STATISTICAL ANALYSIS PLAN

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Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

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LIST OF ABBREVIATIONS

AE	adverse event
ATA	antitherapeutic antibodies
ASCT	autologous stem cell transplant
AUC	area under the concentration-time curve
C_{eoi}	concentration at the end of infusion
C_{max}	maximum concentration
C_{trough}	trough concentration
CI	confidence interval
CR	complete remission
CSR	clinical study report
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
EOT	end of treatment
eCRF	electronic case report form
HL	Hodgkin lymphoma
IHC	immunohistochemistry
IRR	infusion related reaction
IPI	international prognostic index
MedDRA	medical dictionary for regulatory activities
MMAE	monomethyl auristatin E
NCI CTCAE	national cancer institute common terminology criteria for adverse events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PFS	progression-free survival
PK	pharmacokinetics
PN	peripheral neuropathy
PR	partial remission
SAE	serious adverse event
SAP	statistical analysis plan
SMC	safety monitoring committee
SPD	sum of the products of the largest diameter
T_{max}	time at which the maximum concentration occurs
WHO	world health organization

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGN35-025, entitled 'A phase 1/2 study evaluating brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma after failure of frontline therapy'. 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

- To assess the safety profile of brentuximab vedotin administered in combination with nivolumab in patients with relapsed or refractory HL
- To assess the antitumor activity of brentuximab vedotin administered in combination with nivolumab in patients with relapsed or refractory HL

2.2 Secondary Objectives

- To assess the objective response rate (ORR)
- To assess the duration of complete remission (CR) and objective response (OR)
- To assess progression-free survival (PFS) after autologous stem cell transplant (ASCT)

2.3 Additional Objectives

- To assess overall survival (OS)
- To compare the CR rate in patients who relapsed after frontline therapy with the CR rate in patients who were refractory to frontline therapy
- To assess the feasibility of stem cell mobilization and collection after treatment with brentuximab vedotin in combination with nivolumab
- To assess PFS
- To assess pharmacokinetics and antitherapeutic antibody (ATA) incidence of each study drug given in combination
- To assess tumor amplification and expression of PD-L1/L2 and relationship to response
- To assess tumor microenvironment and peripheral immune status

3 STUDY ENDPOINTS

3.1 Primary Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events and laboratory abnormalities
- Complete remission rate following the completion of study treatment

3.2 Secondary Endpoints

- Objective response rate
- Duration of CR and OR
- Progression-free survival post-ASCT

3.3 Additional Endpoints

- Overall survival
- PFS
- Selected PK, ATA, and biomarker endpoints

4 STUDY DESIGN

This is a phase 1/2, open-label, multicenter study designed to evaluate the safety and antitumor activity of brentuximab vedotin treatment combined with nivolumab in patients with relapsed or refractory Hodgkin lymphoma after failure of frontline therapy.

Part 1 of the study will evaluate safety of possible dosing regimens for the combination treatment prior to expansion of enrollment. Following completion of Part 1, Part 2 and 3 of the study will further evaluate safety and efficacy of the combination treatment.

The safety of combination treatment in Part 1 will be evaluated by a Safety Monitoring Committee (SMC) prior to expansion of enrollment in Part 2 to evaluate treatment effect. In Part 1, after 6 patients have been followed through the end of the dose-limiting toxicity (DLT) period, or at the point that 2 or more patients experience a DLT, whichever comes first, the SMC will review all available data and make a recommendation for one of the following:

1. To proceed to Part 2 of the study, expanding enrollment with approximately 50 additional patients treated with the study drugs at the doses and schedule determined to be safe in Part 1 of the study
2. To repeat Part 1 of the study and treat up to 6 additional patients, possibly with a modified dosing regimen
3. To close the study to further enrollment

Following completion of enrollment of Part 1 and Part 2, the study was amended to add Part 3. Approximately 30 additional patients will be enrolled for Part 3.

