Statistical Analysis Plan

Sponsor:	Seattle Genetics, Inc.
Protocol No:	SGN35-023
Version No./Date	5.0/13 July 2016
Title	A Randomized, Open Label, Phase 2 Study of Rituximab and Bendamustine With or Without Brentuximab Vedotin for Relapsed or Refractory CD30-Positive Diffuse Large B-Cell Lymphoma
CRF Version No./Date	12-October-2016/Version 3.1
PRA Project Id:	SGBHEMP2-HEMPH2
SAP Version No./Date:	2.0/19-July-2018

Approvals

Sponsor – sponsor Review. PRA Med Monitor to review and approve.

Sponsor Name:	Seattle Genetics, Inc.
Representative/ Title:	[redacted]
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Medical Monitor/Title:	
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1.0 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Seattle Genetics Protocol SGN35-023.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 24Jun2016 and CRF dated 12Oct2016. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The SAP is to be developed in two stages. The purpose is to "finalize" a SAP so that programming can start earlier in the process. Versions of the SAP up to initial sponsor approval will be known as SAP1. Changes following approval of SAP1 will be tracked in the SAP Change Log and a final version of the SAP, known as SAP2, will be issued for sponsor approval prior to database lock.

1.1 Changes from Protocol

Seattle Genetics ended the study early and therefore only a subset of the analyses planned in the protocol will be produced, in order to prepare an abbreviated clinical study report (CSR). There will be no formal evaluation of the primary or any secondary endpoints. Analyses for the abbreviated CSR will focus on patient disposition, demographics, exposure and safety. The primary endpoint, objective response rate (ORR), will be summarized descriptively. Secondary efficacy endpoints will not be calculated or summarized, and summaries using the efficacy evaluable population will not be presented. Protocol deviation data will not be presented as it is not required for an abbreviated CSR. Pharmacokinetic, Pharmacodynamic and Immunogenicity samples were not analyzed for this study and thus these data will not be presented.

2.0 Study Objectives

2.1 Primary Objective

- To compare the objective response rate (ORR) among subjects with relapsed or refractory CD30-positive diffuse large B-cell lymphoma (DLBCL) or follicular non-Hodgkin lymphoma (NHL) grade 3b receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)

2.2 Secondary Objectives

- To compare Progression Free Survival (PFS) among subjects with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b receiving rituximab and bendamustine plus brentuximab vedotin (treatment arm) with that among subjects receiving rituximab and bendamustine alone (control arm)
- To compare Complete Remission (CR) rate between the 2 arms of the study
- To compare Duration of Response (DOR) between the 2 arms of the study
- To compare Overall Survival (OS) between the 2 arms of the study
- To evaluate the safety and tolerability of the 2 arms of the study

2.3 Exploratory Objectives

- To characterize the incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin among subjects with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b receiving rituximab and bendamustine plus brentuximab vedotin
- To explore the relationship between CD30 expression and clinical responses

- To explore the relationship between potential patient stratification biomarkers and clinical responses
- To evaluate brentuximab vedotin (and monomethyl auristatin E [MMAE]) exposures when administered in combination with rituxumab and bendamustine
- To characterize pharmacodynamic markers such as soluble CD30 in the 2 treatment arms

3.0 Study Design

This is a randomized, open-label, multicenter, Phase 2 clinical trial designed to evaluate the efficacy and safety of brentuximab vedotin in combination with rituximab and bendamustine for the treatment of patients with relapsed or refractory CD30-positive DLBCL or follicular NHL grade 3b after failure of second-line salvage therapy or as second-line treatment in patients ineligible for autologous stem cell transplant (ASCT).

DLBCL or follicular NHL grade 3b will be histologically determined by local pathology assessment, and CD30 expression will be determined by local or central visual assessment of any detectable level of CD30 on tumor cells by immunohistochemistry (IHC; using anti-CD30 BerH2 antibody) to determine eligibility for enrollment.

