



STATISTICAL ANALYSIS PLAN

Product: Brentuximab vedotin

Protocol Number: SGN35-031

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Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Active Comparator, Multicenter, Phase 3 Study of Brentuximab Vedotin or Placebo in Combination With Lenalidomide and Rituximab in Subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)

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LIST OF ABBREVIATIONS

ADA	Antidrug antibody
ADC	Antibody-drug conjugate
ADI	Absolute dose intensity
AE	Adverse event
BICR	Blinded independent central review
BV	Brentuximab vedotin
CAR-T	Chimeric antigen receptor T-cell
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
EQ-5D-5L	EuroQol-5 dimension-5 level
FAS	Full analysis set
GCB	Germinal-center B-cell-like
G-CSF	Granulocyte-colony stimulating factor
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell therapy
HR	Hazard ratio
HRU	Healthcare resource utilization
HSR	Hypersensitivity reaction
IDI	Intended dose intensity
IDMC	Independent data monitoring committee
IPD	Important protocol deviation
IPI	International Prognostic Index
IRR	Infusion-related reaction
ISR	Injection site reaction
ITT	Intent-to-treat
KM	Kaplan-Meier

LLOQ	Lower limit of quantification
LOESS	Locally estimated scatterplot smoothing
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
NCCN FACT-Lym	National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Lymphoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PMN	Peripheral motor neuropathy
PN	Peripheral neuropathy
PR	Partial response
PRO	Patient-reported outcomes
PT	Preferred term
R/R	Relapsed/refractory
RDI	Relative dose intensity
RMST	Restricted mean survival time
RTSM	Randomization and trial supply management
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SCT	Stem cell transplant
SD	Stable disease
SMC	Safety monitoring committee
SMQ	Standardized MedDRA query
SOC	System organ class
SRI	Safety run-in
SSQ	Special search query
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale

1. INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGN35-031, entitled “A Randomized, Double-blind, Placebo-Controlled, Active Comparator, Multicenter, Phase 3 Study of Brentuximab Vedotin or Placebo in Combination With Lenalidomide and Rituximab in Subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL).” Results of the proposed analyses will become the basis of the clinical study report (CSR) for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of “post hoc” or “data driven” analyses will be identified as such in the final 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 Objective

- Evaluate and compare overall survival (OS) between the 2 treatment arms in the intent-to-treat (ITT) population

2.2. Key Secondary Objectives

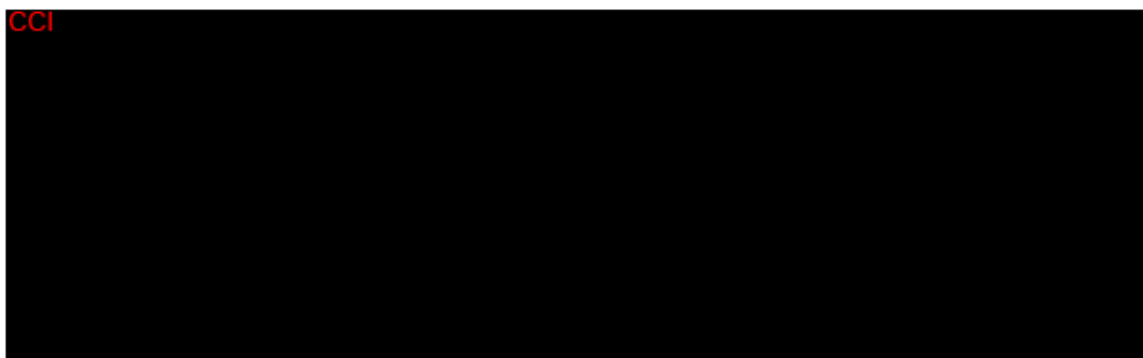
- Evaluate and compare progression-free survival (PFS) per Lugano 2014 by investigator between the 2 treatment arms in the ITT population
- Evaluate and compare the objective response rate (ORR) per Lugano 2014 by investigator between the 2 treatment arms in the ITT population

2.3. Other Secondary Objectives

- Evaluate and compare the complete response (CR) rate per Lugano 2014 by investigator between the 2 treatment arms
- Evaluate and compare duration of response (DOR) per Lugano 2014 by investigator between the 2 treatment arms
- Evaluate the safety and tolerability of the 2 treatment arms
- Evaluate and compare OS between the 2 treatment arms in the CD30-positive population

2.4. Exploratory Objectives

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3. STUDY ENDPOINTS

3.1. Primary Endpoint

- OS

3.2. Key Secondary Endpoints

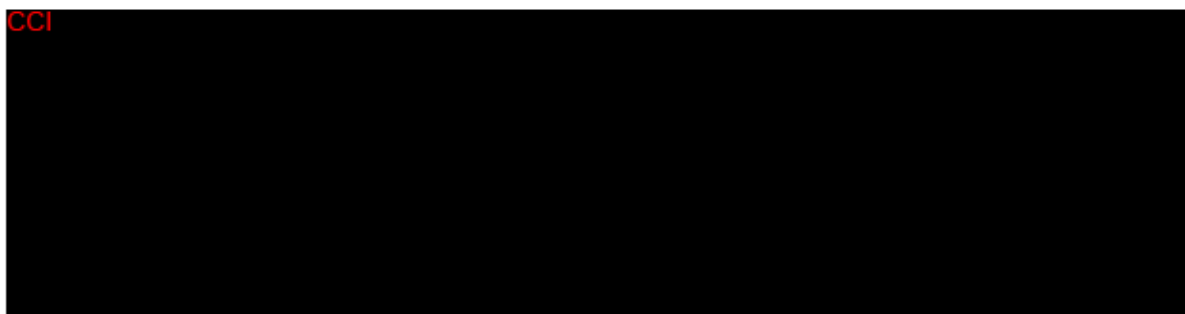
- PFS per Lugano 2014 by investigator
- ORR per Lugano 2014 by investigator

3.3. Other Secondary Endpoints

- CR rate per Lugano 2014 by investigator
- DOR per Lugano 2014 by investigator
- Incidence, severity, and seriousness of adverse events (AEs) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0
- OS in CD30-positive subjects

3.4. Exploratory Endpoints

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4. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, active-comparator, multicenter phase 3 study designed to evaluate the efficacy of brentuximab vedotin in combination with lenalidomide and rituximab versus placebo in combination with lenalidomide and rituximab for the treatment of subjects with R/R DLBCL. All subjects will receive primary granulocyte-colony stimulating factor (G-CSF) prophylaxis.