Patients will be treated for up to four 21-day cycles. Unless subsequently modified based on planned SMC review, treatment will be administered as described in this paragraph. In Parts 1 and 2, the first dose of brentuximab vedotin 1.8 mg/kg will be given on Cycle 1 Day 1. The first dose of nivolumab 3 mg/kg will be given on Cycle 1 Day 8. For Cycle 2 and all subsequent cycles, brentuximab vedotin 1.8 mg/kg followed by nivolumab 3 mg/kg will be given on Day 1. In Part 3, both brentuximab vedotin 1.8 mg/kg and nivolumab 3 mg/kg will be administered on Day 1 of all Cycles. For patients in Part 3 who were previously treated with brentuximab vedotin and had a dose reduction, dose assignment must be discussed with the medical monitor.

Lymphoma response and progression will be assessed by investigators using the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014). CT scans (chest, neck, abdomen, and pelvis) and PET scans will be performed at baseline, at the End of Treatment (EOT), pre-ASCT, and during long-term follow-up; PET is performed with CT scans until the patient is in complete metabolic response (CmR) by PET. Pre-ASCT scans may be waived for patients who had an EOT scan performed within 6 weeks prior. CT scans of diagnostic quality will be performed at Cycle 2 to assess for progression of disease. Long-term follow-up assessments will be performed at the following time points post-ASCT (or for patients who do not undergo ASCT, post-EOT): 100 days and then 6, 9, 12, 18, 24, 30, and 36 months, and then per institutional standard thereafter. A final safety visit will be performed 100 days after the last dose of nivolumab or at EOT (whichever is later) to assess for potential immune-mediated adverse events. Patients will be followed at this schedule until withdrawal of consent, death, or study closure, whichever occurs first.

For Part 3 response assessments were modified to inclue the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC), which allows for an assessment of indeterminate response in cases where apparent progression may be due to the immunomodulatory effects of the treatment and not due to true disease progression.

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 All Enrolled Patients Analysis Set

The All Enrolled Patients analysis set includes all patients enrolled in the study. The All Enrolled Patients set will be used for the primary efficacy analysis. Secondary and additional efficacy endpoints will also be analyzed using this analysis set. Patients will be analyzed according to the dose regimen to which they were enrolled.

5.2 All Treated Patients Analysis Set

The All Treated Patients analysis set includes all patients who receive any amount of brentuximab vedotin or nivolumab. The All Treated Patients set will be used for presentation of safety data and may be used for exploratory analyses of efficacy endpoints.

5.3 Efficacy Evaluable (EE) Analysis Set

The Efficacy Evaluable analysis set includes all patients who had an adequate baseline disease assessment, received any amount of either drug, and subsequently had an adequate response assessment. The Efficacy Evaluable set will be used for exploratory analysis of efficacy endpoints. Patients will be analyzed according to actual dose regimen received.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

This is a phase 1/2 open label study with a formal statistical hypothesis for the primary efficacy endpoint of CR rate. The test of the primary endpoint will be at level $\alpha = 0.05$, using a 1-sided test. There are no formal pre-specified hypotheses associated with the primary safety objective, and no additional hypothesis tests of secondary endpoints.

Descriptive statistics (mean, median, standard deviation, minimum, maximum) will be used to describe continuous variables. Frequencies and percentages will be used to describe categorical variables. The median survival time will be estimated using the Kaplan-Meier method; the associated confidence interval (CI) will be calculated based on the complementary log-log transformation (Collett 1994). Unless otherwise specified, confidence intervals will be calculated at a two-sided 95% level.

Patients will be summarized overall and by dose regimen, unless otherwise specified in section 7. Additional summaries may be performed by selected patient characteristics and for subgroups of interest.

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 CSR.

6.2 Determination of Sample Size

It is anticipated that a total of approximately 55 patients will be enrolled in this study in parts 1 and 2. For Part 3 approximately 30 patients will be enrolled. This number for Part 1 and 2 was chosen in order to enable an adequately powered analysis of the primary endpoint of CR rate and to characterize the safety profile of the combination treatment. This number will be

greater if multiple dose regimens are investigated in Part 1 of the study as only those patients from Part 1 who are treated with the dose regimen chosen for Part 2 will be included in the analysis of the primary endpoint.

The sample size needed to provide adequate power to test the primary endpoint is at least 53. With this sample size, if the true CR rate is 50%, a one-sided exact binomial test at level α=0.05 will reject the null hypothesis of a CR rate less than or equal to 30% approximately 90% of the time. For the given parameters the null hypothesis will be rejected when 22 or more CRs are observed (i.e., CR rate ≥41.5% is observed).

