STATISTICAL ANALYSIS PLAN

Protocol Number:	SGN35-027
Version:	Amendment 6, 29-Nov-2021
Protocol Title:	Multiple Part Clinical Trial of Brentuximab Vedotin in Classical Hodgkin Lymphoma Subjects
Sponsor:	Seagen, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

Product:	Brentuximab vedotin
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The individuals signing below have reviewed and approve this statistical analysis plan.

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Date

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List of Abbreviations

ABVD	doxorubicin, bleomycin, vinblastine, and dacarbazine
AE	adverse event
AECI	adverse event of clinical interest
AN+AD	brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine
A+AVD	brentuximab vedotin, doxorubicin, vinblastine, dacarbazine
BV	brentuximab vedotin
cHL	classical Hodgkin lymphoma
CI	confidence interval
CR	complete response
CRF	case report form
CT	computed tomography
DOCR	duration of complete response
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
eCRF	electronic case report form
EOT	end of treatment
FAS	full analysis set
FDG	fluorodeoxyglucose
FN	febrile neutropenia
G-CSF	granulocyte colony stimulating factor
G-PP	G-CSF primary prophylaxis
HL	Hodgkin lymphoma
IMAE	Immune-mediated adverse event
IR	indeterminate response
IV	intravenous
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PmD	progressive metabolic disease
PN	peripheral neuropathy
PR	partial response

SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SD	stable disease
SMC	safety monitoring committee
SPD	sum of the products of the largest diameter
TEAE	treatment-emergent adverse event

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGN35-027, entitled "Multiple Part Clinical Trial of Brentuximab Vedotin in Classical Hodgkin Lymphoma Subjects". Results of the proposed analyses will become the basis of the clinical study report 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

- Part A: To assess the treatment-emergent febrile neutropenia (FN) rate in subjects with previously untreated, advanced stage, classical Hodgkin lymphoma (cHL) treated with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) and granulocyte colony stimulating factor (G-CSF) primary prophylaxis (G-PP)
- Parts B and C: To assess the complete response (CR) rate at EOT with brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD) in subjects with previously untreated cHL

2.2 Secondary Objectives

Part A:

- To assess the incidence and severity of adverse events of clinical interest (AECI)
- To assess dose intensity, dose reductions, and dose delays related to any component of A+AVD
- To assess primary refractory disease rates
- To assess subsequent anticancer therapy utilization
- To assess end of treatment (EOT) complete response (CR) rates
- To assess physician-reported progression-free survival (PFS) rate at 2 years

Part B and C:

- To assess the safety and tolerability of AN+AD
- To assess the overall response rate (ORR)
- To assess the duration of response (DOR)
- To assess the duration of complete response (DOCR)
- To assess the event-free survival (EFS)
- To assess the progression-free survival (PFS)
- To assess the overall survival (OS)

3 STUDY ENDPOINTS

3.1 Primary Endpoints

- Part A: The febrile neutropenia rate in subjects treated with A+AVD and G-PP
- Part B and C: CR rate at EOT

3.2 Secondary Endpoints

Part A:

- The rates and severity of each AECI
- Mean dose intensity; the rates of dose reduction and dose delays related to any component of A+AVD
- The primary refractory disease rate
- The rates of each subsequent anticancer therapy taken by subjects
- The CR rate at EOT
- Physician-reported PFS

Part B and C:

- Incidence, severity, seriousness, and relatedness of AEs; incidence and severity of lab abnormalities
- ORR
- DOR
- DOCR
- EFS
- PFS
- OS

