mg/kg) per unit of time that the patient received over the entire treatment period. For vincristine and prednisone, ADI is defined as the total actual dose in mg per unit of time that the patient received over the entire treatment period.

RDI is defined as the percent of the intended dose intensity over the entire treatment period: RDI=ADI/IDI * 100

Example 1:

For brentuximab vedotin, consider a patient treated for three cycles. The second dose was delayed for one week, and for the third cycle the infusion was not completed and the patient received less than the full dose, as represented in the following table:

Visit	Intended Dose Regimen (mg/kg)	Intended Dose (mg)	Actual Dose (mg)	Cycle Length
C1D1	1.8	38	38	3 weeks + 1 week delay
C2D1	1.8	38	38	3 weeks
C3D1	1.8	38	19	3 weeks

ADI (per week):

=(1.8 + 1.8 + (1.8*[19/38])) / (3 wks + 1 wk delay + 3 wks + 3 wks) mg/kg per week
=0.45 mg/kg per week

RDI:

=0.45/0.6 * 100
=75%

Example 2:

For vincristine, consider a patient in the standard-of-care arm, treated for 6 cycles. The second dose was delayed for 1 week, and for the third cycle and beyond the dose was reduced, as represented in the following table:

Visit	Intended Dose (mg)	Cycle Length
C1D1	2	3 weeks + 1 week delay
C2D1	2	3 weeks
C3D1	1	3 weeks
C4D1	1	3 weeks
C5D1	1	3 weeks
C6D1	1	3 weeks

ADI (per week):

=(2 + 2 + 1 + 1 + 1 + 1) / (3 wks + 1 wk delay + 3 wks + 3 wks + 3 wks + 3 wks + 3 wks) mg per week
=0.421 mg per week

RDI:

=0.421/0.667 * 100
= 63%

Example 3:

For prednisone, consider a patient treated with CHOP or CHP for six cycles. The second cycle was delayed for one week, and for the fourth cycle and beyond the patient took only 4 of the 5 doses of prednisone, as represented in the following table:

Visit	Intended Dose (mg)	Cycle Length
C1D1	500	3 weeks + 1 week delay
C2D1	500	3 weeks
C3D1	500	3 weeks
C4D1	400	3 weeks
C5D1	400	3 weeks
C6D1	400	3 weeks

ADI (per week):

=(500 + 500 + 500 + 400 + 400 + 400) / (3 wks + 1 wk delay + 3 wks + 3 wks + 3 wks + 3 wks + 3 wks) mg per week
=142 mg per week

RDI:

=142/166.67 * 100
= 85%

7.5 Efficacy Analyses

All efficacy analyses will be presented using the ITT analysis set. All stratified analyses will utilize the stratification factors as entered at the time of randomization. Analyses may also be performed using the subgroups listed in Section 6.9.

7.5.1 Primary Endpoint

7.5.1.1 Progression Free Survival (PFS) per IRF

PFS is defined as the time from the date of randomization to the date of first documentation of PD, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurs first. Note that receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT will not be considered as disease progression or as having started new anticancer therapy. Specifically,

PFS = The earliest of the dates of first documented PD, receipt of subsequent anticancer chemotherapy to treat residual or progressive disease or death – Date of randomization + 1.

If PD is not documented, no subsequent anticancer chemotherapy to treat residual or progressive disease has been initiated, and the patient is alive at the time of the data cutoff or study withdrawal, PFS will be censored as follows:

- If there is no radiographic post-baseline tumor assessment, PFS will be censored at the date of randomization.
- If there are radiographic post-baseline tumor assessments, PFS will be censored at the most recent tumor assessment before the data cutoff or study withdrawal, whichever occurs first.

Specifically,

Censored PFS = max(1, last scan date – date of randomization + 1),

where the last scan is the last CT or PET scan obtained during study.

Full censoring rules for the primary endpoint are detailed in the table below.