For Part 3, no formal hypothesis test is specified. The sample size of 30 patients was chosen to allow adequate precision of estimates for response rates and safety data. For example, if 63% (19/30) of patients have a CR, then the 95% exact CI is (44%, 80%). The sample size of 30 patients is sufficient to perform exploratory biomarker analyses.

For the safety assessment of the combination treatment, a sample size of 55 patients will provide a 94% chance of observing at least one occurrence of an adverse event with a true event rate of 5%.

East 5.4 was used to perform sample size calculations.

6.3 Randomization and Blinding

No randomization will be carried out and no blinding will be enforced as this is an open label trial.

6.4 Data Transformations and Derivations

No data transformations are planned for the primary endpoints.

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 any 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

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.

For efficacy assessments, the date of response will be the latest of all radiologic scan dates for the given restage assessment. The date of progression will be the earliest of all radiologic scan dates for the given restage assessment, or the date of investigator claim of clinical progression. An adequate tumor assessment to determine response must include a radiologic(CT) scan and a PET scan. Determination of progression by radiologic assessment may be based on CT or PET alone if there is clear evidence of PD by one of these modalities. While a radiologic assessment to confirm progression is strongly preferred, an investigator claim of clinical progression is adequate for an assessment of PD.

6.5 Handling of Dropouts and Missing Data

With the exception of AE dates, missing data will not be imputed.

AE dates will be imputed for the purpose of calculating duration of events and treatment-emergent status (see Appendix A for imputation details and Appendix B for treatment-emergent definition). Censoring for time-to-event endpoints will be described in Section 7.5. with each planned analysis, as applicable.

Patients whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate and ORR. Patients with missing values of a variable other than response endpoints (CR and ORR) and time-to-event endpoints (PFS and OS) will be excluded from the analysis of that endpoint unless otherwise specified.

6.6 Multicenter Studies

There are multiple sites in this study; however it is not anticipated that any one site will accrue enough patients to warrant an analysis by site.

6.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed as there is only a single planned hypothesis test of the primary efficacy endpoint.

6.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected summaries. Subgroups may include but are not limited to the following:

- Age (18-64 years, ≥65 years old)
- Gender (Male, Female)
- Categorized weight at baseline(<70, 70-99 and >=100 kg)

- Baseline ECOG performance status (0, 1, 2)

6.9 Covariates

Adjustment for covariates will not take place for analysis of the primary efficacy endpoint of CR rate. Subgroup analyses and covariate adjusted analyses may be carried out for particular covariates of interest. Exploratory analysis of biomarker and pharmacodynamic endpoints may also incorporate covariate adjustment.

6.10 Timing of Analyses

The trial is not designed to allow for early stopping for futility or favorable efficacy results.

Analysis including hypothesis test of the CR rate for the primary endpoint for parts 1 and 2 will be carried out after all patients have had their final response assessment prior to proceeding to ASCT, starting a new anti-cancer therapy, or discontinuing from the study.

Interim summaries of various endpoints may be presented at scientific congresses prior to the final analysis of the primary endpoint. Interim summaries will also be presented to the SMC.

7 PLANNED ANALYSES

7.1 Disposition

An accounting of study patients by disposition will be tabulated overall and by dose regimen

- The number of patients in each analysis set will be summarized.
- The number and percentage of patients who discontinued treatment will be summarized by the primary reason for treatment discontinuation.
- The number and percentage of patients who discontinued the study will be summarized by the primary reason for study discontinuation.
- The number and percentage of screened patients who subsequently enrolled will be summarized.
- Follow up time and subsequent treatment information will be summarized.
- The number of screen failures will be summarized overall and by primary reason for screen failure.

Listings of disposition data will be presented by patient for all enrolled patients, including the primary reasons for end of treatment and end of study for each subject.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be presented as listings and in tabular form overall and by dose regimen using the all enrolled patients analysis set. Demographics and baseline characteristics include age, gender, ethnicity, race, height, and weight.

The following disease specific characteristics will be summarized with respect to initial diagnosis and baseline status (as appropriate):

- initial disease diagnosis
- time from initial diagnosis to first dose of study drug
- time from relapse to first dose of study drug
- number and type of prior therapies
- response to prior lines of therapy
- disease stage
- bulky disease status
- extranodal disease status
- bone marrow disease involvement
- B symptoms
- current disease status relative to fronline treatment.