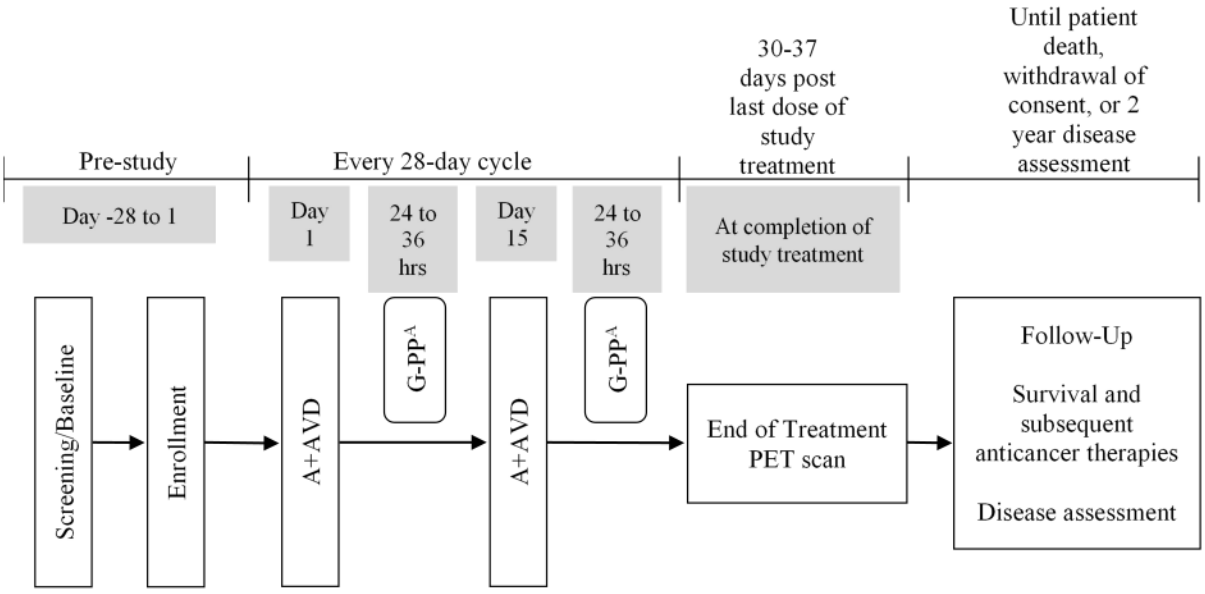
4 STUDY DESIGN

This is an open-label, multiple part, multicenter, phase 2 clinical trial. Part A will assess the incidence of febrile neutropenia, efficacy, and dose intensity in subjects receiving G PP during treatment with A+AVD. Subjects will be treated using institutional standard of care practices for the majority of treatment decisions. A+AVD will be administered as described below on days 1 and 15 of a 28-day cycle, with the addition of G-PP 24–36 hours postdose. Part B will evaluate the efficacy and tolerability of AN+AD in subjects with Stage I or II cHL with bulky mediastinal disease or Stage III or IV cHL. Part C will evaluate the efficacy and tolerability of AN+AD in subjects with Stage I or II cHL without bulky disease. AN+AD will be administered as described below. Subjects will receive up to 6 cycles of treatment in Parts A and B. Subjects in Part C will receive 4 cycles of treatment. For Part C, one interim analysis will be performed after approximately 50 subjects have completed response assessment at EOT. At this interim futility analysis, if the CR rate at EOT is ≤80% (40/50 or fewer subjects with CR at EOT), the sponsor in consultation with the Safety Monitoring Committee (SMC) may decide to stop further enrollment of the trial.

Safety will be monitored by collecting and evaluating information regarding adverse events (AEs) and laboratory test results. A SMC consisting of the study medical monitor, drug safety representative, study site investigators, and study biostatistician will evaluate the safety of AN+AD over the course of the study. Disease assessments will be conducted at Cycle 2 (Parts B and C only) and at EOT. Follow up assessments for Part A will occur per institutional standard of care and must include an EOT PET scan. For Parts B and C, disease assessments will be performed during follow-up every 3 months after the EOT visit for the first year, then every 6 months for 2 additional years. Subjects will then continue in follow-up for 2 additional years (5 years total), with physical exams required every 6 months and disease assessments required every 12 months. PET will continue after EOT if CT scan is positive, following the same schedule as CT scans. An additional safety visit will be required for Parts B and C subjects 100 days after the last dose of nivolumab or 30 days after the last dose of brentuximab vedotin (concurrent with EOT), whichever is later.

