STATISTICAL ANALYSIS PLAN

Protocol Number:	SGN35-032
Version:	Amendment 3; 10-March-2021
Protocol Title:	A dual-cohort, open-label, phase 2 study of brentuximab vedotin and CHP (A+CHP) in the frontline treatment of subjects with peripheral T-cell lymphoma (PTCL) with less than 10% CD30 expression
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APPROVAL SIGNATURES

Product:	SGN35-32 (brentuximab vedotin)
Protocol Number:	SGN35-032
SAP Version:	1
Version Date:	16-July-2021

The individuals signing below have reviewed and approve this statistical analysis plan.

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TABLE OF CONTENTS

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

LIST OF TABLES

LIST OF FIGURES

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

LIST OF ABBREVIATIONS

A+CHP	brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone
ADI	absolute dose intensity
AE	adverse event
ATA	anti-therapeutic antibodies
BICR	blinded independent central review
BV	brentuximab vedotin
cHL	classical Hodgkin lymphoma
CHP	cyclophosphamide, doxorubicin, and prednisone
CI	confidence interval
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EOS	end of study
EOT	end of treatment
FAS	full analysis set
GCP	good clinical practices
ICF	informed consent form
IDI	intended dose intensity
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	Pharmacokinetic
PR	partial response
PT	preferred term
PTCL	peripheral t cell lymphoma
RDI	relative dose intensity
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
SAE	serious adverse event

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

SCT	stem cell transplant
SMQ	standardized MedDRA query
SOC	system organ class
SPD	sum of the products of diameters
WHO	World Health Organization

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1. INTRODUCTION

Protocol SGN35-032 amendment 3, entitled "A dual-cohort, open-label, phase 2 study of brentuximab vedotin and CHP (A+CHP) in the frontline treatment of subjects with peripheral T-cell lymphoma (PTCL) with less than 10% CD30 expression", has two cohorts, positive CD30 expression (≥1% and <10%) cohort and negative CD30 expression (<1%) cohort, and will evaluate the safety and efficacy of A+CHP in subjects with non-sALCL PTCL and tumor CD30 expression <10%. This document outlines the statistical analysis methods to be implemented in this study. Results of the proposed analyses of the primary objectives will become the basis for the clinical study report (CSR) of 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 CSR. Any changes will either be reflected in amendments (to this plan) before the database lock or specifically documented in the CSR.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- To evaluate the objective response rate (ORR) per blinded independent central review (BICR) using Revised Response Criteria for Malignant Lymphoma criteria (Cheson 2007)

2.2. Secondary Objectives

- To evaluate the complete response (CR) rate following completion of study treatment (Cheson 2007)
- To evaluate progression-free survival (PFS) (Cheson 2007)
- To evaluate overall survival (OS)
- To evaluate duration of response (DOR) (Cheson 2007)
- To evaluate ORR per BICR using modified Lugano criteria (Cheson 2014)
- To evaluate the safety and tolerability

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3. STUDY ENDPOINTS

3.1. Primary Endpoints

- ORR per BICR following the completion of study treatment using Revised Response Criteria for Malignant Lymphoma criteria (Cheson 2007)

3.2. Secondary Endpoints

- Complete response rate per BICR (Cheson 2007)
- PFS per BICR (Cheson 2007)
- OS
- DOR per BICR (Cheson 2007)
- ORR per BICR, using modified Lugano criteria (Cheson 2014)
- Type, incidence, severity, seriousness, and relatedness of adverse events
- Laboratory abnormalities

3.3. Additional Endpoints

- ORR, CR rate, DOR, and PFS as assessed by the Investigator using Cheson 2007 criteria (Cheson 2007)