7.3 Protocol Deviations

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

7.4 Treatment Administration

Treatment administration will be summarized overall and for each dosing schedule using the All Treated Patients analysis set. Summary statistics for duration of therapy (weeks) and the number of cycles per patient will be presented, as well as the number and percentage of patients who were treated at each cycle and completed each cycle. Cumulative dose (mg), absolute dose intensity (ADI) and relative dose intensity (RDI) will be described. The number and percentage of patients whose dose was ever modified will be summarized by modification type, cycle and overall (i.e. overall drug administrations for a patient); listings may be presented as well. Dose modifications by dose may also be presented.

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

1. last dose date of any infusional component of study treatment + 21, or;

2. date of death

For the purpose of calculating exposure summaries, duration of treatment is defined as time from the first dose to 21 days after the last dose [(last dose date+21)–first dose date].

Intended Dose Intensity (IDI) is defined as the intended dose of drug (e.g. 1.8 mg/kg) per unit of time. Intended dose is based on the dose which was intended to be administered at the

start of the planned treatment regimen (thus a dose reduction or elimination is not considered planned, even though it may be indicated per protocol due to, e.g., occurrence of AEs). If a patient discontinues treatment for a reason unrelated to AEs, such as progressive disease, then the subsequent doses are not considered as intended for the purpose of calculating dose intensity. The IDI for brentuximab vedotin and nivolumab at possible dose regimens is presented in the following table:

Regimen Component	Intended Dose Regimen	Unit of time per cycle (weeks)	IDI
brentuximab vedotin	1.8 mg/kg	3	0.60
brentuximab vedotin	1.2 mg/kg	3	0.40
nivolumab	3 mg/kg	3	1.00
nivolumab	1 mg/kg	3	0.33

Absolute Dose Intensity (ADI) is defined as the actual dose (e.g. 1.8 mg/kg) per unit of time that the patient received over the entire treatment period.

Relative dose intensity (RDI) is defined as the absolute dose intensity over the intended dose intensity.

$$RDI = ADI/IDI * 100.$$

Example dose intensity calculation

For brentuximab vedotin, consider a patient treated with an intended dose regimen of 1.8 mg/kg for four cycles. The second dose was delayed for one week, and for the third cycle of the infusion was not completed and the patient received less than the full dose. At the fourth cycle the dose is not given at all due to an AE.

Visit	Intended Dose Regimen (mg/kg)	Intended Dose (mg)	Actual Dose (mg)	Cycle Length
C1D1	1.8	38	38	3 weeks + 1 week delay
C2D1	1.8	38	38	3 weeks
C3D1	1.8	38	19	3 weeks
C4D1	1.8	38	0	3 weeks

ADI (per week):

= (1.8 + 1.8 + (1.8*[19/38]) + 0) / (3 wks + 1 wk delay + 3 wks + 3 wks + 3 wks) mg/kg per week

=0.35 mg/kg per week

RDI:

=0.35/0.6 * 100

=58%

7.5 Efficacy Analyses

The test of the primary efficacy endpoint of CR rate will be carried out using the All Enrolled Patients analysis set. Other efficacy analyses will be carried out using the All Enrolled Patients analysis set, and may also be presented using the Efficacy Evaluable analysis set or the All Treated Patients analysis set.

Unless otherwise specified, efficacy analyses will be presented by dose regimen and overall.

Additional exploratory subgroup analyses may be carried out as well.

7.5.1 Primary Efficacy Endpoints

7.5.1.1 Complete Remission (CR) Rate

CR rate is defined as the proportion of patients with best response of CR prior to ASCT or initiation of subsequent antitumor treatment not specified in the protocol. Response is by investigator assessment according to the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014). For Part 3, the response assessment will also incorporate the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2016). Patients whose response to treatment cannot be adequately assessed according to the specified criteria will be classified as non-responders for the purpose of calculating CR rate.