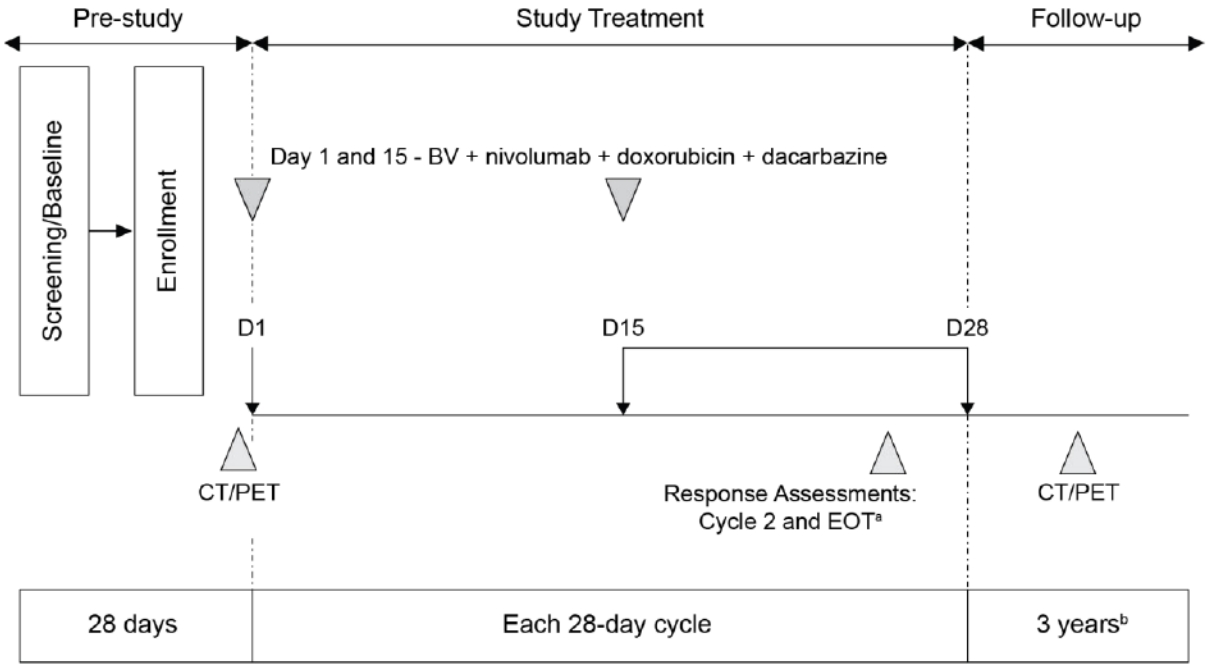
A study schema for Part A is provided in Figure 1 and for Parts B and C in Figure 2. A detailed study assessment schedule can be found in the protocol.

Figure 1: Study design – Part A



A. Note: G-PP should be started 24 to 36 hours from A+AVD and follow instructions in Protocol Section 5.4.3.

Figure 2: Study design – Parts B and C



a Response assessments will include PET and diagnostic-quality CT scan on Day 25-28 of Cycle 2, and at EOT.
b Follow-up period for Parts B and C includes 2 additional years (5 years total).

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 Full Analysis Set

For Part A, the full analysis set (FAS) includes all subjects who receive at least 1 dose of A+AVD (any of the study drugs in the regimen). The FAS will be used for all safety and efficacy analyses. Subject demographics and baseline disease characteristics will be summarized based on FAS.

For Parts B and C, the full analysis set will include all subjects who are enrolled and receive any amount of the combination therapy in the study. A subject is considered enrolled if he/she has met all criteria for participation in the study and has Seagen Inc. approval as documented in the eCRF. The full analysis set will be used as the primary dataset for efficacy and safety analysis. Subject demographics and baseline disease characteristics will be summarized based on the full analysis set.

5.2 Per-Protocol (PP) Analysis Set

For Part A, the per-protocol analysis set (PPS) includes all FAS subjects who received G-PP and did not have any important protocol deviations. The PPS will be used for the analysis for primary endpoint and may be used for analyses for selected secondary endpoints.

5.3 Efficacy-Evaluable (EE) Analysis Set

The Efficacy-Evaluable (EE) set includes all treated subjects who had a baseline disease assessment and completed EOT response assessment.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

Unless otherwise specified, all summary and analyses will be provided by part. All analyses will be descriptive; however, confidence intervals (CIs) may be presented to describe precision of estimates.

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 CIs will be calculated at two-sided 95% level. No multiple comparisons are planned, and no alpha adjustment is needed in this phase 2 study.

Any analysis not described in this plan will be considered exploratory and will be documented in the clinical study report (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 output will be produced using SAS®, version 9.4 or more recent. Other statistical software, if used, will be described in the clinical study report.