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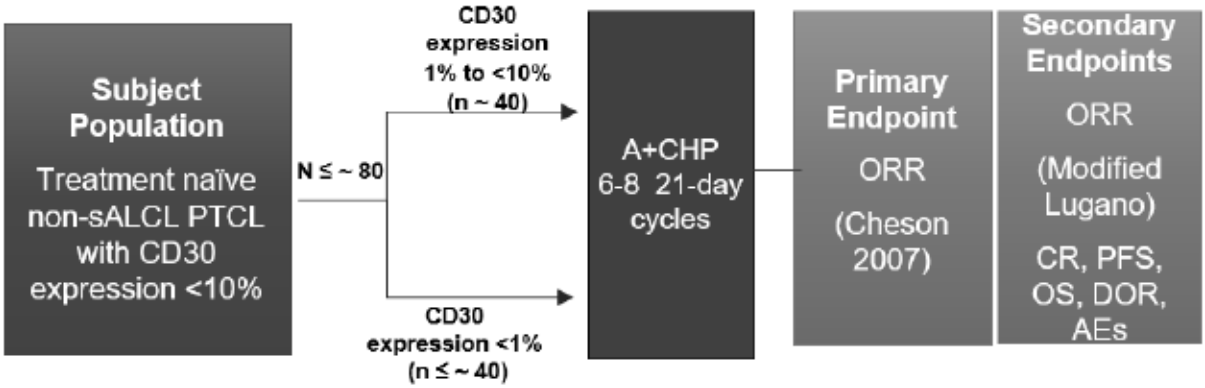
4. STUDY DESIGN

This is a dual-cohort, open-label, multicenter, phase 2 clinical trial designed to evaluate the efficacy and safety of A+CHP in subjects with non-sALCL PTCL and CD30 expression < 10%. An archived tumor biopsy specimen will be submitted to a central pathology lab for confirmation of CD30 expression. Enrollment will be based on CD30 expression per local lab assessment. Only subjects with CD30 expression <10% per central confirmation will be analyzed for the primary and secondary endpoints. Subjects will receive 21-day cycles of A+CHP for a target of 6-8 cycles.

Up to approximately 80 subjects will be enrolled in this study; approximately 40 subjects will be enrolled into the CD30 positive (1% to <10%) cohort and up to approximately 40 subjects will be enrolled into the CD30 negative (<1%) cohort. A study schema is provided in Figure 1.

Figure 1: Study design



5. ANALYSIS SETS

5.1. Full Analysis Set (FAS)

The FAS includes all subjects who receive any amount of brentuximab vedotin or any component of CHP. The full analysis set will be used for efficacy analyses and safety analyses. Demographics and baseline disease characteristics will be summarized based on FAS, unless specified otherwise.

5.2. Intent to Treat Set (ITT)

The ITT set will include all enrolled subjects, regardless of whether subjects receive any amount of brentuximab vedotin or any component of CHP after the completion of enrollment.

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6. STATISTICAL CONSIDERATIONS

6.1. General Principles

Unless otherwise specified, all summary and analyses will be provided by cohort, CD30 negative (<1%) and CD30 positive (≥1% and <10%) per central confirmation. The summary with two cohorts combined may be presented as appropriate.

Similar summaries for selected endpoints will be provided based on CD30 expression by local evaluation. For subjects with central CD30 ≥10% and local CD30 <10%, if any, their data will be listed, but may not be summarized if the number of such subjects is not sufficiently large.

Descriptive comparison of results from the two cohorts (CD30 <1% and CD30 ≥1% to <10%) in this study with historical data in non-ALCL subjects in ECHELON-2 study will be performed separately to demonstrate consistency.

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be used to describe continuous variables. Frequencies and percentages will be used to describe categorical variables. Confidence intervals (CIs) may be presented to describe precision of estimates. The median survival time will be calculated as the smallest observed time for which the value of the estimated survival function is less than or equal to 0.5.

Unless otherwise specified, all CIs will be performed using a two-sided alpha of 0.05. No multiple comparisons are planned and no alpha adjustment is needed because no formal hypotheses are being tested.

All statistical tables, listings and figures will be produced using SAS®, version 9.4 or more recent. Other statistical software, if used, will be described in the CSR.

6.2. Determination of Sample Size

The study is designed to estimate the ORR at a reasonable level of precision. Up to approximately 80 non-sALCL PTCL subjects will be enrolled in this study, with up to approximately 40 subjects in the CD30 negative (<1%) cohort and up to approximately 40 subjects in the CD30 positive (1% to <10%) cohort.