There was a safety run-in period prior to the randomized portion of the study. A safety monitoring committee (SMC), including 3 external members, reviewed data from the first 6 subjects who received open label brentuximab vedotin, lenalidomide, and rituximab. The safety data for the subjects from this run-in period were evaluated after these subjects completed the first cycle of treatment. The SMC did not identify any new safety signals or concerns, and the SMC approved proceeding with the randomized portion of the study.

After completion of the safety run-in period, subsequent subjects will be randomized in a 1:1 manner to receive either brentuximab vedotin or placebo in combination with lenalidomide and rituximab CCI

Subjects will have central pathology lab determination of CD30 expression by visual assessment of CD30 on tumor cells from the most recent biopsy specimen by immunohistochemistry for stratification purposes. CCI

Treatment may continue as long as there is clinical benefit (stable disease [SD] or better) without progression or unacceptable toxicity.

Subjects will be assigned a response status based on imaging and lymphoma assessments. Disease response will be assessed by the investigator according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas, hereafter referred to as "Lugano 2014" (Cheson 2014). Radiographic disease evaluations, including CT scans of neck, chest, abdomen, and pelvis, will be assessed at baseline, then every 6 weeks from randomization until Week 48 (± 7 days), then every 12 weeks (± 7 days) thereafter. A PET scan is required at baseline and every 6 weeks from randomization until Week 48 (± 7 days), then every 12 weeks (± 7 days) thereafter. Once the PET is negative per the investigator, no

further PET scans are required. Scans should be continued until radiographic documentation of disease progression, including for subjects who have discontinued study treatment or initiated subsequent anticancer therapy and are in follow-up.

Safety assessments will include the surveillance and recording of adverse events (AEs), physical examination findings, and laboratory tests.

5. ANALYSIS SETS

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

5.1. Intent-to-Treat (ITT) Analysis Set

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

5.2. Safety Analysis Set

The safety analysis set will include all subjects who were randomized and received any amount of study drug (BV, lenalidomide, or rituximab). Treatment groups will be determined using the actual treatment received, regardless of the randomization treatment assignment. Subjects receiving any dose of BV will be grouped into the experimental group. Subjects who do not receive BV but receive any dose of lenalidomide or rituximab will be grouped into the control group.

5.3. Safety Run-In (SRI) Analysis Set

The safety run-in analysis set will include all subjects who were enrolled and received any amount of study drug (BV, lenalidomide, or rituximab) in the safety run-in part of the study.

5.4. Patient Reported Outcomes Full Analysis Set (PRO FAS)

The PRO FAS will include all randomized subjects who have received any amount of study treatment and have completed at least one PRO assessment at baseline.

5.5. Pharmacokinetics (PK) Analysis Set

The PK analysis set will include all subjects who received BV and from whom at least one blood sample was collected and assayed for ADC or MMAE concentration. Corresponding records of the time of dosing and/or sample collection must also be available. The PK analysis set will be used for PK analyses.

5.6. All Enrolled Subjects Analysis Set

The all enrolled subjects analysis set will include all subjects enrolled in the study (both the safety run-in and randomized portion of the study). Subjects will be included in the treatment group assigned at enrollment.

6. STATISTICAL CONSIDERATIONS

6.1. General Principles

In general, descriptive statistics including number of observations, 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, confidence intervals (CI) will be calculated at a 2-sided 95% level. The 2-sided 95% exact CI using Clopper-Pearson methodology will be calculated for the response rates where applicable (e.g., ORR) (Clopper 1934). For time to event endpoints, the median survival time will be estimated using the Kaplan-Meier (KM) method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994). For Cox regression models the Efron method will be used to handle ties in event times.

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

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

All statistical tables, listings, and figures will be produced using SAS, version 9.4 or more recent. Sample size calculations were performed with East version 6.5. Other statistical software, if used, will be described in the CSR.

6.2. Determination of Sample Size

Approximately 225 subjects will be enrolled in order to provide sufficient power to compare OS between the treatment arms. The null hypothesis of no difference in OS between the experimental and control arms will be tested in the ITT population at a 2-sided alpha of 0.05 using a stratified log-rank test. Assuming median OS of 9 months in the control arm and a hazard ratio (HR) of 0.62, the median OS for the experimental arm is approximately 14.5 months.

The final analysis of OS will be performed after approximately 170 OS events have occurred. An interim analysis of OS for both efficacy and futility will be performed at approximately 128 OS events (0.75 information fraction). A non-binding futility criteria of $HR > 1.1$ will be used at the interim analysis. Efficacy boundaries at the interim and final OS analysis will be determined using an alpha spending approach with an O'Brien-Fleming boundary in order to maintain type I error control at a 2-sided alpha level of 0.05. Example boundaries for each analysis are presented in Table 1 below. Boundaries at the interim and final analysis will be revised to reflect the actual information available as well as any previous alpha spending.

Table 1: Projected OS Efficacy and Futility Boundaries

Analysis	Planned OS Events	Futility Boundary (HR)	Efficacy Boundary P-value (HR) ^a
Interim	128	1.1	0.0196 (0.662)
Final	170		0.0442 (0.734)

^a 2-sided p-value. HR based on planned OS events at analysis.

Under the assumptions above there is approximately 87% power to reject the null hypothesis of no difference in OS in the ITT population. Assuming a 10% risk of drop out from OS follow-up over 12 months, 225 subjects are expected to allow for accumulation of approximately 170 OS events within approximately 18 months of the last subject randomized.

The key secondary endpoints of PFS and ORR per Lugano 2014 by investigator in the ITT population will be tested sequentially using a fixed sequence approach if the null hypothesis associated with the primary endpoint is rejected. In order to provide strong control of the familywise error rate an alpha spending approach with a Pocock boundary will be used for hypothesis testing for PFS and testing of ORR will be based on the first interim analysis. Details of hypothesis testing and multiplicity are presented in Section 6.7.

Approximately 155 PFS are expected to have occurred at the time of the interim analysis and 170 events are expected at the time of the final analysis. Assuming a HR of 0.62 and applying an alpha spending approach at a 2-sided alpha of 0.05 with a Pocock boundary there is approximately 86% power to reject the null hypothesis of no difference in PFS between the treatment arms.

Assuming an ORR of 30% for the control arm and 50% for the experimental arm (equivalent to a common odds ratio of approximately 2.35) and a 2-sided alpha of 0.05 there is approximately 87% power to reject the null hypothesis of no difference in ORR between the treatment arms.

See Section 6.7 for details on multiple testing and Section 6.10 for details on the timing of the analyses.