The primary efficacy hypotheses can be expressed as follows:

H_0: CR Rate for brentuximab vedotin + nivolumab is $\leq$30%

H_A: CR Rate for brentuximab vedotin + nivolumab is >30%

The CR rate at EOT will be calculated using the All Enrolled Patients analysis set and will include all patients in this analysis set who were enrolled at the dose regimen chosen for Part 2. The test of the primary hypothesis will be carried out using a one-sided exact binomial test at level $\alpha = 0.05$, thus the null will be rejected in favor of the alternative if $p < 0.05$ is observed. CR rate and its two-sided 90% (to correspond with the level of the test) exact binomial confidence interval will be calculated (Clopper 1934). Additionally, the two-sided 95% exact binomial confidence interval will be presented as a descriptive summary.

CR rate will also be summarized separately for patients enrolled under dose regimens other than that chosen for part 2 of the study. Overall summaries of CR rate may be presented as well. These summaries will be considered exploratory in nature.

7.5.2 Secondary Efficacy Endpoints

7.5.2.1 Objective Response Rate (ORR)

ORR is defined as the proportion of patients with best response of CR or PR prior to ASCT or initiation of subsequent antitumor treatment not specified in the protocol. Response is by investigator assessment according to the Lugano Classification Revised Staging System for malignant lymphoma (Cheson 2014). Patients whose response to treatment cannot be

adequately assessed according to the specified criteria will be classified as non-responders for the purpose of calculating ORR.

The ORR at EOT will be calculated using the All Enrolled Patients set and its two-sided 95% exact binomial confidence interval will be presented (Clopper 1934). ORR will be presented by dose regimen and overall. Additional summaries of ORR may be presented based on patient demographics of interest. Summaries may also be presented using the All Treated Patients and the Efficacy Evaluable analysis sets.

7.5.2.2 Progression-Free Survival (PFS) after ASCT

PFS after ASCT is defined as the time from ASCT to the first documentation of PD or to death due to any cause, whichever comes first. Patients who do not undergo ASCT or receive additional anti-cancer therapy (such as an alternate salvage regimen) prior to ASCT will not be included in the analysis of this endpoint. Date of ASCT is defined as the reported date of stem cell infusion for ASCT. Documentation of PD should be consistent with the criteria described in section 6.4. Specifically, PFS after ASCT will be calculated as:

PFS after ASCT = Date of first documented PD or death – Date of ASCT + 1.

PFS data will be censored as follows:

- Patients who do not have tumor progression and are still on study at the time of an analysis will be censored at the date of the most recent disease assessment prior to the analysis which was adequate to document progressive disease
- Patients who have started an antitumor treatment (excluding high-dose conditioning regimens pre-ASCT, consolidative radiotherapy pre- or post-ASCT, or consolidative treatment with single-agent brentuximab vedotin post-ASCT) other than the study treatment prior to documented PD will be censored at the date of the most recent disease assessment which was adequate to document PD prior to start of new therapy
- Patients who are removed from study prior to documentation of tumor progression will be censored at the date of the most recent disease assessment prior to study discontinuation which was adequate to document disease progression

If a patient does not have any adequate disease assessments after ASCT their PFS will be censored at one day.

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

Exploratory subgroup analyses may be carried out; these analyses may involve different definitions of events and/or different censoring rules.

7.5.2.3 Duration of Complete Remission

Duration of complete remission is defined as the time from start of the first documentation of complete response (CR) to the first documentation of tumor progression (PD) including radiographic evidence of progression and clinical progression per investigator or to death due to any cause, whichever comes first.

Duration of complete remission will be censored as described below:

- Patients who do not have documented tumor progression and are still on study at the time of analysis will be censored at the date of the most recent disease assessment prior to the analysis which was adequate to document progressive disease
- Patients who have started an antitumor therapy (excludes stem cell transplant or post-ASCT consolidative therapy) other than the study treatment prior to documentation of tumor progression will be censored at the date of the most recent disease assessment prior to start of new therapy which was adequate to document progressive disease
- Patients who are removed from study prior to documentation of tumor progression will be censored at the date of the most recent disease assessment prior to study discontinuation which was adequate to document progressive disease.

If a patient does not have any disease assessments adequate to detect PD after the first documentation of complete response their duration of complete remission will be censored at one day.

Duration of complete remission will only be calculated for the subgroup of patients achieving CR. Duration of complete remission will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median duration of complete remission and its two-sided 95% CI using the complementary log-log transformation method (Collett, 1994) will be calculated.