In the CD30 positive (1% to <10%) cohort with 40 subjects, if 28 responses are observed, the estimated ORR would be 70%, and the associated 2-sided 95% CI using the Clopper-Pearson method would be (53.5%, 83.4%). Additional possible response rates and the associated 95% confidence intervals are shown in Table 1.

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

Table 1: Response rates and associated 95% confidence intervals

N	Observed Responses	Response Rate	2-sided 95% CI using the Clopper-Pearson method
40	30	75%	(58.8%, 87.3%)
40	28	70%	(53.5%, 83.4%)
40	24	60%	(43.3%, 75.1%)
40	20	50%	(33.8%, 66.2%)

6.3. Randomization and Blinding

Not applicable; this is an open-label, single-arm study.

6.4. Data Transformations and Derivations

Age in years will be based on self-reported ages. 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 of Brentuximab Vedotin, Cyclophosphamide, Doxorubicin, and Prednisone.

Other time variables based on two 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

The end-of-treatment (EOT) date will be the date the EOT visit is performed; if an EOT visit is not performed then the EOT date will be either the EOS date or 30 days after the last dose of study drug, whichever is earlier.

Baseline values will be the most recent non-missing measurement prior to the first dose of Brentuximab vedotin, Cyclophosphamide, Doxorubicin or Prednisone, whichever is earlier, on this study.

The change from baseline is the post-baseline value minus the baseline value:

(Post-baseline Value – Baseline Value)

For efficacy assessments, the date of response will be the latest of all radiologic scan dates for the given restage assessment. The date of progression will be the earliest of all radiologic scan dates for the given restage assessment.

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6.5. Handling of Dropouts and Missing Data

With the exceptions noted below, missing data will not be imputed.

AE start dates will be imputed for the purpose of calculating duration of events and treatment-emergent status (see Appendix A for AE partial date imputation and Appendix B for treatment-emergent definition). Censoring for time-to-event endpoints (eg. PFS and DOR) will be described in Section 7 with each planned analysis, as applicable. Subjects whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate and ORR.

6.6. Multicenter Studies

Site-to-site variation will not be adjusted in the analysis. Although there are multiple sites in this study, it is not anticipated that any site will accrue enough subjects to warrant an analysis by site.

6.7. Multiple Comparison/Multiplicity

No multiple comparisons are planned, and no alpha adjustment is needed because no formal hypotheses are being tested.

6.8. Examination of Subgroups

As exploratory analyses, subgroup analyses may be performed for selected endpoints for each cohort, where the sizes of subgroups are not too small (eg. at least 10 subjects in each subgroup per cohort). Subgroups may include, but are not limited to, the following:

- Age (< median, ≥ median)
- Sex (male, female)
- Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0, ≥1)

6.9. Covariates

This is a phase 2, open-label study. Covariates are not considered for adjustment in the analyses.

6.10. Timing of Analyses

No formal interim analyses are planned for this study.

The database cutoff date for the primary analysis will be conducted when all treated subjects in the CD30 positive (≥1% and <10%) cohort have been followed for at least 6 months, discontinued from study, or had 30 days safety follow-up after PD, whichever comes first.

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7. PLANNED ANALYSES

7.1. Disposition

An accounting of study subjects by disposition will be tabulated by cohort and total using all enrolled subjects. Subjects who withdraw from the study will be summarized by primary reason for withdrawal and will be listed with the timing and reason for withdrawal. Subjects who have entered and are still in long term follow-up will also be summarized. A listing of disposition data will be provided for all enrolled subjects.

The number of subjects who signed informed consent, the number of subjects in each analysis set, and the number of subjects enrolled at each site and country will be summarized for all enrolled subjects.

7.2. Demographic and Baseline Characteristics

Demographics and baseline characteristics (including age, gender, ethnicity, race, baseline weight, and ECOG score) will be summarized by cohort using the FAS.