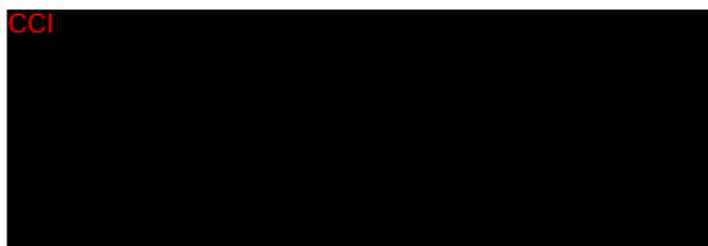
6.3. Randomization and Blinding

This study will have two distinct enrollment periods. The first period is the unblinded SRI. Subjects will be enrolled and receive BV, lenalidomide, and rituximab as described in the protocol. In the second enrollment period subjects will be randomized in a 1:1 ratio to one of the two treatment arms. Treatment assignment in the randomized portion of the study is blinded for both the sponsor and study participants.

The sponsor's study team will also be blinded at the study level to aggregate efficacy data according to a prespecified blinding procedure until the blind is broken for analysis of the primary endpoint. The BICR will also be blinded to treatment assignments.

Randomization will be stratified by:

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Randomization will be performed centrally using a system that will assign a unique subject randomization number but will not specify the actual treatment assignment.

6.4. Data Transformations and Derivations

6.4.1. General

Study day will be calculated as follows for dates on or after the first dose date:

$$\text{study day} = \text{date} - \text{first dose date} + 1$$

For dates prior to the first dose date, study day will be calculated as:

$$\text{study day} = \text{date} - \text{first dose date}$$

For all calculations of study day, the first dose date will be the earliest date of treatment administration for any component of the treatment regimen. If a subject did not receive any study treatment the date of enrollment/randomization will be used instead of the first dose date.

The following unit conversion will be implemented unless otherwise specified:

$$\text{Months} = \text{Days}/30.4375$$

$$\text{Years} = \text{Days}/365.25$$

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. If a subject did not receive any study drug, then enrollment/randomization date will be used instead of first dose of study drug to derive baseline values.

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 the date that the decision is made to end treatment.

6.4.2. Derivation of Response Date

Response date per investigator will be derived. At each response assessment time point, scans to sites of disease can be performed on multiple dates. If the response at a response assessment time point is complete response (CR), partial response (PR), stable disease (SD), or not evaluable (NE) then the date of response will be the latest of all scan dates used to perform assessment for that time point. If the response at a response assessment time point is

progressive disease (PD) then the date of response will be the earliest of all scan dates used for the assessment at that date. Biopsies may also be performed as part of the response assessment. If biopsies are performed at a visit in addition to scans, then the date of the biopsy will also be considered in addition to the dates of the scans when deriving the response date.

Response date per BICR is determined by the BICR as outlined in the BICR charter, and will not be separately derived for analyses based on BICR evaluation.

6.4.3. Adequate Response Assessments

An adequate response assessment must include a radiologic scan with the overall disease response of CR, PR, SD, or PD. If an overall response is not evaluable (NE) it will be considered an adequate response assessment for the purpose of PFS and DOR censoring if required CT scans were performed to monitor for PD. Assessments which are based only on clinical evaluation of disease (i.e., CT or PET scans are not included) will not be considered adequate response assessments.

6.5. Handling of Dropouts and Missing Data

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

Subjects who do not have adequate post-baseline response assessments will be counted as non-responders for analysis of response. Missing AE dates will be imputed for the purpose of calculating duration of events and determining the treatment-emergent status. See Appendix A for the imputation rule.

For the start date of new anticancer therapy, if month and year are present and only day is missing, the date may be imputed. Imputation rules are presented in Appendix C.

For the purpose of deriving relapsed/refractory status for prior lines of therapy missing dates of prior therapy initiation or date of disease transformation may be imputed.

Censoring for time-to-event endpoints will be described in Section 7 with each planned analysis, as applicable.

Unless otherwise specified, lab values that are below the lower limit of quantification (LLOQ) will be assigned the value of LLOQ when a numeric value is required for the analysis (e.g., calculating the mean, assigning the CTCAE grade) and be listed as “<LLOQ” in the listings.

Missing data for PROs will be handled according to the user manual for each individual PRO.

6.6. Multicenter Studies

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

6.7. Multiple Comparison/Multiplicity

Multiple hypothesis tests will be performed in this study to compare the treatment arms for the following endpoints and populations:

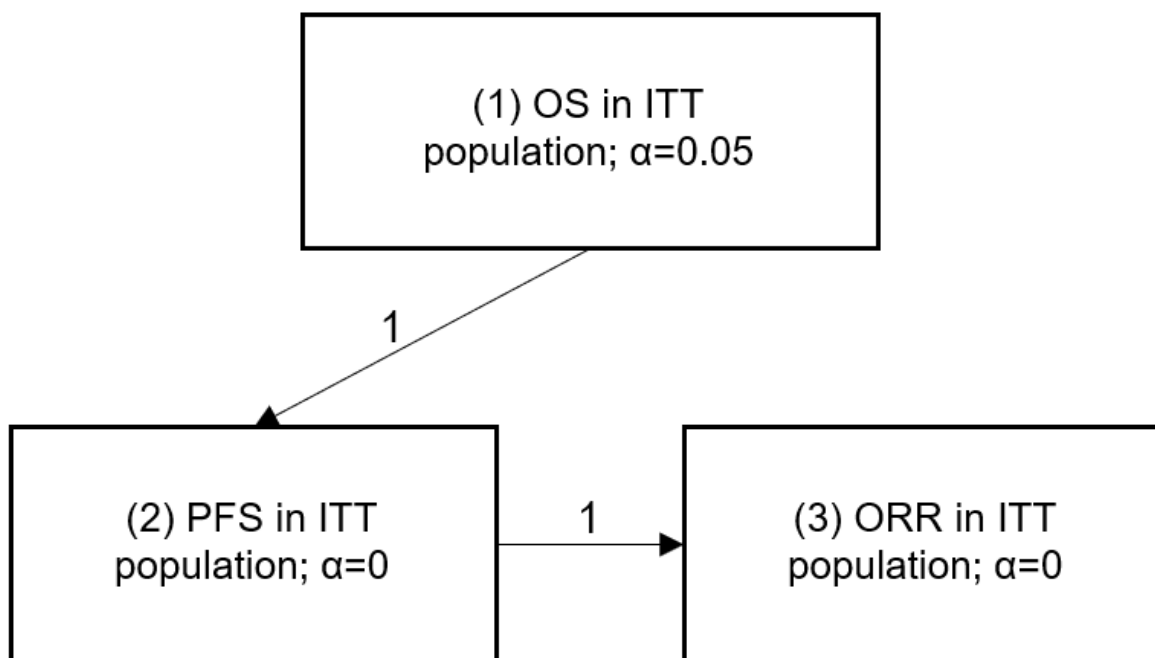
- OS in the ITT population
- PFS per Lugano 2014 by investigator in the ITT population
- ORR per Lugano 2014 by investigator in the ITT population

A graphical approach ([Bretz 2009](#)) is used to represent initial alpha allocation to hypothesis testing for each endpoint, with arrows connecting endpoints to indicate reallocation of initial alpha allocation when hypotheses are rejected. Since an interim and final analysis are planned the following additional considerations will be applied to hypothesis testing to control the overall type I error rate at the 2-sided alpha level of 0.05:

- OS will be tested using an alpha spending approach with an O'Brien-Fleming boundary
- PFS will be tested at the time OS is statistically significant using an alpha spending approach with a Pocock boundary
- ORR will be tested based on the results at the interim analysis of OS

The graphical representation of the testing strategy is presented in [Figure 1](#) and further details are described below.