The study arms include the following:

- Treatment arm: Brentuximab vedotin in combination with rituximab and bendamustine.
- Control arm: Rituximab and bendamustine

The study will include the following periods:

- Screening: Within 28 days prior to randomization.
- Randomization: Patients will be randomized in a 1:1 manner to the treatment and control arm. Randomization will be stratified by second-line age-adjusted International Prognostic Index (sAAIPI) score (0 vs 1 vs 2–3) and duration of remission after initiation of frontline therapy (refractory or relapse <12 months vs relapse ≥12 months).
- Study treatment: Consists of up to six 21-day cycles of combination treatment.

  Patients in the treatment arm who respond to brentuximab vedotin and do not experience excessive toxicity may receive additional single-agent brentuximab vedotin (on Day 1 of each cycle) following combination treatment, for up to an additional 10 cycles (up to 16 total cycles of treatment).

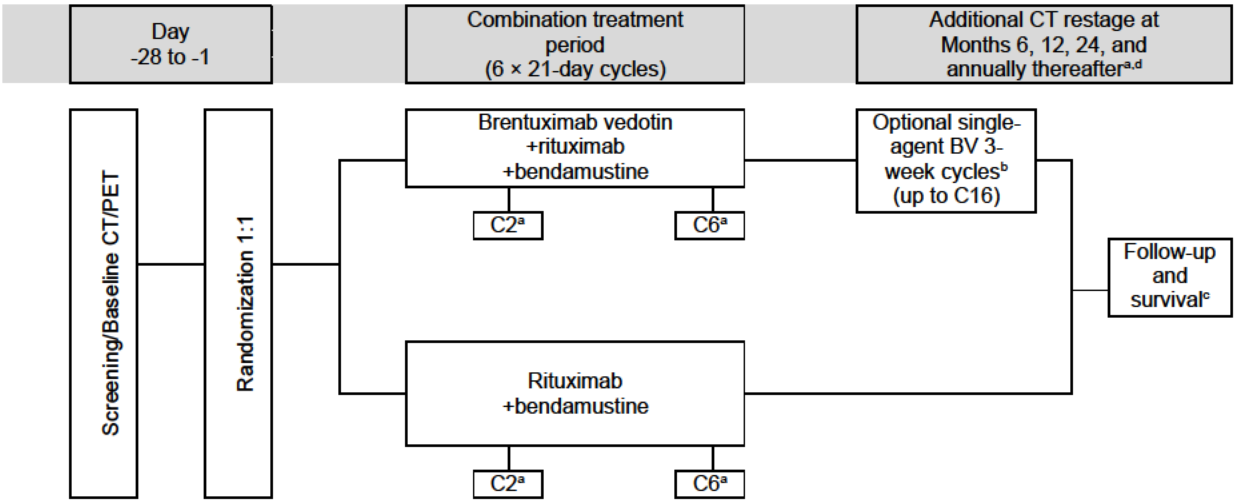
  Study treatment will continue until treatment completion, disease progression, unacceptable adverse events (AEs), patient refusal, Investigator decision, study termination by sponsor or other non-AE reasons. All subjects who discontinue treatment will undergo an end of treatment (EOT) visit.

- Long-Term follow up: All subjects who discontinue treatment will continue to be followed for survival and disease status unless they withdraw from the study.

The planned duration of the study through final primary analysis (ORR is the primary efficacy endpoint) is approximately 2 years from randomization of the first patient, with an additional 2 years until the final analysis of OS and PFS. The study includes a planned formal interim analysis for futility and a planned interim analyses for safety data to be reviewed by the Independent Data Monitoring Committee (IDMC). The interim analysis for futility will be performed after 50% of patients have had the Cycle 2 response assessment. The primary efficacy endpoint (ORR) will be used to assess futility. The safety data will be reviewed after the first 20 patients have completed 2 cycles of therapy and then every 6 months thereafter and as needed.

The study design is presented in Figure 1. Please refer to Protocol Table 2 and 3 for the Study Schedule and Schedule of Follow-up Assessment.