6.2 Determination of Sample Size

For Part A, approximately 40 subjects will be enrolled in order to provide an adequate level of precision for the estimate of the FN rate. If 4 of 40 subjects experience FN, the FN rate is 10% with 95% CI (2.8%, 23.7%) based on the exact Clopper-Pearson method (Collett 1991); if 2 of 40 subjects experience FN, the FN rate is 5% (95% CI: 0.6%, 16.9%); if 6 of 40 subjects experience FN, the FN rate is 15% (95% CI: 5.7%, 29.8%).

For Part B, approximately 50 subjects will be enrolled in order to provide an adequate level of precision for the estimate of the CR rate at EOT. If 45 of 50 subjects have a CR at EOT, the CR rate at EOT is 90% with 95% CI (78.2%, 96.7%) based on the exact Clopper-Pearson method (Collett 1991); if 42 of 50 subjects have a CR at EOT, the CR rate at EOT is 84% (95% CI: 70.9%, 92.8%); if 48 of 50 subjects have a CR at EOT, the CR rate at EOT is 96% (95% CI: 86.3%, 99.5%). The 73% CR rate at EOT observed in the A+AVD arm in the ECHELON-1 trial was considered the relevant benchmark when determining an appropriate sample size for Part B (Connors 2018).

For Part C, approximately 150 subjects will be enrolled in order to provide adequate power to reject the hypothesis that CR rate at EOT is $\leq 90\%$. Assuming a CR rate of 95%, 150 subjects would provide approximately 80% power to reject the null hypothesis of a CR rate at EOT $\leq$

90% with a 1-sided alpha = 0.05 and using an empirical variance estimate (East® v6.4). This sample size calculation accounts for the interim futility analysis which is further described in Section 8.

6.3 Randomization and Blinding

Not applicable.

6.4 Data Transformations and Derivations

6.4.1 General

Reported age in years will be used; if not available, age in years will be calculated with the SAS INTCK function (with method specified as "continuous") 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 study drug.

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

Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study drug.

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 any study drug, whichever is earlier.

6.4.2 Response Assessment

In Part A, the determination of antitumor activity will be based on response assessments made according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014). In Parts B and C, the determination of antitumor activity will be based on objective response assessments made according to Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014) with the incorporation of Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016).

Progressive metabolic disease (PmD), no metabolic response (NmR), partial metabolic response (PmR), or complete metabolic response (CmR) will be determined using PET-based response at each assessment. If only CT-based assessment is performed, response will be categorized as progressive disease (PD), stable disease (SD), partial response (PR), or complete

response (CR). In Parts B and C, if tumor flare or pseudo-progression is suspected, a determination should not be made at that time. PmD/PD includes radiological evidence of progression per Lugano classification criteria (Part A); for Parts B and C, incorporate LYRIC. If clinical progression is determined by the investigator, radiographic staging should also be performed to determine response assessment per Lugano classification criteria. The PET scan metabolic uptake will be graded using the Deauville 5-point scale (Barrington 2010; Biggi 2013) with a score of ≤3 considered to represent a complete metabolic response. Both PET and CT scanning will be required until disease is PET negative; responses will then be followed by CT scan of diagnostic quality only.

Treatment with checkpoint inhibitors, such as nivolumab in Parts B and C, can result in false positive PET imaging. LYRIC criteria recommend repeat PET imaging and/or biopsy within 12 weeks to further evaluate PET-positive (D4 or D5) lesions identified at the EOT response assessment. Repeat PET imaging and/or biopsy within 12 weeks is required to further evaluate PET-positive PD.

If tumor flare or pseudo-progression is suspected by the investigator during subject treatment in Parts B or C, then a clinical response of indeterminate response (IR) will be determined until subsequent evaluation of radiographic imaging or biopsy confirms or refutes PD. There are 3 categories of IR, as follows:

1. IR1: An increase in overall tumor burden (as assessed by the sum of the products of the largest diameter [SPD]) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration;
2. IR2: Appearance of new lesions, or growth of 1 or more existing lesion(s) ≥50% at any time during treatment, occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during treatment; and
3. IR3: An increase in FDG uptake using the 5-Point Scale per the Deauville Criteria of 1 or more lesion(s) without a concomitant increase in lesion size or number.