7.5.2.4 Duration of Objective Response

Duration of objective response 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 (progressive disease, PD) including radiographic evidence of progression and clinical progression per investigator or to death due to any cause, whichever comes first.

Duration of objective response will be censored as described below:

- Patients who do not have documented tumor progression and are still on study at the time of analysis will be censored at the date of the most recent disease assessment prior to the analysis which was adequate to document progressive disease
- Patients who have started an antitumor therapy (excludes stem cell transplant or post-ASCT consolidative therapy) other than the study treatment prior to documentation of tumor progression will be censored at the date of the most recent disease assessment prior to start of new therapy which was adequate to document progressive disease

- Patients who are removed from study prior to documentation of tumor progression will be censored at the date of the most recent disease assessment prior to study discontinuation which was adequate to document progressive disease.

If a patient does not have any disease assessments adequate to detect PD after the first documentation of objective response their duration of objective response will be censored at one day.

Duration of objective response will only be calculated for the subgroup of patients achieving CR or PR. Duration of objective response will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median duration of objective response and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated.

7.5.3 Additional Efficacy Endpoints

7.5.3.1 Overall Survival (OS)

Overall survival is defined as the time from date of enrollment to date of death due to any cause. In the absence of confirmation of death, overall survival time will be censored at the last date the patient is known to be alive. Patients lacking data beyond the date of enrollment will have their overall survival time censored to 1 day.

OS=Date of death – Date of enrollment + 1.

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

7.5.3.2 Progression-Free Survival (PFS)

PFS is defined as the time from enrollment to the first documentation of PD or to death due to any cause, whichever comes first. Specifically, PFS will be calculated as:

PFS = Date of first documented PD or death – Date of enrollment + 1.

Progressive disease should be based on radiologic evidence of progression per investigator, but investigator claim of clinical progression will be considered adequate to document PD. In the case where both PD by radiologic assessment and clinical assessment are made, the earlier of the two possible dates is used as as the date of PD.

Censoring rules are as follows:

- Patients who do not have tumor progression and are still on study at the time of an analysis will be censored at the date of the most recent disease assessment prior to the analysis which was adequate to document progressive disease

- Patients who have started an antitumor treatment (excluding high-dose conditioning regimens pre-ASCT, consolidative radiotherapy pre- or post-ASCT, or consolidative treatment with single-agent brentuximab vedotin post-ASCT) other than the study treatment prior to documented PD will be censored at the date of the most recent disease assessment which was adequate to document PD prior to start of new therapy
- Patients who are removed from study prior to documentation of tumor progression will be censored at the date of the most recent disease assessment prior to study discontinuation which was adequate to document disease progression

If a patient does not have any adequate disease assessments after enrollment their PFS will be censored at one day.

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

An additional exploratory analysis of PFS may be conducted in which clinical assessment will be considered adequate to detect disease progression. Other exploratory analyses of PFS may also be performed. These analyses may involve different definitions of events and/or different censoring rules.

7.5.4 Pharmacokinetic and ATA Analyses

Pharmacokinetic parameters to be estimated for brentuximab vedotin and MMAE include maximum concentration (Cmax) or concentration at the end of infusion (Ceoi), the time Cmax occurred (Tmax), and trough concentration for brentuximab vedotin (Ctrough). For nivolumab, Ceoi and Ctrough will be summarized. The incidence of ATA to brentuximab vedotin and to nivolumab will also be assessed.

If additional pharmacokinetic parameters can be estimated for some subjects, they may also be reported.

7.5.5 Biomarker Analysis

Relationships of biomarkers (e.g., baseline values, absolute and relative changes from baseline) to efficacy, safety and PK parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized.

Summaries will be presented for baseline biomarker levels assessed on peripheral blood and tissue blocks or unstained slides obtained at screening to evaluate potential sensitivity or resistance to brentuximab vedotin and/or nivolumab (e.g., CD30 expression, PD-L1 /L2 amplification and expression). For biomarker analyses on optional tumor biopsies obtained after disease progression or on residual disease at EOT, samples are to be tested for the expression of CD30 and PD-L1/L2 expression and other potential markers to understand potential resistance mechanisms.