Figure 1: Study Schematic



a Positron emission tomography (PET) in addition to computed tomography (CT), unless a documented negative postbaseline PET previously obtained; scans required until disease progression, death, or study closure, whichever comes first

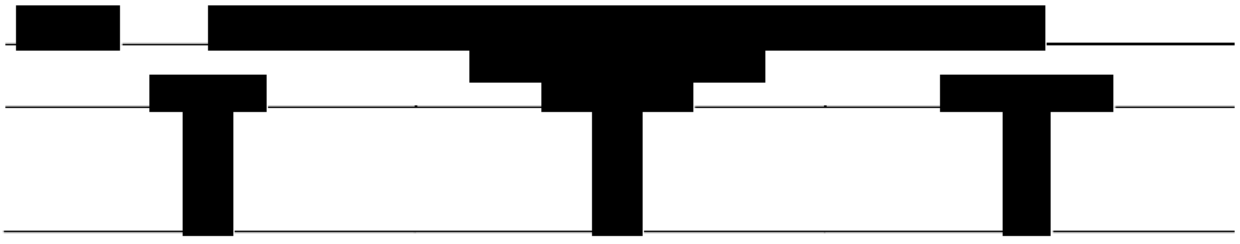
b Only patients who have responded to combination treatment with brentuximab vedotin and not experiencing excessive toxicity

c Survival status should continue after disease progression until death or study closure, whichever comes first

d Time from start of combination treatment (Cycle 1 Day 1)

3.1 Sample Size Considerations

Approximately 110 patients are planned to be randomized in a 1:1 manner (~55 patients per treatment arm). [redacted]



3.2 Randomization

Patients will be randomized in a 1:1 manner to the treatment and control arm. Randomization will be stratified by second-line age-adjusted International Prognostic Index (sAAIPI) score (0 vs 1 vs 2–3) and

duration of remission after initiation of frontline therapy (refractory or relapse <12 months vs relapse ≥12 months). Randomization will be performed using an Interactive Voice and Web Recognition System (IXRS).

3.3 Blinding

This is an open label study.

4.0 Study Variables and Covariates

4.1 Primary Variable

The primary efficacy endpoint of this study is Objective Response Rate (ORR) as defined by the 2014 Lugano Classification[1]. ORR is defined as the proportion of patients who achieve a CR (including CMR) or PR (including partial metabolic response, or PMR) as best response to combination therapy on study. Patients who cannot be assessed for response will be counted as non-responders.

4.2 Secondary Variables

4.2.1 Efficacy

Secondary efficacy variables include: progression-free survival, complete response rate, best clinical response, duration of response, and overall survival. These variables will not be calculated or presented.

4.2.2 Pharmacokinetic/Pharmacodynamic Measurements

Pharmacokinetic, Pharmacodynamic and Immunogenicity samples were not analyzed for this study and thus these variables will not be calculated or presented.

4.2.3 Safety

Safety endpoints will include the following:

- Type, incidence, severity, seriousness, and relatedness of AEs
- Type, incidence, and severity of laboratory abnormalities.
- Incidence and severity of infusion-related and hypersensitivity reactions.

5.0 Definitions

Baseline, Change from Baseline

Baseline is defined as the most recent measurement prior to the first dose of study medication.
Change from baseline is defined as (value at post baseline visit – value at baseline).
Percent change from baseline is defined as [(value at post baseline visit – value at baseline) / value at baseline] * 100%.

Post baseline values for tabulations generally will exclude unscheduled visit values, but unscheduled visit values will be included in listings.

Best Overall Response

Best clinical response is defined as the best response (ordered from best to worst as CR/CMR, PR/PMR, Stable Disease/NMR, or Progressive Disease(PD)/PMD) observed by end of treatment. Patients who have any non-PD response per Lugano, 2014 at the same visit as investigator claim of clinical progression will be counted as a response of disease progression for determination of best response.

Body Mass Index (BMI)

BMI = weight (kg) / (height (m)^2).

Duration of Treatment (Days)

Duration of treatment is defined for brentuximab vedotin, rituximab and bendamustine, respectively, as time from the first study dose to 21 days after the last cycle day 1 dose date, i.e., last cycle day 1 dose date + 21 – first dose date. If death occurs less than 21 days after the last cycle day 1 dose, duration of treatment is defined as Date of death – first dose date + 1.

Enrolled Patients

An enrolled patient is one with a response of “Yes” to the question “If yes, Seattle Genetics or designee approval?” on the Eligibility Criteria Summary CRF page.

