STATISTICAL ANALYSIS PLAN

Protocol Number:	SGN35-028
Version:	Amendment 3; 4-May-2020
Protocol Title:	A phase 2, multicenter, single-arm study of retreatment with brentuximab vedotin in subjects with relapsed or refractory classic Hodgkin lymphoma (cHL) or CD30-expressing peripheral T cell lymphoma (PTCL)
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

Product:	SGN35-28 (brentuximab vedotin)
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The individuals signing below have reviewed and approve this statistical analysis plan.

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LIST OF ABBREVIATIONS

ADI	absolute dose intensity
AE	adverse event
ATA	anti-therapeutic antibodies
BICR	blinded independent central review
BV	brentuximab vedotin
cHL	classical Hodgkin lymphoma
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
RECIL	Response Evaluation Criteria in Lymphoma
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
SAE	serious adverse event
SCT	stem cell transplant
SMQ	standardized MedDRA query
SOC	system organ class
SPD	sum of the products of diameters
WHO	World Health Organization

1 INTRODUCTION

Protocol SGN35-028 amendment 3, entitled "A phase 2, multicenter, single-arm study of retreatment with brentuximab vedotin (BV) in subjects with relapsed or refractory classic Hodgkin lymphoma (cHL) or CD30-expressing peripheral T cell lymphoma (PTCL)", has two cohorts and will evaluate the safety and efficacy of BV in subjects with cHL and systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing PTCL who experienced complete response (CR) or partial response (PR) with a brentuximab vedotin-containing regimen and subsequently experienced disease progression or relapse. 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 assess the antitumor response by blinded independent central review (BICR) of BV retreatment
- To assess the safety and tolerability of retreatment with BV

2.2 Secondary Objectives

- To assess duration of tumor control, including duration of response (DOR) as determined by BICR
- To assess progression-free survival (PFS) of retreatment with BV as determined by BICR
- To assess overall survival (OS)
- To assess complete response (CR) rate per BICR
- To assess antitumor response per investigator of BV retreatment
- To assess DOR per investigator assessment
- To assess PFS per investigator assessment
- To assess CR rate per investigator assessment
- To assess ORR as determined by BICR

2.3 Additional Objectives

- To assess the Pharmacokinetic (PK) and immunogenicity of brentuximab vedotin
- To assess ORR as determined by BICR per Response Evaluation Criteria in Lymphoma (RECIL)

3 STUDY ENDPOINTS

3.1 Primary Endpoints

- BICR reporting of objective response rate (ORR) per modified Lugano response criteria (Cheson 2014)
- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Type, incidence, and severity of laboratory abnormalities

3.2 Secondary Endpoints

- BICR reporting of DOR per modified Lugano response criteria (Cheson 2014)
- BICR reporting of PFS per modified Lugano response criteria (Cheson 2014)
- OS
- Rate of CR per BICR per modified Lugano response criteria (Cheson 2014)
- Investigator reporting of ORR per modified Lugano response criteria (Cheson 2014)
- Investigator reporting of DOR per modified Lugano response criteria (Cheson 2014)
- Investigator reporting of PFS per modified Lugano response criteria (Cheson 2014)
- Rate of CR per investigator per modified Lugano response criteria (Cheson 2014)
- BICR reporting of ORR per Lugano response criteria (Cheson 2014)