Disease specific characteristics will be summarized by cohort using the FAS. These characteristics include, but are not limited to, the following: age, gender, disease diagnosis, time from initial diagnosis to the first dose of study drug on this study, CD30 expression level per local assessment, CD30 expression level per central confirmation, baseline B symptoms, baseline sum of the products of the largest diameters (SPD).

Listings of demographics, and disease characteristic will be provided for the full analysis set.

7.3. Important Protocol Deviations

Important Protocol deviations (defined as protocol violations by Seagen) 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. A list of subjects with important protocol deviations will be presented. Protocol deviations that may affect the study results will be reviewed prior to the database lock.

7.4. Treatment Administration

Treatment administration will be summarized by cohort using the FAS. Summary statistics will be presented for duration of treatment (weeks), and number of cycles. Additionally, number and percent for the number of doses received will be presented. Cumulative dose and average dose per cycle will be summarized in mg and mg/kg for intended dose intensity (IDI), absolute dose intensity (ADI), and relative dose intensity (RDI). The number and percentage of subjects whose dose was ever modified will be summarized by modification type, cycle and overall.

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

Duration of treatment for IV-administrated 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 Day 1 dose date of the last cycle, 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 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 prednisone, IDI is defined as 500 mg/ weeks=166.67 mg/week.

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

RDI is defined as the absolute dose intensity over the intended dose intensity.

ADI/IDI * 100.

Example 1:

For brentuximab vedotin, consider a subject with an intended dose of 1.8 mg/kg who is treated for three cycles (i.e., 9 weeks) where the weight in the electronic case report form used for calculating the dose of infusion was 50 kg. The second dose was delayed for one week, and for the third cycle, the infusion was not completed and the subject 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	90	90	3 weeks + 1 week delay
C2D1	1.8	90	90	3 weeks
C3D1	1.8	90	45	3 weeks

ADI (per week):

=(1.8 + 1.8 + ([45/90] *1.8)) / (3 wks + 1 wk delay + 3 wks + 3 wks) mg/kg per week

= .45 mg/kg per week

RDI:

=0.45/.6 * 100

=75%

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

Example 2:

For prednisone, consider a subject treated with A+CHP for six cycles. The second cycle was delayed for one week, and for the fourth cycle and beyond the subject 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%

A listing of study drug administration on study will be provided.

7.5. Efficacy Analyses

All efficacy analyses will be presented by cohort using the full analysis set. Analyses may also be performed using the subgroups listed in Section 6.8.

7.5.1. Efficacy Endpoints

7.5.1.1. Objective Response Rate

The primary endpoint is objective response rate (ORR) per BICR 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 criteria (Cheson 2007). ORR is defined as the proportion of subjects with CR or PR. Subjects whose response to treatment cannot be adequately assessed according to the specified criteria will be classified as non-responders for the purpose of calculating ORR. The ORR will be summarized by cohort and an exact two-sided 95% CI will be calculated, using the Clopper-Pearson method (Clopper 1934).

The primary analysis on the primary endpoint will be conducted based on the Full Analysis Set with CD30 expression <10% per central confirmation. In the event that there are subjects

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who are enrolled but not treated, a sensitivity analysis will be performed based on ITT set, where the subjects who are enrolled but not treated are counted "non-responders" in the ORR calculation.

The ORR will also be evaluated by BICR per modified Lugano criteria (Cheson 2014) as a secondary endpoint (See Appendix C for details on response assessment according to the Modified Lugano Criteria). In addition, ORR will be assessed by investigator using Revised Response Criteria for Malignant Lymphoma Criteria (Cheson 2007). The ORRs based on these criteria will be summarized similarly.

Up to 6 of the largest dominant nodes or nodal masses will be quantitatively identified at baseline based on the product of diameters (Cheson 2007). The nodes or nodal masses being followed for response assessment will also be quantitatively assessed at each pre-specified time point. SPD of these nodes or nodal masses is defined as the sum of the products of diameters from those nodes or nodal masses being followed for response assessment. The SPD changes from baseline, as well as the SPD change from the previous response assessment (as applicable), at each assessment visit for each subject will be derived. Baseline SPD and the number of subjects with SPD reduction from baseline will be summarized. The maximum percent reduction in SPD from baseline (or minimum percent increase if there is no reduction), will also be summarized and graphically displayed for each subject (e.g., using a waterfall plot).