Randomized Patient

Randomized patients are defined as patients who have a randomization date. All randomized patients should also have a randomization number corresponding to a treatment arm which assigned by the IXRS.

Screened Patients

A screened patient is one with Screening ID on the Enrollment/Screening CRF page.

Study Drug

In this study, study drug refers to the standard of care medication, rituximab and bendamustine, or the investigational or experimental product, brentuximab vedotin.

Patients Disposition

- **Completion of Combination Treatment**
- A patient will be considered completed combination treatment when an End of Treatment CRF page is completed indicating “Complete Treatment” as primary reason for discontinuation.
- **Discontinuation of Study**
- A patient will be considered discontinued from the study when an End of Study CRF page is completed indicating primary reason for discontinuation.
- **Early Discontinuation of Treatment**
- A patient will be considered discontinued from the study early when an End of Treatment CRF page is completed indicating primary reasons other than “Complete Treatment” for discontinuation
- **In Long Term Follow Up**
- A patient will be considered in long term follow up if the response of “Will the patient continue on study for Follow-up?” on the End of Treatment CRF page is Yes and no reason for study discontinuation is provided
- **On Treatment**
- A patient will be considered on treatment if he/she takes at least one dose of study drug and an End of Treatment CRF page is not completed.
- **Off Treatment**
- A patient will be considered off treatment if he/she takes at least one dose of study drug and an End of Treatment or an End of Study CRF page is completed indicating primary reason for discontinuation.
- **On Study**

- A patient will be considered on study if the End of Study CRF page is NOT completed indicating primary reason for discontinuation from study.
- **Off Study**
- A patient will be considered off study if the End of Study CRF page is completed indicating primary reason for discontinuation from study.

6.0 Analysis Populations

6.1 Intent-to-Treat

The intent-to-treat (ITT) Population will include all patients who are randomized. Patients will be grouped according to their randomized treatment group assignment regardless of the treatment they actually received.

6.2 Safety

The safety population will include all patients who are enrolled and received at least 1 dose (any amount) of study treatment (brentuximab vedotin, rituximab, or bendamustine) with treatment assignment based on actual treatment received. (Subjects receiving any amount of brentuximab vedotin during the study will be counted in the treatment arm for the safety analyses.)

7.0 Interim Analyses

Due to the study premature termination, the planned formal interim analysis for futility and the planned interim analysis for safety data will not occur.

8.0 Data Review

8.1 Data Handling and Transfer

Data handling and transfer specifications will be stated and conducted according to the Data Management Plan.

8.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFLs) provides additional data screening.

Review of a TFL dry run on the nearly finalized database will allow for further data review prior to finalization. The dry run TFL will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and the sponsor must approve database lock.

9.0 Statistical Methods

All data collected during this study for all patients will be displayed in data listings, unless otherwise specified. Data listings will be sorted by treatment and patient identifier. Screen failures will be excluded from all tables and listings, except for those describing enrollment. In addition, listings will include all relevant derived variables. Tables that are to be produced for both ITT and Safety Populations will only be presented if the populations are different.

Descriptive statistics (mean, median, standard deviations [SDs], minimum and maximum values) for continuous variables will be presented. Mean and median will be presented to 1 decimal more than original data. SD will be presented to 2 decimals more than original data. Minimum and maximum will

match the decimal points in the original data. For categorical variables, summary measures will include the frequency and percentage (with 1 decimal place) of patients in each category.

The summary tables will be presented by 2 treatment groups (Brentuximab vedotin/rituximab/ bendamustine, rituximab/bendamustine) and overall.

Unless otherwise noted, missing data will not be imputed or carried forward.

All data summaries and tabulations will be prepared with SAS® Version 9.4 or higher.

9.1 Patient Disposition

The number of patients screened, enrolled, and the number and percentage of patients randomized in the study will be presented along with the number and percentage of patients in each analysis population for each treatment arm and overall. All percentages will be based on the number of patients enrolled in the respective treatment arm and overall.

Disposition of patients will be summarized by treatment arm and overall for the ITT and the Safety population. The number and percentage of treated patients, number and percentage of patients who completed combination treatment (6 cycles), number and percentage of patients who prematurely discontinued treatment and who entered long term survival follow up. For patients who had premature discontinuations the reasons for study discontinuation will be summarized. All percentages will be based on the number of patients in the respective treatment arm and overall. A by-patient listing of disposition will also be provided.