See Appendix F of study protocol for further details and criteria for follow-up of a determination of IR.

For subjects with an IR, investigators should use clinical judgement to determine the appropriate course of action for further evaluation. Repeat imaging should be performed according to the Schedule of Events (or sooner if clinically indicated), and PD must be confirmed or refuted based on LYRIC follow-up criteria for IR (Cheson 2016). In addition, biopsy of sites of disease involvement should be strongly considered.

If a subject has a second determination of IR, then subsequent repeat imaging should be performed between 4 and 8 weeks (or earlier if clinically indicated). Follow-up radiographic assessment for subjects with IR is not required if a follow-up biopsy has been performed that

confirms the subject's response. If the subject continues in follow up after confirmation, subsequent follow-up visits should be per the schedule of events.

6.5 Handling of Dropouts and Missing Data

With the exception of the scenarios covered in this section, missing data will not be imputed.

AE dates will be imputed for the purpose of calculating duration of events and treatment-emergent status (see 0 for imputation details and 0 for treatment-emergent definition). Censoring will be described in Section 7 with each planned analysis, as applicable.

Unless otherwise specified, if the numeric value of a laboratory test is not available because it is below the lower limit of quantification (LLOQ), the result will be analyzed as equal to the LLOQ when a numeric value is required (e.g., calculating the mean) and be listed as "< LLOQ" in the listings.

6.6 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.

6.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed in this phase 2 study.

6.8 Examination of Subgroups

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

- Age (12–17 years, 18–64 years, ≥65 years old)
- Age (12-40 years, >40 years old)
- Gender (Male, Female)
- Categorized weight at baseline (≤100, >100 kg)
- ECOG performance status at baseline (0, > 0)
- Baseline B symptoms (present, absent)
- Number of prior treatments, including autologous stem cell transplant (ASCT) (=1, >1)

6.9 Covariates

Covariates are not considered for adjustment in the analyses.

6.10 Timing of Analyses

For Part A, the primary analysis will be performed when all subjects in the full analysis set for Part A have completed the safety reporting period.

For Part B and C, the primary analysis for each part will be performed when all subjects in the full analysis set for that part have had their status determined for the primary endpoint of CR rate at EOT.

7 PLANNED ANALYSES

7.1 Disposition

The number of subjects enrolled, treated with A+AVD or AN+AD, and completing the study will be summarized. An accounting of study subjects by disposition will be tabulated and the number of subjects in each analysis set will be summarized. Subjects who discontinue study treatment will be summarized by reason for discontinuation and will be listed with the timing and reason for discontinuation. Subjects who withdraw from the study will be summarized by reason for withdrawal and will be listed with the timing and reason for withdrawal or termination.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, gender, ethnicity, race, height, weight, body mass index, ECG (normal, abnormal), Ann Arbor Stage, IPS score, bulky disease status, ECOG performance status, bone marrow disease involvement, and B symptoms will be summarized with descriptive statistics for the FAS analysis set.

Listings of demographics and disease characteristics will be provided.

7.3 Protocol Deviations

Important protocol deviations (defined as protocol violations by Seagen, Inc) 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 patients with important protocol deviations will be presented.

7.4 Treatment Administration

Treatment administration will be summarized by Part using the FAS. Summary statistics for duration of each treatment per cycle, the number of cycles and total dose will be presented. The number and percentage of patients who were treated at each cycle and completed each cycle, and patients with dose modification will be summarized. Cumulative dose, absolute dose intensity (ADI) and relative dose intensity (RDI) will be summarized. Listings may be presented as well. For Part A, the number of subjects who received pegylated as well as non-pegylated G-CSF will be summarized by cycle as well as the duration of each. A breakdown of the types of G-CSF medications will also be provided.

Duration of treatment (except when calculating exposure) is defined as the time from first dose date to the earliest of either:

- last dose date + 14 days or;
- date of death

- Start of subsequent anti-cancer therapy
- Analysis data cutoff date if the subject is still on treatment at the time of the analysis

Intended Dose Intensity (IDI) is defined as the intended dose of drug per unit of time according to study protocol. ADI is defined as the actual dose per unit of time that the subject received over the entire treatment period. For the purpose of calculating ADI, treatment period is defined as time from the first dose of study drug to Day 28 of the last treatment cycle, regardless of if death occurs before the end of the cycle. RDI is defined as the ADI over the IDI.

$$RDI=ADI/IDI*100\%$$

7.5 Efficacy Analyses

All efficacy analyses will be presented using the FAS, unless otherwise specified. The PPS will be used for the analysis for primary endpoint and may be used for analyses for selected secondary endpoints for Part A. The EES may be used for selected endpoints for Part B and Part C. Analyses may also be performed using the subgroups listed in Section 6.7.