Situation	Date of Progression or Censoring	Outcome
No baseline and/or post baseline tumor assessment	Day following date of randomization	Censored
No documented progression	Date of last radiographic tumor assessment (or the date of randomization in the absence of a post-baseline radiographic tumor assessment)	Censored
PD documented between scheduled visits	Date of radiologic tumor assessment demonstrating PD	Event
Treatment discontinuation for undocumented progression after the last radiographic tumor assessment	Date of last radiographic tumor assessment or the date of randomization in the absence of a post-baseline radiographic tumor assessment	Censored
New anticancer therapy to treat residual or progressive disease initiated prior to documented progression, including palliative radiotherapy (excludes post-treatment chemotherapy given for stem cell mobilizations, excludes consolidative autologous or allogeneic SCT and excludes post-treatment consolidative radiotherapy)	Start date of new anticancer therapy	Event
Post-treatment consolidative radiotherapy, post-treatment chemotherapy given for stem cell mobilizations, consolidative autologous or allogeneic SCT	Date of last radiographic tumor assessment or the date of randomization in the absence of a post-baseline radiographic tumor assessment	Censored
Death before first PD assessment	Date of death	Event
Death between radiographic tumor assessment visits	Date of death	Event
Death or progression after more than one consecutively missed radiographic tumor assessment	Date of last radiologic tumor assessment prior to missed visits or the date of randomization in the absence of a post-baseline radiographic tumor assessment prior to missed visits	Censored

The primary statistical hypothesis can be expressed in terms of the hazard ratio $\lambda_{Experimental\ arm}/\lambda_{Standard\text{-}of\text{-}Care\ arm}$ where $\lambda_{Experimental\ arm}$ represents the hazard of progression on the experimental arm (A+CHP) and $\lambda_{Standard\text{-}of\text{-}Care\ arm}$ represents the hazard of progression on the standard-of-care arm (CHOP). A hazard ratio <1 indicates that the duration of PFS is prolonged for patients on the experimental arm compared with patients on the standard-of-care arm.

The null and alternative hypotheses can be written respectively as:

$H_0 = \lambda_{Experimental\ arm}/\lambda_{Standard\text{-}of\text{-}Care\ arm} \geq 1$

$H_A = \lambda_{Experimental\ arm}/\lambda_{Standard\text{-}of\text{-}Care\ arm} < 1$

Kaplan-Meier methods will be used to assess PFS. The stratified log-rank test without adjustments for covariates will be used in the primary evaluation of PFS differences between the experimental arm and the standard-of-care arm in the ITT analysis set using an overall

one-sided, α=0.025 level test. All events entered in the database at the time of analysis that have been source-data-verified will be included in the analysis of PFS, [redacted]

Kaplan-Meier Curves depicting PFS in the 2 arms will be generated. Additionally, median PFS and probability of PFS from 3 months to the end of the follow-up period will be reported at 3 month intervals. The two-sided 95% confidence intervals (CI) for the median and 3-month intervals will be calculated using the complementary log-log transformation method (Collett 1994).

The primary analysis of PFS may be performed for each of the subgroups specified in Section 6.9. An analysis may also be performed on the subgroup of patients without consolidative radiotherapy, consolidative autologous or allogeneic SCT. An analysis of PFS per Investigator will also be performed and an evaluation of the agreement between PFS per IRF and PFS per Investigator will be provided.

Descriptive statistics of PFS will be presented for each individual histologic subtype where possible.

Cox regression of PFS may be used to estimate the hazard ratio of the experimental arm to the standard-of-care arm. Baseline covariates may be included in the model in addition to centrally determined CD30 expression level as a continuous variable. The treatment group variable will always be included in the model. Interaction effects may be considered whenever possible.

Sensitivity Analyses

Sensitivity analyses of PFS per IRF will be performed. Sensitivity analyses will include, but will not be limited to, the following:

1. A stratified log-rank analysis using the stratification factors as recorded in the CRF at baseline
2. An analysis where patients receiving SCT or consolidative radiotherapy are censored
3. An analysis where patients receiving new anticancer therapy are censored rather than considered to have had an event
4. An analysis assessing the impact of missing data/assessments where patients who missed one or more of the most recent scheduled assessments are treated as events at the time of the next scheduled assessment on the experimental arm
5. An analysis where initiation of consolidative radiotherapy and undocumented progression (e.g. progression identified by the Investigator on the basis of symptomatic deterioration) are considered events
6. An analysis where, for patients with a CR at EOT, initiation of consolidative radiotherapy or receipt of SCT are considered events