9.2 Important Protocol Deviations

Protocol deviations data will not be presented.

9.3 Demographic and Baseline Characteristics

Demographic and baseline data will be summarized and listed for the ITT population. Variables to be presented include age (years), weight (kg), height (cm), BMI, gender (male, female), ethnicity (Hispanic or Latino, Not Hispanic or Latino), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other), Eastern Cooperative Oncology Group (ECOG) and sAAIPI.

By-patient listings will include demographic and baseline characteristics, initial disease diagnosis, and general medical history.

9.4 Treatments

9.4.1 Extent of Study Drug Exposure

Exposure to treatment will be summarized separately for brentuximab vedotin, rituximab, and bendamustine for patients in the Safety population.

The following summary statistics related to drug exposure will be calculated:

- Number and percentage of patients with at least 1 dose delay per protocol reasons, and the number of doses delayed
- Number and percentage of patients with at least 1 dose reduced per protocol reasons, and the number of doses reduced
- Number and percentage of patients with at least 1 unplanned dose adjustment (which includes interrupted due to AE, interrupted due to other reason, stopped early due to AE, stopped early due to other reason, or dose errors not leading to interruption or stoppage), by reason for unplanned adjustment, and the number of unplanned dose adjustments.

- Number and percentage of patients with at least 1 infusion-related reaction, and the number of infusion-related reactions
- Number and percentage of patients with at least 1 delayed hypersensitivity reaction (>24 hours post last infusion), and the number of delayed hypersensitivity reactions
- Duration of treatment (weeks)
- Number of doses received
- Number of cycles per patient
- Frequency count for patients who receive 1 cycle, 2 cycles, and so on.
- Cumulative dose (mg/kg and mg)
- Average dosage per cycle (mg/kg and mg)

A listing of intended dose regimen, intended dose, actual dose administered, and reasons for dose delayed, dose reduced, dose adjustment, and/or infusion-related reactions will be displayed.

9.4.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug (version: September 2007 or more recent).

All medications will be listed by patient, displaying verbatim name and preferred name, indication, and start and stop dates.

9.5 Efficacy Analyses

9.5.1 Primary Efficacy Variable

Due to the small number of patients recruited in the study there will be no formal assessment of the primary endpoint. The observed ORR (a best response of CR/CMR, PR/PMR) from response assessments up to and including the end of treatment visit as defined in section 4.1, will be presented by treatment arm for the ITT population along with the corresponding exact 90% and 95% confidence intervals (CIs) using the exact binomial method (i.e., Clopper-Pearson method).

A by-patient listing of Response Assessments will be provided.

9.6 Safety Analyses

All the safety endpoints will be summarized in tables and listings for the Safety population unless otherwise specified.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 18.1 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).

9.6.1 Adverse Events

All AEs will be coded by system organ class, MedDRA preferred term, and severity grade using NCI CTCAE Version 4.03.

Treatment-Emergent AEs (TEAEs) are those that first occur or increase in severity from study Day 1 through the EOT visit or 30 days after the last study treatment, whichever is later. See Appendix 3 Treatment Emergent Adverse Event Programming Guide for definition of whether an AE is treatment emergent.

AEs will be summarized by descending frequency of MedDRA preferred term 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 related AE is one that is recorded as "Related" to any of the treatment components (brentuximab vedotin, rituximab, or bendamustine) on the CRF.

A summary table of number and percentage of the AE categories will be provided by treatment arm and total as follows:

- Pre-existing AEs (defined as in Appendix 3)
- All TEAEs
- AEs related to treatment (brentuximab vedotin, rituximab, or bendamustine)
- AEs with outcome of death
- Serious Adverse Events (SAEs)
- SAEs related to treatment (brentuximab vedotin, rituximab, or bendamustine)
- AEs leading to dose delay of treatment (brentuximab vedotin, rituximab, or bendamustine)
- AEs leading to dose interruption (full dose of brentuximab vedotin, rituximab, or bendamustine received)
- AEs leading to dose being stopped early (full dose of brentuximab vedotin, rituximab, or bendamustine not received)
- AEs leading to dose reduction of treatment (brentuximab vedotin, rituximab, or bendamustine)
- AEs leading to treatment discontinuation (brentuximab vedotin, rituximab, or bendamustine)
- Grade 3-5 treatment-emergent AEs
- Infusion-related reaction (IRR) AEs
- Hypersensitivity Reaction (HSR) AEs
- AEs that started during infusion of any study drug
- AEs that started within 24 hours post infusion of any study drug
- AEs of special interest (see Section 9.6.3)
- TEAEs displayed by system organ class and preferred term
- TEAEs displayed by system organ class, preferred term and maximum severity

A listing of all AEs (including non-treatment-emergent AEs) recorded on the CRF will be provided.

9.6.2 Deaths and Serious Adverse Events

SAEs will be summarized as described above and listed.

Deaths, including cause of death and relationship to disease, will be listed.

9.6.3 Adverse Events of Special Interest

The AEs of special interest will be summarized as described above and are detailed below:

- Peripheral Neuropathy: identified using the Standard MedDRA Query (SMQ) "Peripheral Neuropathy" broad search.
- Pulmonary Toxicity: identified using the SMQ "Interstitial Lung Disease" broad search.

- Neutropenia: identified by MedDRA preferred term=”Neutropenia” or “Neutrophil count decreased”
- IRRs: identified by the Investigator as an Infusion-Related reaction on the drug exposure page (of any study drug)

9.6.4 Laboratory Data

Only central safety laboratory data will be summarized. Local safety laboratory data will not be presented. Laboratory results and NCI CTCAE grades for hematology, and serum chemistry will be presented in data listings. Laboratory data values will be converted to standard units.

Hematology lab parameters include red blood cell (RBC) count, white blood cell (WBC) count, hemoglobin, hematocrit and platelets, and the differential includes: neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Serum chemistry tests include: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), amylase, aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatinine, lactate dehydrogenase (LDH), lipase, potassium, phosphorus, sodium, random glucose, creatinine clearance using the Cockcroft-Gault formula, and uric acid.

NCI CTCAE grades will be applied for the lab parameters included in Appendix 4 CTCAE V4.03 Grading for Laboratory Values. Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as “Grade 0,” which is defined as normal.

The worst post baseline NCI CTCAE v4.03 or higher grade will be presented by treatment arm and total for each lab test. Patients with multiple grades will be counted at their highest grade. Patients with at least 1 on-study measurement for each laboratory parameter will be included, regardless of whether or not a baseline assessment is present. Unscheduled lab values will also be considered for determining the maximum CTCAE grade.

9.6.5 Vital Signs

Vital signs will be listed including body temperature, heart rate, blood pressure (diastolic and systolic), weight, height and body surface area (m^2).

9.6.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

A by-patient listing of ECOG performance status will be generated.

9.6.7 Electrocardiograms (ECG)

A by-patient listing of ECG assessments will be generated.

9.6.8 Physical Examinations

Clinically significant findings observed during physical examinations will be recorded on the AE and pre-existing condition CRFs. No analyses for physical examinations will be performed.

9.7 Pharmacokinetics/Pharmacodynamics, Antitherapeutic Antibodies and Disease Characteristics

Pharmacokinetic, Pharmacodynamic and Immunogenicity samples were not analyzed for this study and thus these data will not be presented.

9.8 Methods for Handling Dropouts and Missing Data

With the exception of time-related endpoints, missing observations will not be imputed, unless otherwise noted.

For missing or partial start and stop AE dates, see Appendix 2 Imputation of Partially Unknown Adverse Event Dates for rules.

Note, for all listings the actual value for date (not imputed) will be presented in all data listings and imputed dates will only be used for programming flags, etc.

9.9 Data Transformations and Derivations

Age in years will be calculated with the SAS INTCK function 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. There is no Study Day 0. For all calculations of Study Day, the first dose date will be the earliest date of treatment administration for study drug.