Figure 1: Graphical representation of hypothesis testing in study SGN35-031



- (1) Test OS in the ITT population at initial alpha allocation 0.05.
- (2) Test PFS in the ITT population when OS is significant.
- (3) Test ORR in the ITT population when PFS is significant.

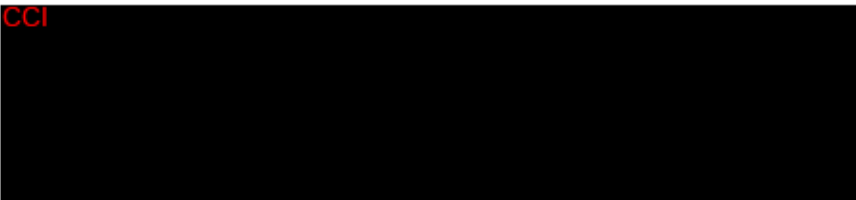
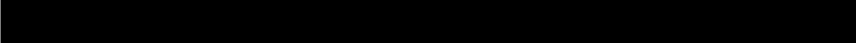
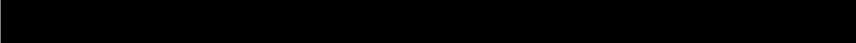
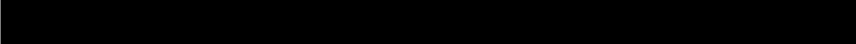
1. Test OS in the ITT population based on a stratified log-rank test at a 2-sided alpha level 0.05. Type I error is controlled using a group sequential alpha spending approach with an O'Brien-Fleming efficacy boundary. A non-binding futility criteria for OS of $HR > 1.1$ will also be used at the interim analysis.
 - a. Perform the interim analysis at approximately 128 events (0.75 information fraction). If the O'Brien-Fleming null hypothesis of no difference in OS between the treatment arms is rejected then proceed to test PFS in step 2; the final OS analysis will be descriptive. If the null hypothesis is not rejected and the study is not stopped due to futility then proceed to the final analysis of OS.
 - b. Perform the final analysis of OS at approximately 170 events. If the null hypothesis of no difference in OS between the treatment arms is rejected then proceed to test PFS in step 2.
2. Test PFS per Lugano 2014 by investigator in the ITT population based on a stratified log-rank test. Type I error is controlled using a group sequential alpha spending approach with a Pocock boundary based on a total planned event count of 170.
 - a. Test the null hypothesis of no difference in PFS between the treatment arms. If the null hypothesis of no difference in PFS between the treatment arms is rejected then proceed to test ORR in step 3.

3. Test ORR per Lugano 2014 by investigator in the ITT population based on the Cochran-Mantel-Haenszel test. In order to control the familywise error rate the hypothesis test is performed using the data cutoff from the interim analysis of OS. No further hypothesis testing is performed after this step.

Analyses not described in this section will be considered descriptive and no hypothesis testing will be performed; any corresponding nominal p-values may be presented for descriptive purposes only.

6.8. Examination of Subgroups

As supportive analyses, PFS and OS endpoints may be analyzed for the following subgroup variables:

- Age (<65 years old, ≥65 years old)
- Sex (Male, Female)
- Race (White, Asian, other categories with sufficient sample size)
- Region (North America, Europe, Rest of World)
- Variables used for randomization stratification:
 - CCI
 - 
 - 
 - 
 - 
- Baseline ECOG PS (0-1, 2)
- Bulky disease (1 or more lesions >7.5cm in the longest dimension)
- Baseline IPI (<3, ≥3)
- Refractory to last prior anti-lymphoma therapy
- Double expressor
- Double- or triple-hit lymphoma

Estimated treatment effect (with a nominal 95% CI) will be provided for each subgroup using an unstratified Cox proportional hazards regression model. If any post-randomization correction occurs for the variables used for randomization stratification then the post-randomization corrected values will be used for subgroup analyses. CD30 expression groups will be according to definitions specified in section 7.5.4.1.

In addition, a subgroup analysis may not be performed if the total number of subjects in a subgroup is too small or too few events are observed (e.g., <10% of the total sample size or event count, respectively). For subgroup variables with more than two levels, pooling may be considered when there is not sufficient sample size within one level.

6.9. Covariates

Stratified analyses will include adjustment for the stratification factors as recorded at randomization. In situations where a stratum cannot be included in a stratified analysis of an

endpoint, it may be necessary to pool strata prior to the analysis. Pooling of strata will occur if <5% of the subjects in the ITT population are present in a specific stratum or if the stratified model otherwise fails to converge. Pooling will be performed sequentially in the following order until the above criteria are met for the remaining strata: CCI [REDACTED]

Sensitivity analysis using post-randomization corrected values for stratification variables may be conducted for primary and key secondary endpoints if the proportion of subjects with post-randomization correction of stratification variables is $\geq 5\%$.

The variables identified for subgroup analysis may also be considered for inclusion in exploratory regression analyses to evaluate estimates of treatment effect after adjustment for these covariates.

6.10. Timing of Analyses

The interim analysis of OS will be performed when approximately 128 OS events have occurred (0.75 information fraction). It is expected that 128 OS events will occur approximately 3 months after randomization of the last subject. The final analysis of OS will be performed after approximately 170 OS events have occurred. It is expected that 170 OS events will occur approximately 18 months from randomization of the last subject.

If the interim analysis of OS is statistically significant then other analyses will be performed at that time, including hypothesis testing of the key secondary endpoints. Other analyses will also be performed at the time of the final analysis of OS.

The estimated duration of the study is approximately 4 years from the randomization of the first subject (including approximately 2.5 years of enrollment and an additional 18 months of follow-up to reach the final analysis of OS).

7. PLANNED ANALYSES

7.1. Disposition

A summary of study subject disposition will be tabulated by treatment arm and total. Summaries will include:

- Reasons for discontinuation of treatment
- Reasons for discontinuations of study
- Number and percentage of subjects on treatment and in follow up
- Follow up time from randomization/enrollment date to last known alive date

Disposition data will be listed by subject as well.