3.3 Additional Endpoints

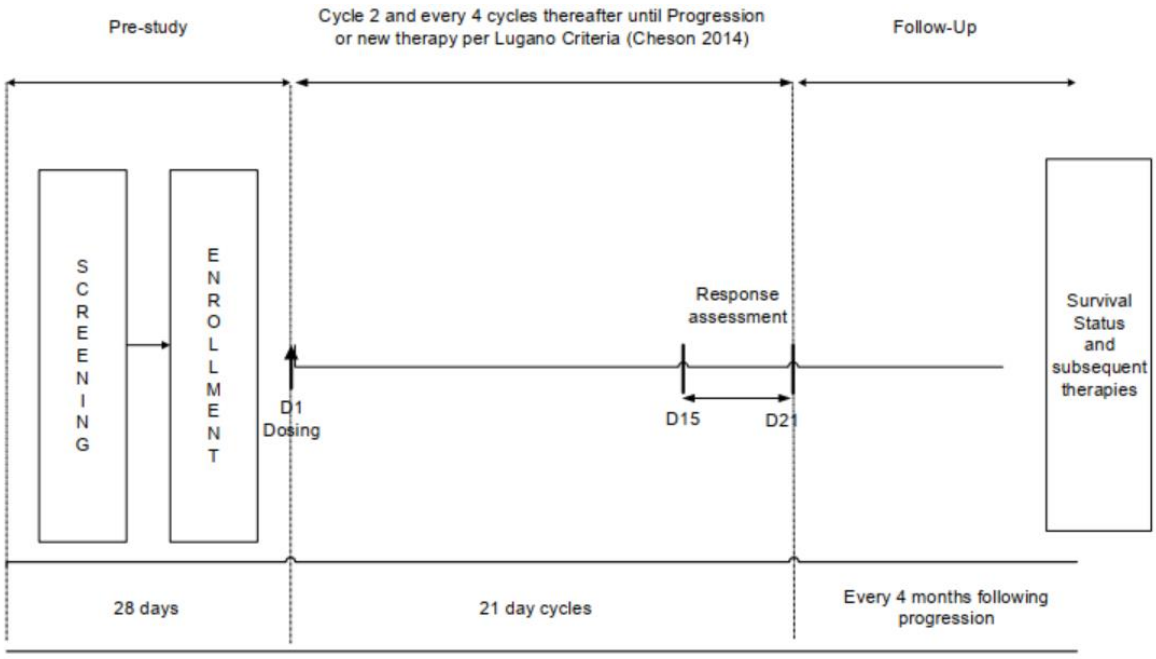
- Brentuximab vedotin PK concentrations and incidence of anti-therapeutic antibodies (ATA) to brentuximab vedotin
- BICR reporting of ORR per RECIL (Younes 2017)

4 STUDY DESIGN

This is a phase 2, multicenter, single-arm study to determine the safety and efficacy of BV in subjects with cHL, sALCL, or other CD30-expressing PTCL who demonstrated an objective response to a prior brentuximab vedotin-containing treatment regimen and subsequently experienced disease progression or relapse. It is anticipated that approximately 80 subjects will enroll in this study: approximately 40 subjects with cHL and approximately 40 subjects with CD30-expressing PTCL. In the PTCL cohort, subjects with sALCL and subjects with other CD30-expressing PTCL will both have an estimated enrollment cap of approximately 50%. Subjects will be administered 1.8 mg/kg BV intravenously (IV), up to a maximum of 180 mg, over 30 minutes once per 21-day cycle. Subjects who previously required a dose reduction due to AEs will start BV at a dose of 1.2 mg/kg and will not escalate to 1.8 mg/kg. Safety of treatment will be monitored throughout the trial via laboratory values and AE collection (Figure 1).

Subjects may continue on treatment for unlimited cycles until any of the following occur: disease progression, unacceptable toxicity, pregnancy, investigator or subject's decision, study closure, or other non-AE reason.

Figure 1: Study design



5 ANALYSIS SETS

5.1 Full Analysis Set (FAS)

The FAS includes all subjects who receive at least 1 dose of BV on this study. 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.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

Unless otherwise specified, all summary and analyses will be provided by cohort. The summary with two cohorts combined may be presented as appropriate. 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.

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.

6.2 Determination of Sample Size

It is anticipated that approximately 40 cHL and 40 CD30-expressing PTCL subjects will be enrolled in this study. This sample size was chosen to allow adequate precision of estimates of response rates.

For the cHL cohort, if 24 responses are observed, the estimated ORR would be 60%, and the associated 2-sided 95% CI using the Clopper-Pearson method (Clopper 1934) would be (43.3%, 75.1%).

For the CD30-expressing PTCL cohort, if 20 responses are observed, the estimated ORR would be 50%, and the associated 2-sided 95% CI using the Clopper-Pearson method (Clopper 1934) would be (33.8%, 66.2%). The 50% ORR for the PTCL cohort was calculated based on a weighted average of subjects with sALCL and other CD30-expressing PTCL, where subjects with sALCL have an ORR of 60% and an estimated enrollment cap of approximately 50%, and subjects with other CD30-expressing PTCL have an ORR of 40% and an estimated enrollment cap of approximately 50%.

