# SeattleGenetics

STATISTICAL ANALYSIS PLAN

Protocol Number: SGN35-017

Version: Version 1 19-SEP-2016

Protocol Title: A phase 2 study of brentuximab vedotin in combination with standard of care treatment (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [RCHOP]) or RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) as front-line therapy in patients with diffuse large B-cell lymphoma (DLBCL)

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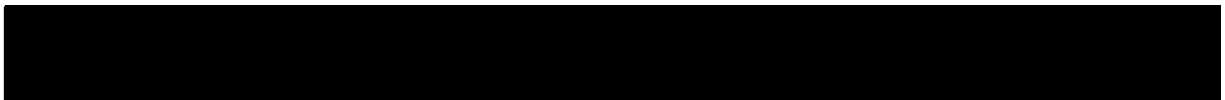
APPROVAL SIGNATURES

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

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LIST OF ABBREVIATIONS

AAIPI	age-adjusted international prognostic index
A+RCHOP	brentuximab vedotin (ADCETRIS®), rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
A+RCHP	brentuximab vedotin (ADCETRIS®), rituximab, cyclophosphamide, doxorubicin, and prednisone
ADC	antibody-drug conjugate
AE	adverse event
CI	confidence interval
CR	complete remission
CSR	clinical study report
DLBCL	diffuse large B-cell lymphoma
ECG	electrocardiogram
ECOG	eastern cooperative oncology group
EOT	end of treatment
eCRF	electronic case report form
GCB	germinal center B-cell
IHC	immunohistochemistry
IRR	infusion related reaction
IPI	international prognostic index
LDH	lactate dehydrogenase
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
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
PFS	progression-free survival
PK	pharmacokinetics
PN	peripheral neuropathy
PR	partial remission
RCHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
SMC	safety monitoring committee
WHO	world health organization

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGN35-017, entitled 'A phase 2 study of brentuximab vedotin in combination with standard of care treatment (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [RCHOP]) or RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) as front-line therapy in patients with diffuse large B-cell lymphoma (DLBCL)'. 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 antitumor activity of brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone, as measured by the CR rate at the end of treatment per investigator assessment in treatment-naive patients with high-intermediate or high risk systemic DLBCL

- To assess the safety profile of brentuximab vedotin administered at dose levels of 1.2 mg/kg versus 1.8 mg/kg in combination with RCHOP or brentuximab vedotin 1.8 mg/kg in combination with RCHP in treatment-naive patients with high-intermediate or high risk systemic DLBCL

2.2 Secondary Objectives

- To assess the antitumor activity of brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone, as measured by the objective response rate (ORR) at the end of treatment per investigator assessment

- To assess the progression-free survival (PFS) associated with brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone

- To assess survival associated with brentuximab vedotin administered in combination with RCHOP or RCHP, and in combination with RCHP versus RCHOP alone

2.3 Additional Objectives

- To assess CD30 expression on tumor specimens

- To assess the pharmacokinetics (PK) of brentuximab vedotin administered in combination with RCHOP or RCHP

3 STUDY ENDPOINTS

3.1 Primary Endpoints

- Complete remission (CR) rate per investigator assessment following the completion of study treatment

- Type, incidence, severity, seriousness, and relatedness of adverse events and laboratory abnormalities

3.2 Secondary Endpoints

- ORR per investigator

- PFS per investigator

- Overall survival (OS)

3.3 Additional Endpoints

- CD30 expression on tumor specimens

- Estimates of selected PK parameters

4 STUDY DESIGN

This study has three parts. Part 1 of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin 1.2 and 1.8 mg/kg when administered in combination with standard RCHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone); this regimen is abbreviated as A+RCHOP. Part 2 of the study is a phase 2, non-randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin 1.8 mg/kg when administered in combination with RCHP chemotherapy (rituximab, cyclophosphamide, doxorubicin, and prednisone); this regimen is abbreviated as A+RCHP. Part 3 of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of brentuximab vedotin 1.8 mg/kg when administered in combination with RCHP chemotherapy compared to RCHOP chemotherapy alone.