The number and percentage of subjects who signed informed consent and the number of subjects in each analysis set will be summarized. The reasons for screen failure will also be summarized and listed.

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

Summaries will be presented for the ITT and SRI analysis sets. Screen failure subjects will be summarized separately.

7.2. Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, sex, ethnicity, race, baseline height, weight, and ECOG score will be listed and summarized.

The following disease specific characteristics will be listed and summarized:

- disease diagnosis, including prior transformed disease status
- CD30 expression
- GCB status
- International prognostic index (IPI) score
- refractory status to front line and most recent line of systemic therapy
- chromosomal and molecular abnormalities in BCL-2, BCL-6, and MYC
- time from initial diagnosis

Summaries and listings of prior therapy will be presented, including the description, type, and number of prior therapies. Details of dates and response to prior therapy will be listed.

Reasons for hematopoietic stem cell transplant and CAR-T therapy ineligibility will be summarized and listed.

Summaries will be presented for the ITT and SRI analysis sets.

7.3. Protocol Deviations

Important protocol deviations (IPDs) 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. IPDs also include deviations from study inclusion/exclusion criteria. IPDs will be summarized by category and a listing of IPDs will be presented.

Summaries will be presented for the ITT and SRI analysis sets.

7.4. Treatment Administration

Treatment administration will be summarized by treatment arm for each individual component of study treatment. Summary statistics for duration of treatment and the number of cycles per subject will be presented, as well as the number and percentage of subjects who were treated at each cycle. Cumulative dose and relative dose intensity (RDI) will be presented. The number and percentage of subjects whose dose was ever modified will be summarized in tables by modification type (dose reduction, dose delay, and dose elimination/hold, or dose discontinuation due to reason other than progressive disease) and overall (i.e., over all drug administrations for a subject). listings of treatment administration and dose modifications will be presented as well.

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

- The latest of the following dates:
 - For BV or rituximab: day 21 of the last dosed treatment cycle
 - For lenalidomide: last date lenalidomide was taken
- Date of death
- Earliest start date of subsequent anti-cancer therapy
- Data cutoff date if the subject is still on treatment at the time of data cutoff

Summaries of dose intensity will be calculated based on the following intended dose intensity values:

- BV/placebo: 1.2 mg/kg per 21 day cycle (due to dose cap at 120 mg, if a subject weight exceeds 100 kg then IDI will be based on 100 kg)
- Lenalidomide: 20 mg per day
- Rituximab IV: 375 mg/m² per 21 day cycle
- Rituximab subcutaneous: 1400 mg per 21 day cycle

Absolute dose intensity (ADI) for lenalidomide is the total mg received divided by the duration of lenalidomide treatment.

ADI for BV and rituximab is based on the following formula:

$$ADI = \frac{\text{sum of doses received in mg/unit}}{\text{duration of treatment (days)}} \times \frac{21 \text{ days}}{\text{cycle}}$$

RDI is calculated as $ADI/IDI \times 100$.

Rituximab RDI is calculated separately for IV and subcutaneous for each subject similar to BV, then averaged as follows:

$$\text{rituximab RDI} = \frac{(RDI_{IV} \times Cycles_{IV}) + (RDI_{subcu} \times Cycles_{subcu})}{Cycles_{IV} + Cycles_{subcu}}$$

Summaries and listings of treatment administration will be presented for the safety analysis set and the SRI analysis set.

7.5. Efficacy Analyses

Efficacy analyses will be presented using the ITT analysis set unless otherwise specified. Unless otherwise specified, efficacy results for the SRI analysis set will be presented as listings due to the limited sample size.

7.5.1. Primary Endpoint: Overall Survival (OS)

OS is the primary endpoint. The trial will be considered positive if the primary endpoint is statistically significant in favor of the experimental arm. Two formal analyses of OS are planned. Details of the efficacy boundaries at each analysis and multiplicity adjustment to ensure control of type I error rate are discussed in Section 6.2 and Section 6.7.

OS is defined as the time from the date of randomization to the date of death due to any cause. Subjects who have not died will be censored at the last known alive date or the data cutoff date, whichever is earlier. Last known alive date is the latest visit or procedure date captured at which the subject is known to be alive. If a subject dies after the data cutoff date for an analysis they will also be censored at the data cutoff date. OS is derived as follows:

$$OS \text{ Time (months)} = \frac{(OS \text{ event or censor date} - \text{randomization date} + 1)}{30.4375}$$

Kaplan-Meier (KM) methods will be used to estimate OS, with estimates presented by treatment arm. The stratified log rank test will be used to obtain a p-value to test the null hypothesis of no difference in OS between the treatment arms. Stratification factor variables will be the randomization stratification factors as entered in the RTSM system. KM estimates of median OS and the 2-sided 95% confidence interval (CI) based on the log-log transformation will be presented (Collett 1994). KM estimates of the 25th and 75th percentiles of OS as well as the minimum and maximum OS times will be presented. KM estimates of the OS rate and 2-sided 95% CI at 3 month intervals will be presented.

For the purpose of describing the treatment effect, a hazard ratio between experimental and control arms and its 95% CI will be estimated using a stratified Cox proportional hazards regression model. Stratification factors will be the same as those used for the stratified log-rank test.

In addition, the proportional hazard assumption will be assessed with the following approach:

- Schoenfeld residuals including LOESS curve will be plotted in SAS using the PHREG procedure via the OUTPUT statement (keyword=RESSCH). With proportional hazards, the LOESS curve is expected to be approximately parallel to the x-axis. Residuals that do not show any trend indicate that the PH assumption is met.

If the results of the above analyses indicate the proportional hazard assumption is not satisfied, alternative methods such as restricted mean survival time (RMST) (Royston 2011; Uno 2014) may be used to describe the treatment effect. RMST is the expected survival time within a fixed follow-up interval and will be calculated as the area under the survival curve from $t=0$ to the minimum of latest observed event time for the two treatment arms. The difference in RMST between the treatment arms will be analyzed using an ANCOVA model adjusting for the randomization stratification factors. The estimated RMST and its 95% CI will be presented. In addition, the Max-Combo test (Kosorok 1999; Karrison 2016) may be performed to compare the two treatment arms.

Sensitivity Analyses for OS

Sensitivity analyses will be performed to support evaluation of OS. No multiplicity adjustment will be performed for the sensitivity analyses presented. The KM and cox regression estimates and summaries presented for OS analysis will be repeated with modification as described below:

- Unstratified analysis: the OS analyses will be repeated with an unstratified log-rank test and an unstratified cox regression model.
- Per protocol analysis: the OS analysis will be repeated, excluding any subjects who had important protocol deviations.
- Stratification error: if the proportion of subjects with post-randomization stratification corrections is $\geq 5\%$ the OS analysis will be repeated with strata levels for stratified analyses determined by the post-randomization corrected values for the stratification variables.