Listings for tumor evaluation and response data will be provided.

7.5.1.2. Complete Response Rate

CR rate is defined as the proportion of subjects with CR following the completion of study treatment (at EOT) according to Revised Response Criteria for Malignant Lymphoma Criteria (Cheson 2007). Subjects whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate. CR by BICR as secondary endpoint and CR by investigator as additional endpoint will be summarized by cohort.

CR rate will be summarized using descriptive statistics and an exact two-sided 95% CI will be calculated using the using the Clopper-Pearson method (Clopper 1934).

7.5.1.3. Duration of Response

Duration of response is defined as the time from start of the first documentation of objective tumor response (CR or PR), according to Revised Response Criteria for Malignant Lymphoma Criteria (Cheson 2007), to the first documentation of objective tumor progression or to death due to any cause, whichever comes first.

Duration of response data will be censored as described below:

- Subjects who do not have objective tumor progression and are still on study at the time of an analysis will be censored on the day following the date of the last radiological disease assessment of measured lesions documenting absence of PD.

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- Subjects who are given antitumor treatment other than the study treatment or stem cell transplant (includes donor lymphocyte infusion) prior to documentation of disease progression will be censored on the day following the date of the last radiological disease assessment prior to the start of new therapy.
- Subjects who are removed from study prior to documentation of objective tumor progression will be censored on the day following the date of the last radiological disease assessment of measured lesions documenting absence of PD.

Duration of response will be estimated using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by cohort. The median duration of response and its two-sided 95% CI using the log-log transformation method (Collett 1994) will be calculated. Duration of responses by BICR as secondary endpoint and DOR by investigator as additional endpoint are to be summarized by cohort.

7.5.1.4. Progression-Free Survival

PFS is defined as the time from start of study treatment to first documentation of objective tumor progression according to Revised Response Criteria for Malignant Lymphoma criteria (Cheson 2007) or to death due to any cause, whichever comes first.

Specifically,

PFS = Date of first documented PD or death – Date of first dose of study treatment + 1.

PFS data will be censored as described in Table 2:

Table 1: PFS Event and Censoring Rules

Situation	Date of Event or Censoring	Outcome
No baseline assessment and/or post baseline tumor assessment	Date of first dose	Censored
Progression documented between scheduled visits	Date of earliest of all radiologic scan dates for the given restage assessment	Event
No documented progression	Date of last visit with adequate response assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate tumor assessment	Censored
New anticancer treatment (with the exception of SCT) started with no claim of progression	Date of last visit with adequate tumor assessment prior to start date of new anticancer therapy	Censored
Death before first PD assessment	Date of death	Event
Death between adequate assessment visits or after subject misses one assessment visit	Date of death	Event
Death after an extended lost-to-follow-up time (two or more missed assessments)	Date of last visit with adequate tumor assessment	Censored

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

Situation	Date of Event or Censoring	Outcome
Death or progression after more than one consecutively missed tumor assessment	Date of last adequate tumor assessment prior to missed visits or Study Day 1 in the absence of a post-baseline tumor assessment prior to missed visits	Censored

PFS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by cohort. The median PFS and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated. PFS by BICR as secondary endpoint and PFS as additional endpoint by investigator are to be summarized by cohort.

7.5.1.5. Overall Survival

OS is defined as the time from date of first dose to date of death due to any cause. Specifically,

OS=Date of death – Date of first dose + 1.

In the absence of confirmation of death, overall survival time will be censored at the last date the subject is known to be alive (i.e., date of last contact). The last contact date will be derived based on data points including, but not limited to, start/end dates from subsequent cancer-related therapy, last date subject known to be alive from Long-term follow-up assessment, and end of study date. Subjects lacking data beyond the date of first dose will have their overall survival time censored to 1 day.

OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by cohort. The median OS and its two-sided 95% CI using the log-log transformation method (Collett 1994) will be calculated if the median is reached.

7.5.2. Safety Analyses

The FAS will be used to summarize all safety endpoints. AEs will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

Laboratory values will be graded using NCI CTCAE, Version 4.03.

Concomitant medications will be coded using WHODrug Global version 2021MarB3 or higher.

Adverse Events

AEs will be summarized by descending frequency of MedDRA preferred term unless otherwise specified. For incidence reporting, if a subject reports more than one AE that was coded to the same SOC or PT, the subject will be counted only once for that specific SOC or PT. For summaries by maximum severity, multiple occurrences of events at each SOC or PT within a subject are counted only once at the highest severity.

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

A treatment-emergent AE (TEAE) is defined as a newly occurring or worsening AE after the first dose of Brentuximab Vedotin, Cyclophosphamide, Doxorubicin or Prednisone on the current study through the end of the safety reporting period. Unless documented as a pre-existing condition, AEs with unknown start date will be counted as treatment-emergent. See Appendix B for details regarding treatment-emergent classification.

A summary of AEs will be provided by cohort for the following:

- Pre-existing AEs
- All TEAEs
- TEAEs related to brentuximab vedotin
- TEAEs related to CHP
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent SAEs related to brentuximab vedotin
- Treatment-emergent SAEs related to CHP
- TEAEs leading to dose modification of brentuximab vedotin
- TEAEs leading to dose modification of cyclophosphamide or doxorubicin
- TEAEs leading to treatment discontinuation
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum severity. At each SOC or PT, multiple occurrences of events within a subject are counted only once at the highest severity
- Grade 3 - 5 TEAEs
- Infusion related reactions by preferred term
- Summary of TEAEs of peripheral neuropathy (standardized MedDRA query [SMQ])
- Summary of onset of treatment emergent peripheral neuropathy (SMQ)
- Summary of improvement and resolution of treatment-emergent peripheral neuropathy (SMQ)

Listings will be presented for all AEs, SAEs, AEs leading to treatment discontinuation, and AEs leading to death.

Peripheral neuropathy

Peripheral Neuropathy (PN) is defined by the PN MedDRA SMQ broad search. The incidence of PN at baseline will be summarized. The incidence of treatment-emergent and treatment-related PN will each be summarized by PT and severity. The incidence of PN leading to treatment discontinuation or requiring dose modification will be summarized. Time to onset, resolution, and improvement of PN events will be summarized.

Subjects with any event of treatment-emergent PN will be categorized into groups according to the following criteria:

- Resolution of all events
- At least 1 event resolved, but all other PN events did not improve

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

- Improvement of at least 1 event
    - All events either improved or resolved
    - Some events improved, some events resolved and some events neither improved nor resolved
    - Some events improved but no events resolved
- No improvement or resolution of any events

The number of subjects will be summarized for the categories defined as above.

Resolution of selected AEs will be defined as event status of recovered/resolved or recovered/resolved with sequelae; or return to baseline or lower severity as of the latest assessment for pre-existing events. The date of resolution is defined as follows: for events with an onset after the first dose date, if event outcome is "recovered/resolved" or "recovered/resolved with sequelae", then the date of resolution is the event end date; for events ongoing at baseline, if event severity returns to baseline severity or lower as of the last recorded severity, then the date of resolution is the date of severity change to baseline or lower severity.

For events that are not resolved, improvement is defined as decrease by at least one grade from worst grade as of the latest assessment. The date of improvement is defined as follows: for events that did not resolve and decrease by one grade or more from the worst post-baseline severity as of the last recorded severity (i.e., severity did not subsequently worsen), then the date of improvement is the start date when the post-baseline grade becomes lower than the worst grade for the first time without any subsequent grade(s) equal to the worst grade.

Time to resolution is computed from start date of first treatment emergent episode of the event or start date of newly onset event after first dose of treatment drug to date of resolution. Time to improvement is computed from start date of the worst grade of the event. Time to resolution /improvement will be summarized at the event level.