In Part 1, a total of approximately 50 patients will be randomized 1:1 into 2 dosing cohorts of 1.2 or 1.8 mg/kg brentuximab vedotin administered in combination with RCHOP. Randomization in this part of the study is for the purpose of evaluating the safety of 1.2 mg/kg and 1.8 mg/kg brentuximab vedotin in combination with RCHOP. Randomization will be stratified by high-intermediate or high risk disease (defined in section 6.3) . The safety of the combination of brentuximab vedotin and RCHOP will be assessed by a Safety Monitoring Committee (SMC).

In Part 2, up to 25 patients will be enrolled into a dosing cohort with 1.8 mg/kg brentuximab vedotin administered in combination with RCHP. The safety of the combination of brentuximab vedotin and RCHP will also be assessed by the SMC.

In Part 3, a total of approximately 50 patients will be randomized 1:1 into either 1.8 mg/kg brentuximab vedotin administered in combination with RCHP or RCHOP alone. Randomization in this part of the study is for the purpose of evaluating the safety of 1.8 mg/kg brentuximab vedotin in combination with RCHP versus standard RCHOP chemotherapy. Randomization will be stratified by high-intermediate or high risk disease. The safety of the combination of brentuximab vedotin and RCHP will also be assessed by the SMC.

Brentuximab vedotin, rituximab, cyclophosphamide, doxorubicin, and vincristine will be administered on Day 1 of every 21-day cycle, for up to 6 cycles. Prednisone will be administered orally on Days 1-5 of every 21-day cycle. Disease response will be assessed by the investigator, based on the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).

Radiographic assessments, including CT scans of chest, neck, abdomen, and pelvis, will be performed at Screening/Baseline, at 5 weeks post last dose of study treatment, every 4 months after the last scan for the first 2 years, and every 6 months thereafter until progression, death, or study closure, whichever comes first

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   Modified Intent-to-treat (mITT) Analysis Set

The mITT analysis set will include all patients who receive any amount of brentuximab vedotin or any component of RCHOP. Randomized patients 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 patients who receive any amount of brentuximab vedotin or any component of RCHOP. For randomized patients (Parts 1 and 3), treatment group will be determined using the actual treatment received, regardless of the randomization treatment assignment. For Part 1, patients receiving 1.8 mg/kg of brentuximab vedotin will be grouped into the 1.8 mg/kg A+RCHOP arm, while patients never recieving 1.8 mg/kg of brentuximab vedotin will be grouped into the 1.2 mg/kg A+RCHOP arm. For Part 3, patients receiving any dose of brentuximab vedotin will be grouped into the A+RCHP arm. Patients who do not receive brentuximab vedotin but any dose of any component of RCHOP will be grouped into the RCHOP arm.

5.3 CD30-positive Analysis Set

The CD30-positive analysis set will include all patients who receive any amount of brentuximab vedotin or any component of RCHOP and who are CD30-positive per the central laboratory.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

Parts 1 and 3 of this study are phase 2, randomized, open-label studies with formal statistical hypotheses for the primary efficacy endpoint. Part 2 of this study is a phase 2, non-randomized, open-label study with no formal statistical hypothesis for the primary efficacy endpoint. For all parts of the study, there are no formal pre-specified statistical hypotheses for the primary safety objective.

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.

All analyses will be evaluated separately for each part of this study; Part 1 will be evaluated by dosing cohort, Part 2 will be evaluated as a single dose cohort, and Part 3 will be evaluated by treatment arm.

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 9.3 or more recent. Other statistical software, if used, will be described in the CSR.

6.2 Determination of Sample Size

Part 1

In order to guarantee enrollment of no less than 25 patients per cohort, approximately 50 patients will be randomized in Part 1 of this study. The null hypothesis is assumed to be a 70% CR rate in both cohorts combined. The alternative hypothesis is that the CR rate is ≥84%. With a two-sided alpha level of 0.10 and a sample size of 50 patients, the study has 73% power to reject the null hypothesis when the true CR rate is 84%.

For safety evaluations, with a sample size of 50 patients, the study would provide an 88% chance of observing at least 3 occurrences (6%) of a clinically relevant adverse event (AE)

with a true event rate of 10%. Within each cohort, at least 25 patients would provide a 93% chance of observing at least 1 occurrence (5%) of a clinically relevant AE with a true event rate of 10%.