7.5.2. Key Secondary Endpoints

7.5.2.1. Progression Free Survival (PFS) per Lugano 2014 by Investigator

PFS per Lugano 2014 by Investigator is a key secondary endpoint. Formal analyses of PFS are planned at the time that the primary endpoint is significant. Details of the hypothesis testing and multiplicity adjustment to ensure control of type I error rate are discussed in Section 6.2 and Section 6.7.

PFS is defined as the time from the date of randomization to the date of first documentation of PD or to death due to any cause, whichever occurs first. Response assessment for determination of PD will be according to the Lugano 2014 response criteria. If one of the scenarios for censoring outlined in table 2 below is met at the time of analysis then the subject will be censored. PFS is derived as follows:

$$PFS\ Time\ (months) = \frac{(PFS\ event\ or\ censor\ date - randomization\ date + 1)}{30.4375}$$

PFS event and censoring rules for the primary analysis are described in Table 2.

Table 2: PFS Event and Censoring Rules for Primary Analysis

Scenario	Date of event/censoring	Outcome
Progressive disease (PD)	Date of PD	Event
Death before first PD assessment	Date of death	Event
Alive, no post-baseline response assessments	Date of randomization	Censored
No documented PD or death	Date of last adequate response assessment	Censored
Initiation of new non-palliative anticancer therapy after study treatment and prior to experiencing a PFS event	Date of last adequate response assessment prior to initiation of new anticancer therapy	Censored
Death or PD right after two or more consecutive missed or NE response assessments	Date of last adequate response assessment prior to the missed visits	Censored

PFS will be analyzed using similar methods as the primary endpoint, including evaluation of the proportional hazards assumption. Similar summaries will be presented, with appropriate adjustment to account for differences in endpoint duration (e.g., PFS rates may be presented at shorter intervals).

If the primary endpoint is not significant, then PFS will not be tested; analyses will be non-inferential and p-values presented will be considered descriptive.

Sensitivity Analyses for PFS

Sensitivity analyses will be performed to support evaluation of the primary endpoint. No multiplicity adjustment will be performed for the sensitivity analyses presented. The KM and cox regression estimates and summaries presented for the primary analysis will be repeated with modification as described below:

- Unstratified analysis: analyses will be repeated with an unstratified log-rank test and an unstratified cox regression model.
- No censoring for new anticancer therapy: the scenario of initiation of new anticancer therapy after study treatment and prior to a PFS event will not be considered a censoring event.
- No censoring for missed visits: the scenario of death or PD right after two or more consecutive missed or NE response assessments will not be considered a censoring event.
- Clinical progression event: clinical progression will also be considered a PFS event.
- Per protocol analysis: the primary analysis will be repeated, excluding any subjects who had important protocol deviations.

- Stratification error: if the proportion of subjects with post-randomization stratification corrections exceeds 5% the primary analysis will be repeated with strata levels for stratified analyses determined by the post-randomization corrected values for the stratification variables.
- BICR assessment: An analysis of PFS with determination of response by BICR assessment may be performed.

7.5.2.2. Objective Response Rate (ORR) per Lugano 2014 by Investigator

ORR per Lugano 2014 by Investigator is a key secondary endpoint. Formal analyses of ORR are planned at the time the primary endpoint is significant. In order to control the familywise error rate the hypothesis testing for ORR will be performed using the data cutoff from the interim analysis of OS. Details of the hypothesis testing and multiplicity adjustment to ensure control of type I error rate are discussed in Section 6.2 and Section 6.7.

ORR per Lugano 2014 by Investigator is defined as the proportion of subjects with a response assessment of CR or PR per the Lugano 2014 response criteria as assessed by the investigator. Only response with dates prior to a response of PD or initiation of new anticancer therapy will be included in the derivation of ORR. Subjects whose disease response cannot be assessed will be counted as non-responders for calculating the ORR.

The ORR and the 2-sided 95% exact CI will be calculated for each treatment arm. The difference in ORR between treatment arms and the associated 95% CI will also be presented. Additional comparison of ORR between the two treatment arms will be based on a 2-sided Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization stratification factors ([Mantel 1959](#)). The p-value from the CMH test will be reported. Objective response will also be listed by subject.

Sensitivity analyses of ORR based on BICR assessment may also be performed.

7.5.3. Other Secondary Endpoints

Efficacy analyses for other secondary endpoints are presented below. No hypothesis testing will be performed for these endpoints.

7.5.3.1. Complete Response (CR) Rate per Lugano 2014 by Investigator

CR rate per Lugano 2014 by Investigator is defined as the proportion of subjects with best response of CR per the Lugano 2014 response criteria as assessed by the investigator. Only response with dates prior to a response of PD or initiation of new anticancer therapy will be included in the derivation of CR rate. Subjects whose disease response cannot be assessed will be counted as non-responders for calculating the CR rate.

Methods of analysis and presentation of CR rate will be similar those used for ORR, with the exception that hypothesis testing of CR rate will not be performed.

Sensitivity analyses of CR rate based on BICR assessment may also be performed.

7.5.3.2. Duration of Response (DOR) per Lugano 2014 by Investigator

DOR is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression per the Lugano 2014 response criteria as assessed by the investigator or death due to any cause, whichever occurs first. The same censoring rules used in the main analysis of PFS will be applied for the analysis of DOR. Duration of response will only be calculated for subjects achieving a CR or PR.

Kaplan-Meier (KM) methods will be used to estimate DOR, with estimates presented by treatment arm. KM estimates of median DOR and the 2-sided 95% confidence interval (CI) based on the log-log transformation will be presented (Collett 1994). KM estimates of the 25th and 75th percentiles of DOR as well as the minimum and maximum DOR will be presented. KM estimates of the proportion of responders without PD or death and 2-sided 95% CI at 2 month intervals will be presented. A log rank test will be used to present a nominal p-value and a hazard ratio between experimental and control arms and its 95% CI will be estimated using a stratified Cox proportional hazards regression model.

Sensitivity analyses of DOR rate based on BICR assessment may also be performed.

7.5.3.3. OS in CD30-Positive Subjects

An analysis of OS will be performed in the subgroup of CD30-positive subjects. CCI

The OS endpoint used in this analysis will be identical to the endpoint used for the primary analysis. Methods of analysis and presentation of results will be similar to those for the primary endpoint, with the exception that analyses will be unstratified, no hypothesis testing is performed, and no sensitivity analyses will be performed.