7. An analysis where patients who discontinue treatment for undocumented progression after the last radiographic tumor assessment are considered to have had an event at the time of treatment discontinuation; and where patients who die or progress after more than one consecutively missed radiographic tumor assessment are considered to have had an event on the date of death or progression

8. An analysis following EMA censoring guidelines where receipt of new anticancer therapy is not considered an event nor a reason for censoring and where patients who die or progress after more than one consecutively missed radiographic tumor assessment are considered to have had an event on the date of death or progression

No p-values will be calculated and no formal adjustments for multiplicity will be made when performing the above sensitivity analyses.

7.5.2 Secondary Efficacy Endpoints

7.5.2.1 PFS per IRF in Patients with sALCL

PFS per IRF in patients with sALCL is defined in the same manner as PFS per IRF (see Section 7.5.1.1). For this endpoint, PFS per IRF will be analyzed in the subset of patients with a central pathology confirmed diagnosis of sALCL.

7.5.2.2 Complete Remission Rate (CR rate)

CR rate is defined as the proportion of patients with CR per IRF following the completion of study treatment (at EOT or the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Patients whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate.

The CR rate between the experimental arm and the standard-of-care arm will be tested using the Cochran-Mantel-Haenszel (CMH), stratified by the randomization stratification factors (see Section 6.3). The absolute CR rate and exact two-sided 95% confidence interval using the Clopper-Pearson method (Clopper 1934) will also be summarized by treatment group.

7.5.2.3 Objective Response Rate (ORR rate)

ORR is defined as the proportion of patients with CR or partial remission (PR) per IRF following the completion of study treatment (at EOT or the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Patients whose disease response cannot be assessed will be scored as non-responders for calculating the ORR.

The ORR between the experimental arm and the standard-of-care arm will be tested using the Cochran-Mantel-Haenszel (CMH), stratified by the randomization stratification factors (see Section 6.3). The absolute ORR and exact two-sided 95% confidence interval using the Clopper-Pearson method (Clopper 1934) will also be summarized by treatment group.

7.5.2.4 Overall Survival (OS)

OS is defined as the time from randomization to death due to any cause. Specifically,

OS=Date of death – Date of randomization + 1

For a patient who is not known to have died by the end of study follow-up, observation of OS is censored on the date the patient was last known to be alive (i.e., date of last contact). Patients lacking data beyond the day of randomization will have their survival time censored on the date of randomization (i.e., OS duration of 1 day).

The stratified log-rank test without adjustments for covariates will be used in the evaluation of OS differences between the experimental arm and the standard-of-care arm. OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by treatment group. Additionally, median PFS and probability of PFS from 3 months to the end of the follow-up period will be reported at 3-month intervals by treatment group. The two-sided 95% confidence intervals (CI) for the median and 3-month intervals will be calculated using the complementary log-log transformation method (Collett 1994).

7.6 Safety Analyses

The safety analysis set will be used to summarize all safety endpoints.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 15.1 or higher).

Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.03 or higher).

Concomitant medications will be coded using WHO Drug (version: June 2012 or more recent).

7.6.1 Adverse Events

Adverse events (AEs) will be summarized by descending MedDRA preferred term unless otherwise specified. For incidence reporting, if a patient reports more than one AE that was coded to the same system organ class or preferred term, the patient will be counted only once for that specific system organ class or preferred term.

A treatment-emergent AE is defined as a newly occurring or worsening AE after the first dose of any study drug component. Unless documented as a pre-existing condition, AEs with unknown start date will be counted as treatment emergent. Summary of AEs will be provided by treatment group and total for the following:

- Pre-existing Adverse Events,
- All treatment-emergent AEs,
- AEs related to blinded study treatment,
- AEs related to CHP,