Part 2

In order to guarantee enrollment of no fewer than 25 evaluable patients, approximately 25 patients will be enrolled in Part 2 of this study. Although there is no formal statistical hypothesis, a sample size of 25 patients is considered adequate to detect antitumor activity of A+RCHP within this group of CD30-positive DLBCL patients. For safety evaluations within Part 2, a sample size of 25 would provide a 93% probability of observing at least 1 (5%) occurrence of a clinically relevant AE with a true event rate of 10%.

Part 3

In order to guarantee enrollment of no fewer than 50 evaluable patients, approximately 25 patients will be randomized to each arm in Part 3 of this study. The null hypothesis is assumed to be a 70% CR rate in the RCHOP arm. The alternative hypothesis is that the CR rate is ≥90% in the A+RCHP arm. With a two-sided alpha level of 0.20 and a sample size of 50 patients, the study has 70% power to reject the null hypothesis when the true CR rate is 90%.

For safety evaluations, with a sample size of 50 patients, the study would provide an 88% chance of observing at least 3 occurrences (6%) of a clinically relevant AE with a true event rate of 10%. Within each cohort, at least 25 patients would provide a 93% chance of observing at least 1 occurrence (5%) of a clinically relevant AE with a true event rate of 10%.

6.3   Randomization and Blinding

Parts 1 and 3 of this study are randomized, open-label studies. Part 2 is a single-arm study .

In Part 1, approximately 50 patients will be randomized in a 1:1 manner to receive either 1.2 mg/kg or 1.8 mg/kg of brentuximab vedotin plus RCHOP.

In Part 3, approximately 50 patients will be randomized in a 1:1 manner to receive either 1.8 mg/kg brentuximab vedotin combined with RCHP or RCHOP alone.

Randomization for Parts 1 and 3 will be stratified by high-intermediate versus high risk group.

- High-intermediate risk includes patients with either:

    o   IPI Score: 3

    o   Age-adjusted IPI Score: 2

- High risk includes patients with either:

    o   IPI Score: 4–5

o   Age-adjusted IPI Score: 3

Randomization will be centrally performed using a system that will assign a unique patient randomization number and specify the actual treatment assignment.

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 brentuximab vedotin or any component of RCHOP.

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:

$$Months = Days / 30.4375$$

$$Years = Days / 365.25$$

For Parts 1 and 3, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study drug (brentuximab vedotin or any component of multiagent chemotherapy.

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. Patients who have a response of stable disease (SD) or better per Cheson at the same visit as investigator claim of clinical progression will be counted as response per Cheson for determination of best clinical response. An adequate tumor assessment must include a radiologic scan. However, an investigator claim of clinical progression is adequate for an assessment of disease progression for best clinical response if a radiologic scan was not performed.

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 **Error! Reference source not found.** for imputation details and 0 for treatment-emergent definition). Censoring will be described in Section **Error! Reference source not found.** with each planned analysis, as applicable.

Unless otherwise specified,pharmacokinetic and safety lab values which are recorded or provided as being less than x.x will be included in figures and summaries as x.x/2. For the purpose of grading, lab values reported as less than x.x will be imputed as x.x.

6.6 Multicenter Studies

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

6.7 Multiple Comparison/Multiplicity

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

6.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected 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)

- CD30 expression by IHC (<1%, 1-10%, and ≥10%)

- IPI/aaIPI risk group (high-intermediate vs high)

- Cell of origin (GCB vs non-GCB)

6.9 Covariates

For Parts 1 and 3, stratifieds analyses specified in Section 7 will include adjustment for the stratification factors as recorded at randomization. The following covariates may be considered in exploratory regression analyses of the efficacy endpoints. Interaction effects may be considered whenever possible.

- Baseline CD30 expression

- Histology (DLBCL vs. Transformed)

- Baseline EBV status

- Cell of Origin

6.10 Timing of Analyses

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

The final primary analysis of CR at EOT per investigator will occur after the last patient enrolled on the studystudyhas completed treatment. The database cutoff date for the primary analysis will be determined once all study patients have completed treatment. Subsequent cutoff dates may be defined and corresponding database locks may occur to allow for more precise estimates of time-to-event endpoints.

7 PLANNED ANALYSES

7.1 Disposition

An accounting of study patients by disposition will be tabulated by arm and total for each study part for all enrolled patients. Reasons for discontinuation of treatment and study will be summarized. The number and percentage of patients who signed informed consent and the number of patients in each analysis set will be summarized.