7.5.4. Exploratory Endpoints

CCI

CCI

7.6. Safety Analyses

Safety analyses will be based on the safety analysis set and presented by treatment arm and total unless otherwise specified. Analyses will also be presented for the SRI analysis set. If notable imbalance in one or more baseline characteristics are observed between treatment arms, subgroup analyses may be performed to evaluate their potential impact on safety.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 26.0 or higher).

Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 5.0 or higher).

Concomitant medications will be coded using WHO Drug (version: 2023 03 or more recent).

7.6.1. Adverse Events

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

A treatment-emergent AE (TEAE) is defined as a newly occurring or worsening AE after the first dose of study treatment through the end of the safety reporting period. See 0 for details regarding treatment-emergent classification. An overall summary of AEs will be provided by treatment arm and total. Summaries of AEs will also be provided by treatment arm for the following:

- All TEAEs
- Grade 3 or higher TEAEs
- Treatment-emergent serious AEs (SAEs)
- TEAEs leading to death
- TEAEs leading to dose modification will be summarized and will include:
 - Dose modification of any individual study drug
 - Discontinuation of overall study treatment
 - Any dose modification (delay, reduction, elimination, or discontinuation) as well as individual types of dose modifications of BV or placebo
 - Any dose modification (hold, reduction, elimination, or discontinuation) as well as individual types of dose modifications of lenalidomide
 - Any dose modification (delay, elimination, or discontinuation) as well as individual types of dose modifications of rituximab
- TEAEs reported as infusion-related reactions (IRRs), hypersensitivity reactions (HSRs), and injection site reactions (ISRs) will be summarized as follows:
 - IRR to BV or placebo
 - IRR or HSR or ISR to BV or placebo
 - IRR to rituximab
 - IRR or HSR or ISR to rituximab
- TEAEs leading to dose interruption of BV or placebo
- TEAEs leading to dose interruption of rituximab
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum severity
- TEAEs related to any component of the study treatment and related to BV or placebo will be summarized separately for the following categories:
 - TEAEs

- Grade 3 or higher TEAEs
- Treatment emergent SAEs
- TEAEs leading to overall treatment discontinuation
- TEAEs leading to death

In addition, exposure adjusted analyses may be presented to account for differing safety reporting periods due to differences in treatment duration between treatment arms, if appropriate.

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

Peripheral Neuropathy (PN)

Classification of PN events will be based on the standardized MedDRA query (SMQ), broad. Summaries of peripheral motor neuropathy (PMN) are based on a special search query (SSQ) within the PN SMQ which includes the PTs Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peroneal nerve palsy, Muscular weakness, Hypotonia or Muscle atrophy. Analyses of PN will be presented for the PN SMQ and the PMN SSQ by treatment arm and overall unless otherwise specified.

Summaries of PN TEAEs will be presented overall and by PT in descending frequency for the following categories:

- All TEAEs
- TEAEs by PT and maximum severity
- Treatment emergent SAEs
- Treatment related TEAEs
- TEAEs leading to any dose modification
- TEAEs leading to dose modification of BV or placebo
- TEAEs leading to overall discontinuation of study treatment

Summaries of time from first dose to first onset of PN will be presented by treatment arm and overall. Time to first onset of any grade, worst grade, and each severity grade will be presented. Summaries will include median, mean, standard deviation, and minimum and maximum time to onset. A KM analysis of time to onset will also be performed for any grade of PN, with subjects without PN censored at the latest date of participation in the safety reporting period.

Summaries of PN outcomes will be presented by treatment arm and total for subjects with PN events. PN events will be classified in the following categories:

- Resolution: AE outcome is resolved or resolved with sequelae, or has returned to baseline or lower severity with no subsequent increase in severity
- Improved: decreased by at least one severity grade from worst grade with no increase in severity grade thereafter

- No improvement: Criteria for resolution or improvement are not satisfied

Subjects will be classified in the following categories based on the outcomes of the PN events experienced by the subject at the time of analysis:

- Resolution of all PN: all PN events have resolved
- Improvement of PN:
 - Improvement of all PN: all PN events have resolved or improved
 - Partial improvement: At least one but not all PN events have resolved or improved
- No improvement of PN: No PN events have resolved or improved

The number of subjects with ongoing PN at last follow-up will be summarized, as well as the maximum severity of the ongoing PN events for those subjects.

Time to resolution and improvement of PN events will be summarized overall and by maximum severity of the PN event. Summaries will include median, mean, standard deviation, and minimum and maximum time to resolution or improvement.

7.6.2. Clinical Laboratory Parameters

Clinical laboratory data will be summarized for lab tests including chemistry and hematology. Results and change from baseline will be summarized by visit for each treatment arm and in total. Results will also be listed by visit for each subject. Results will be presented in standardized units where applicable.

Laboratory results will be graded per NCI CTCAE and summaries of maximum post-baseline grade will be presented by treatment arm. Shift tables of change from baseline grade to maximum post-baseline grade will also be presented for each treatment arm.

CD4 counts for subjects with HIV and endocrinology labs will also be listed by visit.

7.6.3. ECOG Performance Status

Worst post-baseline ECOG score and ECOG score by visit will be summarized for each treatment arm and total. Shifts from baseline to the worst post-baseline score will be summarized by treatment arm. ECOG scores will also be listed by visit for each subject.

7.6.4. Vital Signs

Vital sign measurements will be listed by visit for each subject.

7.6.5. Electrocardiograms (ECGs)

ECG results, including interpretation and clinical significance, will be listed for each subject.

7.6.6. Concomitant Medications

Concomitant medications will be listed by subject.

G-CSF use will be summarized overall and by cycle for each treatment arm. G-CSF use will also be listed by cycle for each subject.

7.6.7. Pregnancy

The number of subjects who had a pregnancy test as well as the result of the pregnancy test will be summarized by treatment arm and total. Pregnancy test results will also be listed by subject.

7.6.8. Deaths

The number of total deaths, deaths that occur within 30 days of last study treatment, and deaths that occur more than 30 days after last study treatment as well as the relationship to disease will be summarized by treatment arm and total. In addition, specific cause of death will be summarized by treatment arm and total. Cause of death due to AE will be reported as the MedDRA preferred term with fatal outcome. Details of deaths will be listed by subject.

7.7. Pharmacokinetics and Immunogenicity Endpoints

7.7.1. Pharmacokinetics

Concentrations of ADC and MMAE will be summarized using descriptive statistics (including geometric mean and coefficient of variation) at each PK sampling time point for the PK analysis set. Analyses will be presented using the PK analysis set.

If performed, population PK and exploratory PK/pharmacodynamic, PK/safety, or PK/efficacy analyses will be described in a separate analysis plan and the results reported separately from the CSR.