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 calculated using informed consent date and birth date as (informed consent date - birth date)/365.25 truncated to the whole number.

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.

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 BV 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.

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 primary efficacy endpoint and selected secondary endpoints, 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)
- Best tumor response achieved with the most recent prior treatment of BV or BV-containing regimen (CR, vs non-CR)

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 primary analysis will be conducted when all treated subjects have been followed for at least 6 months, discontinued from study, or had 30 days of safety follow-up after progressive disease (PD), whichever comes first.

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 the FAS, 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: disease diagnosis, time from diagnosis to the first dose of study drug on this study, time from the most recent disease progression to the first dose of study drug on this study, time from completion of previous treatment with BV to the first dose of study drug on this study, best response to most recent prior therapy, best response to most recent prior BV therapy, baseline B symptoms, baseline sum of the products of the largest diameters (SPD).

Subsequent cancer-related therapies received after the end of the re-treatment of BV will be summarized using the FAS. These summaries include, but are not limited to, the following: use of subsequent palliative cancer-related radiotherapy, systemic therapy for progressive disease, systemic therapy for relapsed disease, maintenance, consolidative radiotherapy, systemic therapy for secondary malignancy, autologous hematopoietic stem cell transplant (SCT), allogeneic hematopoietic SCT, syngeneic stem cell transplant, number of subsequent cancer-related therapies.

Listings of demographics, baseline disease characteristics, and subsequent cancer-related therapies will be provided.

7.3 Important 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. 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 (months), 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.

Duration of treatment (except when calculating exposure) is defined as time from the first dose of BV on the study to 21 days after the last dose of the current study [(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].

IDI is defined as the intended dose of drug (mg/kg) per unit of time. For subjects whose intended dose is 1.8 mg/kg, this is 1.8 mg/kg/3 weeks = 0.6. For subjects whose intended dose is 1.2 mg/kg, this is 1.2 mg/kg/3 weeks = 0.4.

ADI is defined as the actual dose (mg/kg) per unit of time that the subject received over the entire treatment period. For the purpose of the ADI calculation, the duration of treatment is to be used is [(last dose date +21) – first dose date], including for those whose death date may be less than 21 days after the last study dose.

Example:

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. For the last treatment, 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)
C1D1	1.8	90	90
C2D1	1.8	90	90
C3D1	1.8	90	45

ADI = (1.8 + 1.8 + ((45/90) *1.8)) mg/kg / 9 weeks

≈ .5 mg/kg per week

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

ADI/IDI * 100.

A listing of BV 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) by BICR, according to the Modified Lugano Criteria for Response Assessment (Cheson 2007) (See Appendix C for details on response assessment according to the Modified Lugano Criteria). 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 ORR will also be evaluated by investigator per modified Lugano criteria (Cheson 2014) as a secondary endpoint. In addition, ORR will also be assessed according to Lugano Criteria for Response Assessment (Cheson 2014) (See Appendix C for details on response assessment according to the Lugano Criteria) per BICR and the ORR will also be assessed according to RECIL (Younes 2017) per BICR. 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).

Up to 3 target lesions will be quantitatively identified at baseline based on the longest diameters (Younes 2017). Sum of the longest diameters of these nodes or nodal masses will be summarized and graphically displayed by cohort similarly to SPD.

Listings for tumor evaluation and response data will be provided.

7.5.1.2 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 the Modified Lugano Criteria for Response Assessment (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.
- Subjects who are given antitumor treatment other than the study treatment or SCT (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.
- Subjects who have disease progression or death after missing two or more consecutive radiologic tumor assessments will be censored at the date of last visit with adequate tumor assessment prior to missed scans.

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 and DOR by investigator are to be summarized by cohort.

Duration of response will also be calculated for the subgroup of subjects with CR.