The number of patients enrolled in each country and at each site will be summarized. Follow up time and subsequent treatment information will be summarized.

Disposition data will be listed by patient for all enrolled patients.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, gender, ethnicity, race, baseline height, weight, body mass index, B symptoms, ECG results, and ECOG score will be listed and summarized; summaries will be presented for each study part using the mITT analysis set. Disease specific characteristics, including DLBCL disease diagnosis, time from diagnosis, disease stage at onset of diagnosis, and IPI score will be summarized and listed for each study part using the mITT analysis set. . A comparison of the stratification factors as recorded at randomization and as recorded in the CRF at baseline will be presented.

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 safety analysis set. A list of patients with important protocol deviations will be presented.

7.4 Treatment Administration

Treatment administration will be summarized for each study part using the safety 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 for brentuximab vedotin and each component

of RCHOP. 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. The IDI for brentuximab vedotin and each component of RCHOP is presented in the following table:

Regimen Component	Intended Dose Regimen	Unit of time (weeks)	IDI
brentuximab vedotin	1.8 mg/kg	3	0.60
brentuximab vedotin	1.2 mg/kg	3	0.40
rituximab	375 mg/m2	3	125.00
cyclophosphamide	750 mg/m2	3	250.00
doxorubicin	50 mg/m2	3	16.67
vincristine	2 mg	3	0.667
prednisone	500 mg	3	166.67

Absolute Dose Intensity (ADI) is defined as the actual dose per unit of time that the patient received over the entire treatment period. For vincristine and prednisone, ADI is defined as the total actual dose in mg 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 1:

For brentuximab vedotin, consider a patient in the 1.8 mg/kg arm treated for three 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, as represented in the following table:

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

ADI (per week):

$$= (1.8 + 1.8 + (1.8*[19/38])) / (3 \text{ wks} + 1 \text{ wk delay} + 3 \text{ wks} + 3 \text{ wks}) \text{ mg/kg per week}$$
$$= 0.45 \text{ mg/kg per week}$$

RDI:

$$= 0.45/0.6 * 100$$
$$= 75\%$$

Example 2:

For vincristine, consider a patient treated for 6 cycles. The second dose was delayed for 1 week, and for the third cycle and beyond the dose was reduced, as represented in the following table:

Visit	Intended Dose (mg)	Cycle Length
C1D1	2	3 weeks + 1 week delay
C2D1	2	3 weeks
C3D1	1	3 weeks
C4D1	1	3 weeks
C5D1	1	3 weeks
C6D1	1	3 weeks

ADI (per week):

$$=(2 + 2 + 1 + 1 + 1 + 1) / (3 \text{ wks} + 1 \text{ wk delay} + 3 \text{ wks} + 3 \text{ wks} + 3 \text{ wks} + 3 \text{ wks} + 3 \text{ wks}) \text{ mg per week}$$
$$=0.421 \text{ mg per week}$$

RDI:

$$=0.421/0.667 * 100$$
$$= 63\%$$

Example 3:

For prednisone, consider a patient treated for six cycles. The second cycle was delayed for one week and for the fourth cycle and beyond the patient took only 4 of the 5 doses of prednisone, as represented in the following table:

Visit	Intended Dose (mg)	Cycle Length
C1D1	500	3 weeks + 1 week delay
C2D1	500	3 weeks
C3D1	500	3 weeks
C4D1	400	3 weeks
C5D1	400	3 weeks
C6D1	400	3 weeks

ADI (per week):

=(500 + 500 + 500 + 400 + 400 + 400) / (3 wks + 1 wk delay + 3 wks + 3 wks + 3 wks + 3 wks) mg per week

=142 mg per week

RDI:

=142/166.67 * 100

= 85%

7.5 Efficacy Analyses

All efficacy analyses will be presented using the mITT analysis set. In addition, efficacy analyses may be presented for all enrolled or randomized patients.

Analyses may also be performed using the subgroups listed in Section 6.8. Where appropriate, analyses may be adjusted using the covariates listed in Section **Error! Reference source not found.**.

7.5.1 Efficacy Endpoints

7.5.1.1 Complete Remission Rate

CR rate is defined as the proportion of patients with CR per investigator following the completion of study treatment (EOT) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Patients whose disease response cannot be evaluated per Cheson will be scored as Not Evaluable for calculating the CR rate in the mITT analysis set.