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.

7.6 Safety Analyses

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

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 18.0 or higher).

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

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

7.6.1 Adverse Events

Adverse events (AEs) will be listed and summarized by MedDRA preferred term, severity, and relationship to study drug in descending frequency unless otherwise specified. The incidence of all AEs, treatment-emergent AEs, and treatment-related AEs will be tabulated. 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 brentuximab vedotin or nivolumab. The incidence of AEs will be tabulated by preferred term and presented by dose regimen and overall. Summaries will also be presented for AEs occurring prior to start of ASCT and on or after start of ASCT, where start of ASCT is defined as the start date of conditioning regimen for ASCT. Summaries of AEs will also be provided dose regimen and overall for the following:

- Pre-existing Adverse Events
- All treatment-emergent AEs
- AEs related to brentuximab vedotin
- AEs related to nivolumab
- Serious Adverse Events (SAEs)
- SAEs related to brentuximab vedotin
- SAEs related to nivolumab
- AEs leading to dose delay of brentuximab vedotin or/and nivolumab
- AEs leading to dose reduction of brentuximab vedotin or/and nivolumab
- AEs leading to dose interruption (full dose received) of brentuximab vedotin or/and nivolumab

- AEs leading to dose elimination of brentuximab vedotin or/and nivolumab
- AEs leading to treatment discontinuation
- AEs that started during infusion,
- AEs that started within 24 hours post infusion,
- Treatment-emergent AEs by system organ class, preferred term and maximum severity; at each system organ class or preferred term, multiple occurrences of events within a patient are counted only once at the highest severity
- Grade 3 – 5 treatment-emergent AEs
- Treatment-emergent AEs by system organ class and preferred term
- AEs of peripheral neuropathy identified by the broad search MedDRA SMQ "peripheral neuropathy"
- Infusion related reactions due to brentuximab vedotin, or/and nivolumab
- Onset of infusion reactions related to brentuximab vedotin, or/and nivolumab by preferred term by cycle

Listings will be presented for all adverse events, serious adverse events, adverse events leading to treatment discontinuation, and adverse events leading to death.

7.6.1.1 Adverse Events of Special Importance

Adverse events of peripheral neuropathy, infusion related reactions, immune-related AEs, and other rare serious AEs may be considered AEs of special importance.

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

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

Time to resolution is computed from start date of first treatment emergent episode of the event or start date of newly onset event after first dose of treatment drug to date of resolution.

Time to improvement is computed from start date of the worst grade of the event. Time to resolution /improvement will be summarized at the event level.

For summaries of events or summaries of patients with events ongoing at EOT, EOT is defined as the EOT visit or 30 days after the last dose of either study drug.

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

Peripheral Neuropathy

Peripheral Neuropathy (PN) is defined by the peripheral neuropathy MedDRA SMQ broad search. The incidence of PN at baseline will be summarized. The incidence of treatment-emergent and treatment-related PN will each be summarized by 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 all 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.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.

Infusion related reactions

Infusion related reactions (IRR) are defined as any event indicated as IRR by the investigator. The incidence of IRR will be summarized by preferred term and severity. The incidence of IRR leading to treatment discontinuation or requiring dose modification will be summarized for each infusional study drug component. The number of cycles of treatment to first onset of IRR will be summarized.

7.6.1.2 Clinical Laboratory Parameters

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

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

7.6.2 Concomitant Medications

Concomitant medications will be summarized by the WHO Drug substance name and listed by patient. Transfusions, colony-stimulating factors, corticosteroids, and erythropoietin stimulating agents will also be summarized by the WHO Drug substance name. Summaries will also be presented for the subset of patients who had any IRR reported, as well as for the subset of patients who had any immune-related AE reported.

7.6.3 Deaths

Summaries of deaths will be presented by dose regimen and overall. Deaths that occur within the safety reporting period (i.e., within 30 days of last study treatment with brentuximab vedotin or 100 days of nivolumab, whichever is later) will be presented, as well as deaths that occur beyond this time point. In addition, primary cause of death will be summarized by descending MedDRA preferred term (unless otherwise specified) and summarized by dose regimen and overall. Death information will be listed by patient.