- Serious Adverse Events (SAEs),
- SAEs related to blinded study treatment,
- SAEs related to CHP,
- AEs leading to dose reduction of blinded study treatment,
- AEs leading to dose reduction of cyclophosphamide or doxorubicin,
- AEs leading to dose delay of blinded study treatment,
- AEs leading to dose delay of cyclophosphamide or doxorubicin,
- AEs leading to dose interruption of blinded study treatment (full dose received),
- AEs leading to dose interruption of cyclophosphamide or doxorubicin (full dose received),
- AEs leading to the dose of blinded study treatment being stopped early (full dose not received),
- AEs leading to the dose of cyclophosphamide or doxorubicin being stopped early (full dose not received),
- AEs leading to discontinuation of blinded study treatment,
- AEs leading to discontinuation of cyclophosphamide, doxorubicin, or prednisone
- Treatment-emergent AEs by system organ class, preferred term and maximum severity. At each system organ class or preferred term, multiple occurrences of events within a patient are counted only once at the highest severity,
- Grade 3 - 5 treatment-emergent AEs,
- Treatment-emergent AEs by system organ class and preferred term,
- AEs of peripheral neuropathy identified by the broad search MedDRA SMQ "Peripheral neuropathy"

Additional analyses of peripheral neuropathy may also be presented.

7.6.2 Clinical Laboratory Parameters

Clinical laboratory data (hematology, serum chemistry and coagulation panel) will be summarized by treatment group. All laboratory results through the end of treatment visit will be presented in standardized units by treatment group. Both observed data and changes from baseline for chemistry and hematology will be summarized with descriptive statistics. In addition, laboratory data will be summarized by the worst post-baseline NCI CTCAE grade for each parameter.

Laboratory results and NCI CTCAE grades for hematology, and serum chemistry will be presented in data listings. Normal ranges will be documented and out-of-range values will be flagged.

7.6.3 ECOG Performance Status

ECOG status will be summarized for each visit by treatment group. Shifts from baseline to the best and worst post-baseline score will be tabulated by treatment group.

7.6.4 Concomitant Medications

Concomitant medications will be summarized by the WHO Drug substance name by treatment group and total and listed by patient.

7.6.5 Deaths

The total number of deaths, deaths that occur within 30 days of last study treatment, deaths that occur more than 30 days after last study treatment, primary cause of death and relationship to disease will be summarized by treatment group and total.

7.7 Additional Endpoints

The ITT analysis set will be used to summarize all additional endpoints.

7.7.1 Antitherapeutic Antibody (ATA) Incidence Rate

The ATA incidence rate is defined as the proportion of patients that develop ATA at any time during the study. ATA incidence will be summarized by treatment group.

7.7.2 Medical Resource Utilization (MRU)

Medical resource utilization data include medical care encounters (e.g., hospital admissions or major diagnostic procedures) related to study treatment or treatment for lymphoma.

Medical resource utilization (MRU) data will be summarized using descriptive statistics by treatment group. Additional statistical modeling may be performed separately in post hoc analyses.

7.7.3 Quality of Life (QoL)

Quality of life is measured using the QLQ-C30, FACT/GOG-NTX, and EQ-5D scores patient-reported outcome (PRO) instruments.

The FACT/GOG-NTX assesses changes in quality of life, and includes an additional concerns subscale for assessing treatment-induced neurologic symptoms (sensory, hearing, motor, dysfunction). The neurotoxicity subscale of this tool consists of 11 questions. The FACT/GOG-NTX manual for scoring and handling missing data will be used for scoring and handling of missing data.

The QLQ-C30 consists of 5 subscales on functioning (physical, role cognitive, emotional, social), 3 symptom scales (fatigue, pain, nausea/vomiting), and a global quality of life scale as well as questions on symptoms and the financial impact of cancer and treatment. The EORTC QLC-C30 manual will be used for scoring and handling of missing data.

PRO instrument total and subscale scores will be summarized with descriptive statistics by treatment group and visit. In addition, change from baseline will be tabulated by treatment

group and visit. Descriptive summaries of individual items may also be presented. Additional statistical modeling may be performed separately in post hoc analyses.

7.7.4 Pharmacokinetics

Antibody drug-conjugate (brentuximab vedotin), total antibody, and unconjugated drug (MMAE) levels in serum or plasma will be summarized with descriptive statistics at each PK sampling time point. Any additional PK and PK/PD analyses may be performed and presented in a separate report.

7.7.5 Biomarkers

Exploratory correlative studies will be defined in a separate analysis plan and reported in a separate report.