The primary efficacy hypotheses for parts 1 and 3 can be expressed as follows:

Part 1:

H_0: CR Rate for brentuximab vedotin +RCHOP is <70%

H_A: CR Rate for brentuximab vedotin +RCHOP is ≥84%

Part 3:

H_0: CR Rate for A+RCHP −CR rate for RCHOP=0

H_A: CR Rate for A +RCHP - - CR rate for RCHOP $\geq 20\%$

The CR rate and its exact two-sided 90% and 80% confidence intervals (for Parts 1 and 3, respectively) using the Clopper-Pearson method (Collett 1991) will be calculated.

7.5.1.2 Objective Response Rate

ORR is defined as the proportion of patients with CR or PR at EOT according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007), as assessed by the investigator. Patients whose disease response cannot be evaluated will be scored as Not Evaluable for calculating the ORR in the mITT analysis set.

The ORR per investigator and its exact two-sided 95% confidence interval using the Clopper-Pearson method (Collet 1991) will be calculated for each study part.

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

7.5.1.3 Duration of Complete Remission

Duration of complete remission (CR) is defined as the time from first documentation of CR to the first documentation of progressive disease , death due to any cause, or receipt of subsequent anticancer chemotherapy (excludes post-treatment consolidative radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT), whichever comes first. Progressive disease includes radiologic evidence of progression per investigator.

Duration of CR data 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 last disease assessment documenting absence of progressive disease

- Patients who have started an antitumor therapy other than the study treatment (excludes post-treatment consolidative radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT) prior to documentation of tumor progression will be censored at the date of the last disease assessment 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 last disease assessment documenting absence of progressive disease.

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

7.5.1.4   Duration of Response

Duration of response is defined as the time the first documentation of objective response (CR or PR) to the first documentation of progressive disease (PD) , death due to any cause, or receipt of subsequent anticancer chemotherapy other than the components of the study treatment regimen (excludes post-treatment consolidative radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT), whichever comes first. Progressive disease is defined as radiologic evidence of tumor progression per investigator.

Duration of response data 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 last disease assessment documenting absence of progressive disease

- Patients who have started an antitumor therapy other than the study treatment (excludes post-treatment consolidative radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT) prior to documentation of tumor progression will be censored at the date of the last disease assessment 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 last disease assessment documenting absence of progressive disease.

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

7.5.1.5   Progression-Free Survival

PFS is defined as the time from randomization (or enrollment for Part 2 patients) to first documentation of progressive disease, death due to any cause, or receipt of subsequent anticancer chemotherapy other than components of the study treatment regimen (excludes post-treatment consolidative radiotherapy, post treatment chemotherapy for the purpose of

mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT), whichever comes first. Specifically:

PFS=Date of first documented PD, death, or new therapy–Date of randomization+1.

Progressive disease includes radiologic evidence of progression per investigator.

PFS is defined based on the table below:

Table 1:   PFS Event Rules for Primary Analysis

Situation	Date of Progression or Censoring	Outcome
No baseline assessment	Date of first dose of any component of study treatment	Censored
Progression documented between scheduled visits	Date of last radiological assessment of target lesions or Date of first observation of new lesion (if progression is based on appearance of new lesion)	Event
No documented progression	Date of last visit with adequate response assessment[a] (or Study Day 1 in the absence of a post-baseline tumor assessment)	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate tumor assessment[a]	Censored
New subsequent anticancer chemotherapy (other than components of the study treatment regiment) started with no claim of progression (excludes post-treatment consolidative radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT)	Start date of new anticancer therapy	EventEvent
Death before first PD assessment	Date of death	Event
Death between adequate assessment visits or after patient misses one assessment visit	Date of death	Event
Death after an extended lost-to-followup time (two or more missed assessments)	Date of last visit with adequate tumor assessment[a]	Censored

a   as defined in Section **Error! Reference source not found.**

Additional details of 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 last disease assessment documenting absence of progressive disease

- Patients who have started an antitumor therapy other than the study treatment (excludes post-treatment consolidative radiotherapy, post treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT) prior to documentation of tumor progression will be considered an event at the start of new therapy

- Patients who are removed from study prior to documentation of tumor progression will be censored at the date of the last disease assessment documenting absence of progressive disease.