7.5.1 Primary Endpoints

7.5.1.1 Part A

For Part A, the rate of FN is the primary endpoint. The FN rate is defined as the proportion of subjects who experience treatment emergent FN. FN rate and the exact two-sided 95% Cis using the Clopper-Pearson method (Collett 1991) will be calculated.

7.5.1.2 Part B and C

For Part B and C, the primary endpoint is the CR rate at EOT. CR rate at EOT is defined as the proportion of subjects with CR at EOT, according to the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016). Subjects who do not have an EOT assessment will be scored as non-responders for calculating the CR rate at EOT.

CR rate at EOT and the exact 2-sided 95% CIs using the Clopper-Pearson method (Collett 1991) will be calculated.

For Part C a hypothesis test will be performed. The null and alternative hypotheses are:

- Null hypothesis: CR rate at EOT $\leq 90\%$
- Alternative hypothesis: CR rate at EOT $> 90\%$

The null hypothesis will be tested at a 1-sided alpha of 0.05. The associated p-value will be calculated based on the normal approximation with an empirical estimate of the variance. If $p < 0.05$ is observed, the null hypothesis will be rejected in favor of the alternative hypothesis.

If enrollment in Part C is stopped prior to completion, no hypothesis testing will be performed.

7.5.2 Secondary Endpoints

7.5.2.1 Part A

Primary Refractory Disease Rate

The primary refractory disease rate is defined as the proportion of patients with less than CR or relapse within 3 months of EOT according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas.

The primary refractory disease rate and its exact two-sided 95% confidence interval using the Clopper-Pearson method (Collett 1991) will be calculated.

Complete Response Rate at EOT

Complete response (CR) rate is defined as the proportion of patients with CR according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas.

The CR rate and its exact two-sided 95% confidence interval using the Clopper-Pearson method (Collett 1991) will be calculated.

Physician Reported Progression-Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from start of study treatment to first documentation of objective tumor progression or to death due to any cause, whichever comes first. Subjects without progression or death will be censored on the date of the last radiological assessment of measured lesions. Subjects lacking an evaluation of tumor response after their first dose will be censored on their first dose date.

The physician-reported PFS will be analyzed using the Kaplan-Meier method and Kaplan-Meier plots will be provided. PFS rates and the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

7.5.2.2 Part B and C

Complete Response Rate

CR rate is defined as the proportion of subjects with CR at EOT, according to the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC). Subjects who do not have an EOT assessment will be scored as non-responders for calculating the CR rate at EOT.

The CR rate and its exact two-sided 95% confidence interval using the Clopper-Pearson method (Collett 1991) will be calculated.

Objective Response Rate

ORR is defined as the proportion of subjects with CR or partial response (PR) at EOT according to the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016) in subjects.

The CR rate at EOT and its exact two-sided 95% confidence interval using the Clopper-Pearson method (Collett 1991) will be calculated.

Duration of Response

Duration of response (DOR) is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression (per the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016) or death, whichever comes first. Subjects without progression or death will be censored using the same censoring rule as PFS. Duration of response will only be calculated for the subgroup of subjects achieving a CR or PR.

Duration of complete response (DOCR) is defined as the time from start of the first documentation of complete tumor response (CR) to the first documentation of tumor progression (per the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016) or death, whichever comes first. DOCR will only be calculated for the subgroup of subjects achieving CR. Censoring will be in a manner similar to DOR.

Duration of response will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median duration of response and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated.

Progression-free Survival

PFS is defined as the time from start of study treatment to first documentation of objective tumor progression or death. Subjects without progression or death will be censored on the date of the last radiological assessment of measured lesions. Subjects lacking an evaluation of tumor response after their first dose will be censored on their first dose date.