7.8 Exploratory Analyses

The following exploratory analyses may also be presented using the ITT analysis set.

- Duration of response per IRF
- Duration of response per Investigator
- PFS per Investigator
- CR rate at EOT per Investigator
- ORR at EOT per Investigator
- Clinical response at EOT per IRF
- Clinical response at EOT per Investigator
- Evaluation of agreement between IRF and Investigator for clinical response, CR and ORR at EOT
- Change from baseline to EOT of the sum of the products of diameters of nodes or nodal masses (SPD)
- Maximum SPD reduction at EOT
- Failure-free survival
- B-symptom resolution
- Cutaneous lesion resolution
- Proportion of patients PET negative per IRF at Cycle 4
- Proportion of patients PET negative per IRF at EOT
- Proportion of patients PET negative per Investigator at Cycle 4
- Proportion of patients PET negative per Investigator at EOT
- Onset, resolution and characterization of neuropathy based on the Total Neuropathy Score-nurse assessment

- Summary Deauville Scale PET assessments per IRF at Cycle 4
- Summary of PET Standard Uptake Values (SUV) per IRF at Baseline, Cycle 4 and EOT and change in maximum SUV from Baseline

8 INTERIM ANALYSIS

An Independent Data Monitoring Committee (IDMC) will periodically monitor the trial for safety. After each periodic safety review, the IDMC will make a recommendation to the sponsor to continue the study as planned or stop the study for safety concerns. The IDMC will review expedited SAEs as they arise [redacted]

[redacted]

In addition, an ongoing, real-time review of serious adverse events will be conducted by Seattle Genetics Pharmacovigilance.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Original Protocol

There are no changes from the current version of the protocol.

9.2 Changes from the Original SAP

Changes from the original Statistical Analysis Plan are as follows:

9.2.1 Version 2 Changes

- [redacted]
- [redacted]

9.2.2 Version 3 Changes

- Elevated ORR per IRF from Exploratory analysis to Secondary Objective/Secondary Endpoint
- ORR per IRF removed from Exploratory Analyses
- Clarified type of radiotherapy in PFS censoring rules and Exploratory Analyses

- Added Exploratory Analyses to summarize additional assessment of PET scans by the IRF (Deauville Scale and SUV)
- Specified an additional sensitivity analysis for the primary endpoint

9.2.3 Version 4 Changes

- Definition of Consolidative SCT added to study design for clarification
- [redacted]
- Updated definition of AE imputation rules to match the current Seattle Genetics standards
- Specified use of CRF age when available due to changes in ability to collect full birth date in all countries
- Definition for the date of progression per investigator has been added for clarification
- Pooling strategy for stratified analyses clarified to address scenario where no further pooling can be done
- [redacted]
- PFS censoring dates have been updated from study day 1 or first dose date to the date of randomization for consistency
- Post-treatment radiotherapy that triggers PFS censoring in the absence of progression in the PFS censoring table clarified as consolidative for consistency
- Statement regarding descriptive statistics of PFS for each subtype was added per request from CDRH
- PFS sensitivity analysis following EMA censoring guidelines added to support submission to EMA
- Clarification that no p-values will be calculated for PFS sensitivity analyses
- Definition of the completion of study treatment has been clarified for analysis of CR and ORR rates
- Approximately added to timing of futility analysis for clarification

9.2.4 Version 5 Changes

- [redacted]
- Clarified that new anticancer therapy for progressive disease will also be considered a PFS event.

10 REFERENCES

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M and Diehl V (2007). Revised response criteria for malignant lymphoma. J Clin Oncol 25: 579-86.

Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413.

Collett D (1994). Interval-censored survival data. Modelling survival data in medical research. Boca Raton, Fla., Chapman & Hall/CRC: 237-251.

Westfall PH and Krishen A (2001). Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. Journal of Statistical Planning and Inference 99: 25-40.

APPENDIX A: IMPUTATION OF PARTIALLY UNKNOWN ADVERSE EVENT DATES

The algorithm below should be used to impute pre-existing condition and adverse event (AE) start dates for which only partial information is known. For ease of reading, both pre-existing conditions and AEs will be referred to as AE for the remainder of this document. The algorithm should be applied to every AE record on a record by record basis. AE start dates should be imputed before imputation of AE condition end date in all cases. The AE condition end date should only be used in the imputation of the AE start date if it a full known date.