Patients who are given post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT will continue to be followed and have their event times censored as above as necessary.

Specifically, censored PFS will be calculated as:

Censored PFS=max (1, last disease assessment date–date of randomization+1),

Where the last disease assessment date is the date of the last disease assessment obtained during study.

Kaplan-Meier Curves depicting PFS will be generated for each study part. 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).

A sensitivity analysis of PFS will be performed where patients who discontinue treatment for investigator claim of clinical progression after the last radiographic tumor assessment are considered to have had an event at the time of treatment discontinuation. In addition, a sensitivity analysis of PFS will be performed where PFS is censored at the last radiographic tumor assessment prior to the receipt of new anticancer therapy in the absence of progression.

7.5.1.6   Overall Survival

The primary analysis of overall survival (OS) will be based on the ITT analysis set. Overall survival is defined as the time from randomization to date of death due to any cause:

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

In the absence of confirmation of death, OS will be censored at the last date the patient is known to be alive.

Kaplan-Meier Curves depicting OS will be generated for each study part. Additionally, the two-sided 95% confidence intervals (CI) for the median OS and 3-month intervals will be calculated using the complementary log-log transformation method (Collett 1994). Percentage of OS at various time intervals (e.g., every year) will also be calculated using the Kaplan-Meier estimate.

7.5.1.7   CD30 Expression

CD30 expression by IHC will be summarized with descriptive statistics for each study part using the CD30-positive analysis set.   CD30 expression by IHC will be listed by patient using the safety analysis set.

7.5.1.8   Pharmacokinetics

Antibody drug-conjugate brentuximab vedotin total antibody, and unconjugated drug (MMAE) PK in serum levels will be summarized with descriptive statistics (including geometric mean and coefficient of variation) at each PK sampling time point using the safety analysis set. PK data from this study may be analyzed by non-compartmental analysis (NCA) methods,, although the sparse collection times may only allow reporting individual results and summary statistics. If performed, additionaladditional PK analyses will be described in a separate analysis plan and the results may be reported separately from the CSR. Any formal PK/PD analyses will be performed outside of Biometrics and may be presented in a separate report.

7.5.1.9   Pharmacodynamic (PD) 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.

7.6   Safety Analyses

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

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 16.0 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 will be summarized by MedDRA preferred term in descending frequency unless otherwise specified. For incidence reporting, if a patient reports more than one AE that was coded to the same system organ class or preferred term, the patient will be counted only once for that specific system organ class or preferred term.

A treatment-emergent AE is defined as a newly occurring or worsening AE after the first dose of brentuximab vedotin or any component of RCHOP. See 0 for details regarding treatment-emergent classification. An overall summary of AEs will be provided by cohort and total for each study part. Summaries of AEs will also be provided by cohort and total for each study part for the following:

- Pre-existing Adverse Events,

- All treatment-emergent AEs,

- AEs related to brentuximab vedotin,

- AEs related to RCHOP, / RCHP,

- Serious Adverse Events (SAEs),

- SAEs related to brentuximab vedotin,

- SAEs related to any component of RCHOP/ RCHP,

- AEs leading to dose delay of brentuximab vedotin,

- AEs leading to dose reduction of brentuximab vedotin,

- AEs leading to dose interruption (full dose received) of brentuximab vedotin,

- AEs leading to the brentuximab vedotin dose being stopped early (full dose not received),

- AEs leading to dose reduction of rituximab, cyclophosphamide, doxorubicin, or vincristine,

- AEs leading to dose interruption (full dose received) of rituximab, cyclophosphamide, doxorubicin, or vincristine,

- AEs leading to the rituximab, cyclophosphamide, doxorubicin, or vincristine dose being stopped early (full dose not received),

- 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,

- Infusion related reactions due to rituximab,,

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

7.6.1.1   Adverse Events of Special Importance

Adverse events of peripheral neuropathy, pulmonary toxicity, infusion related reactions opportunistic infections, hematologic toxicities, hyperglycemia, hepatotoxicity, viral hepatitis, secondary malignancies, 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, whichever occurred later.