7.5.1.3 Progression-Free Survival

PFS is defined as the time from start of study treatment to first documentation of objective tumor progression according to the Modified Lugano Criteria for Response Assessment (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 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.
- Subjects who are given antitumor treatment other than the study treatment or SCT (includes donor lymphocyte infusion) will be censored on the day following the date of the last radiological disease assessment of measured lesions documenting absence of PD prior to the start of antitumor treatment.
- 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.
- Subjects lacking an evaluation of tumor response after their first dose will have their event time censored at Day 1.
- Subjects who have disease progression or death after missing two or more consecutive radiologic tumor assessments will be censored at the date of last visit with adequate tumor assessment prior to missed scans.

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 and PFS by investigator are to be summarized by cohort.

7.5.1.4 Complete Response Rate

CR rate is defined as the proportion of subjects with CR according to the Modified Lugano Criteria for Response Assessment (Cheson 2014). Subjects whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate. CR by BICR and CR by investigator 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).

7.5.1.5 Overall Survival

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

OS=Date of death – Date of enrollment + 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 Pharmacokinetics and Immunogenicity Endpoints

7.5.2.1 Pharmacokinetics

Brentuximab vedotin ADC and MMAE concentrations in serum or plasma will be measured using sensitive, qualified assays. Select PK parameters, including trough concentration (C_{trough}) and concentration and the end of infusion (C_{eoi}), will be summarized and reported by cohort using the full analysis set with available data. Brentuximab vedotin ADC and MMAE concentrations will be reported by subject at each PK sampling time point.

7.5.2.2 Antitherapeutic Antibody Incidence Rate

The ATA incidence rate is defined as the proportion of subjects free of confirmed ATA at enrollment in the current study that develop ATA at any time during the retreatment period. Overall ATA incidence will be summarized by cohort using the FAS.

Additionally, the incidence of ATA will be summarized at each collection time point.

7.6 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 22.0 or higher and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

Laboratory values will be graded using NCI CTCAE, Version 5.0 or higher.

Concomitant medications will be coded using WHODrug Global version 2020MarB3.

7.6.1 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.

A treatment-emergent AE (TEAE) is defined as a newly occurring or worsening AE after the first dose of BV on the current study. Unless documented as a pre-existing condition, AEs with unknown start date will be counted as treatment-emergent.

TEAEs are defined as TEAEs that are determined by the investigator to be related to the BV treatment on study.

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

- Pre-existing AEs

- All TEAEs
- TEAEs related to brentuximab vedotin
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent SAEs related to brentuximab vedotin
- TEAEs leading to dose delay
- TEAEs leading to dose modification
- TEAEs leading to dose elimination
- TEAEs leading to treatment discontinuation
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum 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.

7.6.1.1 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
- 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.

Motor neuropathy will be defined as PN events meeting any of the criteria below:

- Coded to a MedDRA PT of either ‘peripheral motor neuropathy’ or ‘peripheral sensorimotor neuropathy’, ‘peroneal nerve palsy’
- Verbatim AE term contains “motor”, “weakness”, or “palsy”

The incidence of treatment-emergent motor neuropathy will be summarized by PT and severity. Time to resolution and improvement of motor neuropathy events will be summarized.

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.

7.6.2 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 with descriptive statistics. In addition, laboratory data will be summarized by the worst post-baseline grade, by NCI CTCAE v5.0 or higher 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.

7.6.3 ECOG Performance Status

ECOG data will be listed by subject.

7.6.4 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.

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

8 INTERIM ANALYSIS

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

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. 2014;32(27):3059-68.

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

Collett D. Interval-censored survival data. Modelling survival data in medical research. London, Chapman & Hall. 1994:237-51.

Younes A, Hilden P, Coiffier B, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol. 2017;28(7):1436-47.

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

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

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 patient, determine the first dose date, which is the earliest date the patient 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'

    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.

Appendix C Integrated PET and CT Response According to Modified Lugano Criteria and Original 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 patients must have FDG-avid disease at baseline.

Assessment of response, according to the original (unmodified) Lugano criteria (Cheson 2014), will be undertaken in the same manner as for modified Lugano, with the exception that if the PET response is PR the integrated response will be PR, irrespective of CT response.

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