- AE day and month are missing:
    - If the year is the same as the year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was pre-dose:
- AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of investigational agent)
    - If the year is the same as the year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was post-dose:
- AE start date will be imputed as the minimum of (AE condition end date*, first dose date of investigational agent)
    - If the year is before the year of first dose of investigational agent:
- AE start date will be imputed as the minimum of (AE condition end date*, December 31st see example 2 below)
    - If the year is after the year of first dose of investigational agent:
- AE start date will be imputed as the minimum of (AE condition end date*, January 31st see example 2 below)
- AE month only is missing:
    - Treat day as missing and replace both month and day according to the above procedure
- AE day only is missing:
    - If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was pre-dose:
- AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of investigational agent)
    - If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was post-dose:

- AE start date will be imputed as the minimum of (AE condition end date*, first dose date of investigational agent)
    - If the month/year is before the month/year of first dose of investigational agent:
- AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)
    - If the month/year is after the month/year of first dose of investigational agent:
- AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

*only use condition end date if known and full end date is available.

The following algorithm should be used to impute AE condition end dates. The AE records for a condition/event should be sorted by the imputed start dates then record position (order of entry into the eCRF). After sorting, if any condition end date month/year is greater than any subsequent record end date month/year, then change the imputed start day only to end of month. Repeat as necessary.

For all records excluding the last chronological record for a condition/event:

- AE condition end date will be imputed as the start date of the subsequent record

For the last chronological record for a condition/event:

- If outcome is “recovered/resolved”, “recovered/resolved with sequelae”, or “fatal” apply the following:
    - If only year is provided for the end date and year is equal to the year of the last dose date:
        - AE condition end date will be imputed as the minimum of (last dose date + 30, death date, data extraction date, December 31st of the end date year)
    - If only year is provided for the end date and year is not equal to the year of the last dose date:
        - AE condition end date will be imputed as the minimum of (death date, data extraction date, December 31st of the end date year)
    - If month and year are provided for the end date:
        - AE condition end date will be imputed as the minimum of (death date, data extraction date, last day of the end date month/year)
- If outcome is “recovering/resolving”, “not recovered/resolved”, “unknown”, or blank:
    - AE condition end date will not be imputed.

Example 1

AESPID 1: Condition/Event HEADACHE
First dose date 01JAN2012

Prior to imputation

Start date	*Condition end date*	*Severity*	*Outcome*	*Onset*
UNUNK2011	15APR2012	1	not recovered/resolved	pre-ICF
15APR2012	UNMAY2012	2	recovering/resolving	post 1st dose
UNMAY2012	UNJUN2012	1	not recovered/resolved	post 1st dose
UNJUN2012	UNJUN2012	3	recovering/resolving	post 1st dose
UNJUN2012	10JUL2012	2	recovering/resolving	post 1st dose
10JUL2012	--	1	not recovered/resolved	post 1st dose

Post imputation

Start date	*Condition end date*	*Severity*	*Outcome*
31DEC2011	15APR2012	1	not recovered/resolved
15APR2012	31MAY2012	2	recovering/resolving
31MAY2012	30JUN2012	1	not recovered/resolved
30JUN2012	30JUN2012	3	recovering/resolving
30JUN2012	10JUL2012	2	recovering/resolving
10JUL2012	--	1	not recovered/resolved

Example 2 (highlights choice of last day of the month as opposed to the 1st or the 15th)

AESPID 4: Condition/Event NAUSEA
First dose date 01APR2012

Prior to imputation

Start date	*Condition end date*	*Severity*	*Outcome*	*Onset*
UNUNK2011	25APR2012	1	not recovered/resolved	pre-ICF
25APR2012	UNAPR2012	2	recovering/resolving	post 1st dose
UNAPR2012	04MAY2012	1	recovered/resolved	post 1st dose

Post imputation

Start date	*Condition end date*	*Severity*	*Outcome*
31DEC2011	25APR2012	1	not recovered/resolved
25APR2012	31APR2012	2	recovering/resolving
31APR2012	04MAY2012	1	recovered/resolved