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 other peripheral neuropathy events did not improve

- Improvement of at least one event

    o All events either improved or resolved

    o Some events improved, some events resolved and some events neither improved nor resolved

    o Some events improved but no events resolved

- No improvement or resolution of any events

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

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

- Resolved (all events resolved)

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

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

- Worsened (at least one event worsened)

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

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

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

- Coded to a MedDRA preferred term of either 'peripheral motor neuropathy' or 'peripheral sensorimotor neuropathy', 'peroneal nerve palsy'

- Verbatim AE term contains "motor", "weakness", or "palsy"

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

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 by study part for each infusional study drug component. The number of cycles of treatment to first onset of IRR will be summarized.

The incidence of occurrence of treatment-emergent PN (SMQ) and IRRs will be tabulated. Within each interval, an incidence will be presented which represents the percentage of patients who had the event (e.g., the start of an event, an ongoing event or changing severities) during the duration relative to the number of the patients at risk of developing the events if he/she received treatment at the beginning of the duration but had not developed the event.

7.6.1.2   Clinical Laboratory Parameters

Clinical laboratory data (hematology, serum chemistry and coagulation panel) will be summarized for each study part by treatment group. All laboratory results through the end of treatment visit will be presented in standardized units by study part. 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   ECOG Performance Status

ECOG status will be summarized at each visit for each study part. Shifts from baseline to the best and worst post-baseline score will be tabulated.

7.6.3   Concomitant Medications

Concomitant medications will be listed by patient.

7.6.4 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 cohort and total. In addition, primary cause of death will be summarizedby descending MedDRA preferred term (unless otherwise specified) and summarized by cohort and total. 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, the SMC will review accumulating safety data after 10 patients in each cohort (N=20) have completed treatment and after all patients in both dose cohorts have completed treatment (N=50). If Grade 3 neuropathy (sensory or motor) is observed in >20% of patients in either dosing cohort, that dose level will have exceeded the stopping criteria. If the 1.8 mg/kg brentuximab vedotin cohort exceeds the stopping criteria, but acceptable safety is observed at 1.2 mg/kg during the first SMC review, patients receiving treatment at 1.8 mg/kg will be dose reduced to 1.2 mg/kg, randomization will cease, and all remaining patients will be enrolled and treated at 1.2 mg/kg brentuximab vedotin. If the SMC determines that the risks outweigh the benefits of study treatment at both dose levels, no further patients will be enrolled.

In Part 2 of the study, the SMC will review accumulating safety data after 10 patients have completed treatment and after all patients have completed treatment. If the SMC determines that the risks outweigh the benefits of study treatment with 1.8 mg/kg A+RCHP, no further patients will be enrolled in Part 2 and the study will be halted. For those patients still receiving therapy, treatment with standard of care or appropriate treatment will continue outside of the study at the discretion of the investigator.

In Part 3 of this study, the SMC will review accumulating safety and efficacy data after 12 patients (approximately equal numbers of patients in each arm) have completed treatment and an EOT response assessment. The SMC will also review data after 24 patients have completed treatment an EOT response assessment. If the SMC determines that the risks outweigh the benefits of study treatment with 1.8 mg/kg A+RCHP, the SMC may recommend that no further patients be enrolled in Part 3 and the study may be halted. For those patients still receiving therapy, treatment with standard of care or appropriate treatment will continue outside of the study at the discretion of the investigator.

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

- Age will be calculated using the SASINTCK function rather than the calculation of Informed consent date-birthdate/365.25

- For the primary endpoint of CR rate at the End of Treatment, Exact two-sided 90% and 80% confidence intervals (for parts 1 and 3, respectively) will be calculated.

10 REFERENCES

Cheson B, Pfistner B, Juweid M, Gascoyne R, Specht L, Horning S, Coiffier B, Fisher R, Hagenbeek A, Zucca E, Rosen S, Stroobants S, Lister T, Hoppe R, Dreyling M, Tobinai K, Vose J, Connors J, Frederico M and Diehl V (2007). Revised response criteria for malignant lymphoma. Journal of Clinical Oncology 25: 579-586.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. Boca Raton, Fla., Chapman & Hall/CRC: 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 **Error! Reference source not found.** prior to determination of TEAE classification. Details of the TEAE classification are as follows:

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

4. **Baseline AEs:** classify an AE as a baseline AE if it satisfies both of criteria a and b 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:

        The stop date is the same as or a later date than the first dose date of any study treatment

        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

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

5. **Post-baseline AEs:** classify an AE as post-baseline if it meets either of criteria a or b 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

6. 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:

7. **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).