7.7.2. Antidrug Antibody (ADA) Incidence Rate

The ADA incidence rate is defined as the proportion of subjects that develop ADA at any time during the study. BV related ADA incidence will be summarized using the safety analysis set.

7.7.3. Pharmacodynamic and Mechanism of Action Biomarkers

The analyses for pharmacodynamic biomarkers and for biomarkers related to drug mechanism(s) of action will be defined in a separate Biomarker Analysis Plan and may be included in a separate report.

7.8. Patient Reported Outcomes (PRO) and Healthcare Resource Utilization (HRU)

PRO assessments will include the EuroQOL 5-dimensions (EQ-5D-5L), NCCN FACT-Lym, and HRU questionnaires.

EQ-5D-5L and NCCN FACT-Lym compliance and completion rate will be summarized for each scheduled assessment by treatment arm using the ITT analysis set. Compliance rate is defined as the proportion of subjects who completed the instrument among those who are

expected to complete at a given visit. Completion rate is defined as the proportion of subjects who completed the instrument.

7.8.1. EuroQol-5D-5L

The EQ-5D-5L is a 5-item self-reported measure of functioning and well-being, which assesses 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). Responses to the 5 items are then converted to a weighted health state index (utility score) based on values derived from general population samples. This health utility score is between 0 and 1, where 0 is death and 1 is perfect health. In addition to the utility score, this questionnaire also records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analogue scale (VAS).

The following statistics will be calculated for EQ-5D-5L by treatment arm and by scheduled assessments for treatment arm:

- Compliance rate for EQ-5D-5L assessment
- Completion rate for EQ-5D-5L assessment
- Summary statistics of the actual value and change from baseline for VAS and Health State Index Score
- Summary of Dimension Scores

Analyses will be based on the PRO FAS.

7.8.2. FACT-Lym

The FACT-Lym is used to assess patient reported quality of life in subjects with non-Hodgkin lymphoma. Data are captured as a likert-scale responses to a series of question items across various quality of life subscales. Scoring will be performed according to the FACT-Lym scoring manual.

The following statistics will be calculated for FACT-Lym by treatment arm and by scheduled assessments for treatment arm:

- Compliance rate for FACT-Lym assessment
- Completion rate for FACT-Lym assessment
- Summary statistics of the actual value and change from baseline for subscale, item, and overall scores

Analyses will be based on the PRO FAS.

7.8.3. Healthcare Resource Utilization (HRU)

HRU summaries be presented by treatment arm using the ITT analysis set. Summaries will include the types of hospital visit, reason for hospital visit, and descriptive summaries of the duration of hospital visit. Cumulative HRU, including length of stay, hospitalizations, and ER visits will also be summarized by treatment arm.

7.9. Additional Analyses

7.9.1. Subsequent Cancer-Related Therapy

The type and regimen of subsequent anticancer therapies after discontinuation from study treatment will be summarized by treatment arm. For subjects that were ineligible to receive stem cell transplant (SCT) at baseline but later received an SCT, the reason they became eligible to receive SCT will be summarized. Details of subsequent anti-cancer therapies will be listed by subject.

Summaries of subsequent anticancer therapy will be presented using the safety analysis set.

7.9.2. COVID-19 Impacts

COVID-19 impacts will be summarized and listed. Subjects with suspected or confirmed case of COVID-19 will be listed. Analyses will be presented for the ITT and the SRI analysis set.

8. INTERIM ANALYSIS

During the open label, safety run-in portion of the trial a Safety Monitoring Committee (SMC) including 3 external members reviewed data from the first 6 subjects who received open label BV, lenalidomide, and rituximab. Details of the interim data review performed by the SMC are described in the SMC charter.

During the randomized portion of the trial an Independent Data Monitoring Committee (IDMC) consisting of independent expert physicians and biostatisticians will periodically monitor the trial for safety and will review expedited SAEs as they arise. The IDMC conduct of ongoing safety reviews will be documented in the IDMC Charter.

An interim analysis of OS is planned after approximately 128 OS (ie, 0.75 information fraction) events have occurred. The IDMC will review the results of the interim OS analysis and make a recommendation on whether the study should be unblinded. If the study is unblinded based on the results of the OS interim analysis then additional analyses, including specified hypothesis testing of the key secondary endpoints, will be performed. If the study is not unblinded based on the results of the interim analysis then the study will continue until the final analysis of OS.

9. CHANGES FROM PLANNED ANALYSES

9.1. Changes from the Original Protocol

There are no changes in planned analyses from the current protocol.

9.2. Changes from the Original SAP

Not applicable.

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.

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	30 APR2012	2	recovering/resolving
2	02 APR2012	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 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 0 prior to determination of TEAE classification. The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through 110 days after the last dose of rituximab or 30 days after the last dose of brentuximab vedotin or lenalidomide, whichever is later. 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”
 - d. **Note: at an interim timepoint, if an AE is classified as both a ‘baseline AE’ and a ‘post baseline AE’ due to data issues, the AE is to be considered a ‘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:
 - i. 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), and has onset date within the safety reporting period then check the following criteria:
 - 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'
 - If the post-baseline AE is reported as related to study treatment then assign TEAE flag to 'Y'
 - If the baseline AE is not a serious AE and the post-baseline is a serious AE then assign TEAE flag to 'Y'
 - If any of these criteria are satisfied then the post-baseline AE and all subsequent episodes of the same AE should have TEAE flag = 'Y'. Otherwise, assign TEAE flag to 'N'
 - d. If the post-baseline AE is not a continuing event of a baseline AE and has onset date within the safety reporting period then assign TEAE flag to 'Y'. Otherwise assign TEAE flag to 'N'

Appendix C: Imputation of new anticancer therapy dates

New anticancer therapy start date will be imputed if both month and year are present and only day is missing.

If the year of the New anticancer therapy start date is the same as the year of the EOT date,

- If the month of new anticancer therapy start date is the same as the month of the EOT date, then its start date will be imputed as the EOT date.
- If the month of the new anticancer therapy start date is later than the month of the EOT date, then its start date will be imputed as the first day of the month.
- If the month of the new anticancer therapy start date is earlier than the month of the EOT date, then the new anticancer therapy start date will be imputed as the last day of the month.

If the year of the new anticancer therapy start date is later than the year of the EOT date, then the new anticancer therapy start date will be imputed as the first day of the month.

If the EOT date is missing, then for the purpose of the imputation the EOT date will be considered the end-of-study (EOS) date or 110 days after the last dose of any study drug, whichever is earlier.

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eSignature Approval	PPD Clinical Development 19-Jan-2024 01:19:29 GMT+0000
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