PFS will be analyzed using the Kaplan-Meier method and Kaplan-Meier plots will be provided. PFS rates and the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Event-Free Survival

Event-free survival (EFS) is defined as the time from the start of study treatment to the first documentation of objective tumor progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease, whichever occurs first. Subjects without progression, death, or receipt of subsequent anticancer therapy to treat residual or progressive disease will be censored on the date of the last radiological assessment of measured lesions. Subjects lacking an evaluation of tumor response after their first dose will be censored on their first dose date.

EFS will be analyzed using the Kaplan-Meier method and Kaplan-Meier plots will be provided. EFS rates and the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Overall Survival

Overall survival is defined as the time from start of study treatment to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive.

OS will be analyzed using the Kaplan-Meier method and Kaplan-Meier plots will be provided. OS rates and the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

7.6 Safety Analyses

The FAS will be used to summarize all safety endpoints. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 24.0 or higher). Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.03). Concomitant medications will be coded using WHO Drug.

7.6.1 Adverse Events

Adverse events will be summarized by MedDRA preferred term in descending frequency of occurrence 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 study drug. See Appendix B for details regarding treatment-emergent classification. For Part A, AEs will be assessed during the study from Day 1 dosing and through 30 days following last dose of study drug. For Parts B and C, AEs will be assessed during the study from Day 1 dosing and through 30 days following the last dose of brentuximab vedotin, doxorubicin, or dacarbazine, or 100 days following the last dose of nivolumab, whichever is later. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

An overall summary of AEs will be provided for each Part. Summaries of AEs will also be provided for the following:

- All treatment-emergent AEs
- TEAEs related to brentuximab vedotin
- TEAEs related to AN+AD
- Serious Adverse Events (SAEs)
- SAEs related to brentuximab vedotin
- TEAEs leading to dose modification (discontinuation, delay, reduction, elimination) of any component of A+AVD (Part A)
- TEAEs leading to dose modification (discontinuation, delay, reduction, elimination) of any component of AN+AD (Part B & C)

- AEs leading to death
- Treatment-emergent AEs by system organ class and preferred term
- Treatment-emergent AEs by SOC, PT and maximum severity
- Grade 3 or higher TEAEs
- Treatment-emergent Immune-Mediated Adverse Events (Part B & C only)
- 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)

All adverse events, serious adverse events, adverse events leading to treatment discontinuation, and adverse events leading to death will be listed.

7.6.2 Adverse Events of Clinical Interest

Peripheral Neuropathy

Peripheral Neuropathy (PN) is defined by the peripheral neuropathy 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 preferred term 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 other peripheral neuropathy events did not improve
- Improvement of at least one 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.

Additionally, subjects with any event of treatment-emergent PN will be categorized into 4 groups according to the worst outcome of all events as follows:

- Resolved (all events resolved)
- Improved (at least one event improved, all other events improved or resolved)

- Same (at least one event the same, all other events the same, improved or resolved)
- Worsened (at least one event worsened)

The number of subjects will be summarized for each of the 4 categories. For events that are not resolved nor improved, 'the same' is defined as the last recorded post-baseline grade for the event is the same as the grade at the time the event became treatment-emergent; worsening is defined as increase by at least one grade from the grade at the time the event became treatment-emergent to the grade at the time of latest assessment.

In addition, treatment-emergent PN events will be summarized in a shift table comparing the baseline grades to the worst post-baseline grades for pre-existing PN events, and comparing the grades of the first onset PN events to the worst-post-baseline grades for newly onset events after first dose of treatment drug. Treatment-emergent PN events will also be summarized in a shift table comparing the worst grades to the last grades prior to and at EOT (or the last grades on study, or subsequent lowest grade on study). If the outcome of event is Recovered/Resolved or Recovered/Resolved with Sequelae, then the grade of such event is defined as 0. If the subject has multiple events with the same preferred term ongoing at the time point of interest, then the grade is the worst grade of these events.

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

- Coded to a MedDRA preferred term 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 preferred term and severity. Time to resolution and improvement of motor neuropathy events will be summarized.