8 INTERIM ANALYSIS

An SMC consisting of all Principal Investigators and the sponsor's Medical Monitor will monitor the trial for safety and efficacy and will convene periodically during the study.

In Part 1 of the study, an SMC will monitor the trial for safety and provide guidance regarding possible enrollment of additional patients in Part 1 and possible expansion of enrollment in Part 2. Initially 6 patients will be enrolled in Part 1. If a patient discontinues treatment for reasons other than a DLT prior to 6 patients completing the DLT evaluation period then they will be replaced (as long as the arm remains open). These patients will be monitored for DLT throughout the DLT evaluation period. The SMC will review safety data and provide recommendations when either of the following occurs:

1. 2 or more of the patients in the current arm are determined to have had a DLT based on the protocol definition.
2. 6 patients complete the DLT evaluation period (by either remaining on treatment or having a DLT).

On review of all available data, the SMC may determine that the classification of DLT was not appropriate for one or more of the patients, in which case enrollment may resume if the target of 6 patients has not yet been reached. However, if 2 or more patients were determined to have experienced DLT, then expansion will not occur as the next step. Based on SMC recommendations, additional patients may be enrolled at modified treatment and/or dosing levels. These additional patients will then be assessed for DLT in the same manner described above to determine if it is appropriate to expand enrollment. If it is determined by the SMC that due to safety concerns no additional dose levels or schedules should be enrolled, then the study will be closed to enrollment.

An ongoing real-time review of serious AEs (SAEs) in all parts of this study will be conducted by the Seattle Genetics Program Safety Monitoring Team.

Additionally, 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

There are no changes from the original protocol.

10 REFERENCES

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

Collett D (1994). Interval-censored survival data. Modelling survival data in medical research. London, Chapman & Hall: 237-251.

APPENDIX A: IMPUTATION OF PARTIALLY UNKNOWN ADVERSE EVENT DATES

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

AE day and month are missing

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

AE month only is missing

- Treat day as missing and replace both month and day according to the above procedure

AE day only is missing

- If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was pre-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of investigational agent)
- If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was post-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, first dose date of investigational agent)

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

* Only use condition end date if known and complete end date is available.

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

After sorting the AE records, apply the following rules to partial or missing AE condition end dates:

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

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

For the last chronological record for a condition/event

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

Example 1

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

Prior to imputation

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

Post imputation

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

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

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

Prior to imputation

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

Post imputation

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

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) Determine the first/earliest dose date of any study treatment (for combination studies this includes any component of the regimen)

2) **Baseline AEs:** classify an AE as a baseline AE if it satisfies both of criteria 1 and 2 below:

    1. The onset period field is: "started before the signing of informed consent"; or "started after consent but before the first dose of any study treatment"; or, the onset period field is missing and the AE start date is prior to the first dose date of any study drug (step 1, above).
    2. The stop date satisfies either of i or ii below:
        i. The stop date is the same as or a later date than the first dose date of any study treatment
        ii. The stop date is missing with outcome equal to
            - recovering/resolving (this outcome may or may not be associated with a date), or
            - not recovered/not resolved, or
            - unknown.
            - Note: if the AE has no outcome or stop date provided, the CRF data should be queried

    Note: If the event ended on Day 1 (the date of first dose of any study drug) it will be considered a baseline event.

3) **Post-baseline AEs:** classify an AE as post-baseline if it meets either of criteria 1 or 2 below:

    1. The onset period of the AE is "started after the first dose of any study treatment"
    2. The onset period of the AE is missing and the AE start date is the same as or a later date than the first dose date of any study treatment

4) Compare post-baseline AEs to baseline AEs using the lower level term (LLT) and determine classification. **Note that classification may not be possible and the TEAE variable will be missing**:

    1. Classify all baseline AEs as not treatment emergent (not TEAEs).
    2. If a baseline and post-baseline AE have the same LLT but the post-baseline AE has a greater CTC grade then classify the post-baseline AE as a TEAE. If the post-baseline

grade is less than or equal to the baseline grade then the post-baseline AE is not a TEAE.

3. If there are no baseline AEs with a matching LLT for the post-baseline AE then classify the post-baseline AE as a TEAE.
4. If the post-baseline AE is uncoded then classify the post-baseline AE as a TEAE.

NOTE:

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.

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).