For summaries of events or summaries of subjects with events ongoing at EOT, EOT is defined as the EOT visit or 30 days after the last dose of the study drug, whichever occurred later.

Time to onset of TEAEs is defined as time from the date of first dose to start date of first treatment emergent episode of the event or start date of newly onset event after first dose of treatment drug. In the analyses of time to onset by grade, the events should be excluded where the specified grade only occurs after a higher grade.

7.5.3. Clinical Laboratory Parameters

Clinical laboratory data (CBC with differential and serum chemistry panel) will be summarized by cohort. Both observed data and changes from baseline will be summarized

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

with descriptive statistics. In addition, laboratory data will be summarized by the worst post-baseline grade, by NCI CTCAE v4.03 for each parameter.

Laboratory results and NCI CTCAE grades will be presented in data listings. All laboratory results through the end of treatment visit will be presented in standardized units.

7.5.4. ECOG Performance Status

ECOG data will be listed by subject.

7.5.5. Concomitant Medications

Concomitant medications will be summarized by the WHO Drug substance name and listed by subject. The number and percentage of subjects taking concomitant medications from screening through the end of the on-study period will be tabulated by cohort.

7.5.6. 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, and relationship to disease will be summarized by cohort and total. Death information will be listed by subject.

8. INTERIM ANALSES

No formal interim analyses are planned.

9. CHANGES FROM PLANNED ANALYSES

9.1. Changes from the Original Protocol

Not applicable

9.2. Changes from the Original SAP

Not applicable

10. REFERENCES

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090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

11. APPENDICES

APPENDIX A. IMPUTATION OF PARTIALLY UNKNOWN ADVERSE EVENT DATES

For an adverse event (AE) with a partial start or end date, if it can be determined that the event occurred prior to the date of first dose of study treatment, the partial date will not be imputed; Otherwise, the partial date will be imputed using the rules described below. AE start dates should be imputed before imputation of AE condition end date in all cases.

Incomplete AE Start Date:

AE day only is missing

If the month/year is the same as the month/year of first dose of any study treatment:

AE start date will be imputed as the first dose date of any study treatment

If the month/year is after the month/year of first dose of any study treatment:

AE start date will be imputed as the first day of the month

AE day and month are missing, or month only is missing

If the year is the same as the year of first dose of any study treatment:

AE start date will be imputed as the first dose date of any study treatment

If the year is after the year of first dose of any study treatment:

AE start date will be imputed as January 1st

AE day, month and year are missing, or year only is missing

AE start date will be imputed as the first dose date of any study treatment

If AE condition end date* is not missing, and the imputed start date is after the end date, the start date will be set to the AE condition end date.

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

Incomplete AE End Date:

If AE outcome is "not recovered/resolved", "unknown", or blank: AE condition end date will not be imputed.

If AE outcome is "recovering/resolving", "recovered/resolved", "recovered/resolved with sequelae", or "fatal" apply the following:

AE day only is missing

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

AE condition end date will be imputed as the minimum of (death date, data extraction date, last day of the end date month/year, EOS date)

AE day and month are missing, or month only is missing

If the 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, EOS date)

If the 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, EOS date)

AE day, month and year are missing, or year only is missing

AE condition end date will not be imputed

Within a single record, if the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Example

AE Number 4: Condition/Event NAUSEA
First dose date 02APR2012

Prior to imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	UNAPR2012	2	recovering/resolving
2	UNAPR2012	04MAY2012	1	recovered/resolved

Post imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	30APR2012	2	recovering/resolving
2	02APR2012	04MAY2012	1	recovered/resolved

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

APPENDIX B. DEFINITION OF THE TERM "TREATMENT-EMERGENT" WITH RESPECT TO AE CLASSIFICATION

The algorithm below should be used to determine whether an AE is classified as a treatment-emergent adverse event TEAE. A TEAE is defined as any AE which worsens in severity during the safety reporting period or is newly occurring at any time, where newly occurring means that the AE was not present at baseline. For ease of reading, both pre-existing conditions and AEs will be referred to as AEs for the remainder of this document. AE dates should be imputed in accordance with the algorithm detailed in Appendix A prior to determination of TEAE classification. Details of the TEAE classification are as follows:

1. For each subject, determine the first dose date, which is the earliest date the subject receives any amount of study drug.
2. **Baseline AEs:** classify an AE record as baseline AE if it satisfies both criteria a and b below:
   a. AE onset satisfies either of i, ii or iii below:
      i. Onset date is prior to the first dose date
      ii. Onset date is the same as the first dose date, and Onset Period is "started after consent but before the first dose of any study treatment" or Onset Time Relative to Study Treatment is "started before first infusion or before infusion on any dosing day"
      iii. Onset Period is "started before the signing of consent" or "started after consent but before the first dose of any study treatment"
   b. AE end date satisfies either of i or ii below:
      i. End date is the same as or after the first dose date
      ii. End date is missing with outcome equal to
         – recovering/resolving, or
         – not recovered/not resolved, or
         – unknown or missing
3. **Post-baseline AEs:** classify an AE record as post-baseline AE if it meets either of criteria a, b or c below:
   a. Onset date is after the first dose date
   b. Onset date is the same as the first dose date, and Onset Period is "started after the first dose of any study treatment" or Onset Time Relative to Study Treatment is not "started before first infusion or before infusion on any dosing day"
   c. Onset Period is "started after the first dose of any study treatment"
4. **TEAE flag** will be derived as follows:
   a. For all AE records that have an end date prior to the first dose date, assign TEAE flag to 'N'

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

b. For all baseline AEs, assign TEAE flag to 'N'

c. For post-baseline AEs:

- If the post-baseline AE is a continuing event of a baseline AE (i.e., events with the same AE identifier, where AE identifier is the number before the colon in SDTM AE.AESPID), then compare the post-baseline AE to the most recent baseline AE with the same AE identifier (to be referred to as "baseline AE" below). Assign TEAE flag to 'Y' for the applicable post-baseline AE records if a post-baseline AE record meets any of the following worsening criteria based on relatedness, seriousness or CTCAE grade:
  - If the post-baseline AE is related to treatment, or
  - If the post-baseline AE meets the criteria for an SAE and the most recent baseline AE was not an SAE, or
  - If the post-baseline AE has a higher CTCAE grade

  All subsequent episodes of the same AE should have TEAE flag = 'Y'.
- Otherwise, assign TEAE flag to 'N'
- If the post-baseline AE is not a continuing event of a baseline AE, then assign TEAE flag to 'Y'

NOTE: For summaries which include only treatment emergent AEs, include all AEs which have at least one record classified as a TEAE as well as those AEs for which TEAE status could not be determined (e.g., the value of the TEAE variable may be missing if the event cannot be identified as baseline or post-baseline – missing information on the AE CRF should be queried). Only exclude those AEs which were determined to not be treatment emergent for all records.

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

APPENDIX C. INTEGRATED PET AND CT RESPONSE ACCORDING TO MODIFIED LUGANO CRITERIA

The primary determination of antitumor efficacy will be ORR according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas modified to take into account CT response in the event of a PET PR (modified Lugano criteria). The disease assessment on the basis of PET and CT response according to modified Lugano criteria is summarized in the table below:

PET Response	CT Response		Integrated Response
CR	Any		CR
PR	CR, PR		PR
	Non-CR, Non-PR		SD
SD	Any		SD
PD	Any		PD
	Prior PET response[a]	CT Response	
Not done or	CR	Non-PD	CR[b]
Not evaluable	non-CR	Non-PD	NE
	Any	PD	PD
No FDG-avid disease at baseline [c]	No disease present (NE)		NE
	PD		PD

NE=not evaluable.

a "Prior PET response" refers to the latest prior PET assessment that was evaluable. PET responses may be carried forward over multiple CT assessments.

b A CR according to PET will be carried forward irrespective of CT response, until CT shows PD or is assessed as NE.

c Per protocol all subjects must have FDG-avid disease at baseline.

090177e1a130ae61\Approved\Approved On: 17-Jul-2021 01:35 (GMT)

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