7.6.3 Clinical Laboratory Parameters

All laboratory results will be presented in standardized units. Both observed value and changes from baseline will be summarized with descriptive statistics for each scheduled visit. Shift from baseline to maximum post-baseline NCI CTCAE grade will be summarized for each lab test. Treatment-emergent laboratory abnormalities will also be summarized. Treatment-emergent laboratory abnormalities include the abnormalities, reported during study, that were new or worsening in grade or any abnormality when baseline grade was unknown. If baseline grade and post-baseline grade were in different directions for a bi-directional lab test (e.g., from baseline high to post-baseline low), it is also considered treatment-emergent abnormality.

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. A separate listing of laboratory results with CTCAE grade 3 or higher will be presented.

7.6.4 ECOG Performance Status

Shifts from baseline to the best and worst post-baseline score will be tabulated for each Part.

7.6.5 Vital Signs

Vital sign measurements (systolic and diastolic blood pressure, heart rate, and body temperature) will be listed by patient for each time point and presented graphically for each vital sign by scheduled visit.

7.6.6 Concomitant Medications

Concomitant medications will be summarized by the WHO Drug ATC class and preferred name. The number and percentage of subjects taking concomitant medications will be tabulated. Concomitant medications will be listed by subject.

8 INTERIM ANALYSES

An SMC will be responsible for monitoring patient safety in Parts B and C of the study.

One interim futility analysis will be performed for Part C after approximately 50 subjects have completed response assessment at EOT. At this interim futility analysis, if the CR rate at EOT is ≤80%, the sponsor in consultation with the SMC may decide to stop further enrollment of Part C of the trial.

Interim data from the study may be presented at scientific meetings such as the annual meetings of the American Society of Clinical Oncology and the American Society of Hematology.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Original Protocol

Key changes are summarized below. For more details, please refer to protocol Appendix J.

Changes in Amendment 1

- Changed Serious Adverse Event reporting information
- Revised long-term follow-up (LTFU) information to indicate that participants will remain in LTFU for up to 2 years from the End of Treatment visit
- Replaced the International Prognostic Index (IPI) score sheet with International Prognostic Score (IPS) information.

Changes in Amendment 2

- Added Part B: Treatment of cHL subjects with brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD)
- Revision of the study population to a total of 90 subjects
- Revised inclusion/exclusion criteria

- Revised the EOT visit procedures

Changes in Amendment 3

- Added Part C: Treatment of early stage cHL subjects with brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD)
- Modified inclusion criterion

Changes in Amendment 4

- Part B: Added subjects with Ann Arbor Stage I cHL with bulky mediastinal disease
- Part C: Changed "non-bulky" to "without bulky" for subjects with Ann Arbor Stage I or II cHL enrolled in Part C
- Adjusted exclusion/inclusion criteria.

Changes in Amendment 5

- Added interim analysis for Part C.
- Subjects with Stage I or II cHL without bulky disease will be assigned to Part C.
- Added a hypothesis test for Part C CR rate.

Changes in Amendment 6

9.2 Administrative changes and clarifications.Changes from the Original SAP

Changes in Version 2

- Added analyses for Part B and Part C.
- Added change logs for protocol amendment and SAP.
- Changed duration of treatment to last dose date+14 days.
- Updated TEAE algorithm in Appendix B.

Changes in Version 2.1

- Added the definition of efficacy evaluable analysis set.
- Updated the calculation of CR rate at EOT. Subjects who do not have an EOT assessment will be scored as non-responders for calculating the CR rate at EOT.
- Added protocol Amendment 6 to change logs.

10 REFERENCES

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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.

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

The algorithm below should be used to determine whether an adverse event (AE) is classified as a treatment-emergent adverse event (TEAE). A TEAE is defined as any AE which is newly occurring or worsening in severity, 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"

Note: at interim timepoint, if an AE is classified as both 'baseline AE' and 'post-baseline AE' due to data issues, the AE is to be considered 'post-baseline AE' in the derivation of TEAE flag.

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 CTCAE grade of the post-baseline AE to the CTCAE grade of the most recent baseline AE with the same AE identifier:
            - If the post-baseline AE has a higher CTCAE grade, then assign TEAE flag to 'Y'. All subsequent episodes of the same AE should have TEAE flag = 'Y' regardless of the CTCAE grade.
            - 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:

1. **For summaries which include only treatment emergent AEs include all AEs which are classified as TEAEs 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.**
2. **Events that have an end date prior to the first dose date (e.g. protocol procedure related events) should be classified as not treatment emergent (not TEAEs).**

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