Other time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

The following unit conversion will be implemented unless otherwise specified:

Weeks = Days / 7

Months = Days / 30.4375

Years =Days / 365.25

10.0 Validation

PRA seeks to ensure the quality of the results provided for the study in the form of TFLs, and the derived datasets used in their creation, through the following processes:

The entire set of TFLs will be checked for completeness and consistency prior to its delivery to the client by the lead analysis programmer, and the lead statistician, following PRA processes,.

The PRA validation process will be repeated any time TFLs are redelivered using different data. Execution of this validation process will be documented through the study Table of Programs that will be provided to Seattle Genetics at study conclusion.

11.0 References

[1] Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 32(27): 3059-67, 2014.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ADC	Antibody-drug conjugate
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
ATA	Antitherapeutic antibodies
ATC	Anatomic Therapeutic Classification
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence intervals
CMH	Cochran-Mantel-Haenszel
CMR	Complete metabolic response
COO	Cell of origin
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-Cell Lymphoma
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
ITT	Intention-to-treat
IXRS	Interactive Voice and Web Recognition System
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
NCI	National Cancer Institute

NHL	Non-Hodgkin lymphoma
NMR	No metabolic response
NE	Non evaluable
ORR	Objective Response Rate
OS	Overall Survival
PET	Positron emission tomography
PFS	Progression Free Survival
PD	Progressive Disease
PMR	Partial metabolic response
RBC	Red blood cell
sAAIPI	Second-line age-adjusted International Prognostic Index
SAP	Statistical analysis plan
SAE	Serious Adverse Event
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TFL	Tables, figures, and listings
WBC	White blood cell
WHO	World Health Organization

Appendix 2 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 a full known date.

1. AE day and month are missing:
    a. If the year is the same as the year of first dose of any study treatment (for combination studies this implies any component of the regimen) and the onset period indicates that the start of the AE was pre-dose:
        i. AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of any study treatment)
    b. If the year is the same as the year of first dose of any study treatment and the onset period indicates that the start of the AE was post-dose:
        i. AE start date will be imputed as the minimum of (AE condition end date*, first dose date of any study treatment)
    c. If the year is before the year of first dose of any study treatment:
        i. AE start date will be imputed as the minimum of (AE condition end date*, December 31st) - see example 2 below
    d. If the year is after the year of first dose of any study treatment:
        i. AE start date will be imputed as the minimum of (AE condition end date*, January 31st) - see example 2 below
2. AE month only is missing:
    a. Treat day as missing and replace both month and day according to the above procedure
3. AE day only is missing:
    a. If the month/year is the same as the month/year of first dose of any study treatment and the onset period indicates that the start of the AE was pre-dose:
        i. AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of any study treatment)
    b. If the month/year is the same as the month/year of first dose of any study treatment and the onset period indicates that the start of the AE was post-dose:
        i. AE start date will be imputed as the minimum of (AE condition end date*, first dose date of any study treatment)
    c. If the month/year is before the month/year of first dose of any study treatment:
        i. AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)
    d. If the month/year is after the month/year of first dose of any study treatment:

i. 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 full end date is available.

The following algorithm should be used to impute AE condition end dates:

1. The AE records for a condition/event should be sorted by the imputed start dates then record position (order of entry into the eCRF).
    a. 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.
    b. Repeat step 1.
2. After sorting the AE records, apply the following rules to partial or missing AE condition end dates:
    a. For all records excluding the last chronological record for a condition/event:
        i. AE condition end date will be imputed as the start date of the subsequent record
    b. For the last chronological record for a condition/event:
        ii. If outcome is “recovered/resolved”, ”recovered/resolved with sequelae”, or “fatal”:
            1. AE condition end date will be imputed as the minimum of (last dose date + 30, death date, data extraction date, or last day of month if month and year known, or last day of year if only year is known)
        iii. If outcome is “recovering/resolving”, “not recovered/resolved”, “unknown”, or blank:
            1. 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
15JAN2013	UNUNK2013	2	recovering/resolving	post 1st dose
UNUNK2013	UNFEB2013	2	not 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
15JAN2013	31JAN2013	2	recovering/resolving
31JAN2013	UNFEB2013	2	not recovered/resolved

Example 2a:

Prior to imputation:

Start date	*Condition end date*	*Severity*	*Outcome*	*Onset*
15FEB2013	UNUNK2013	2	recovering/resolving	post 1st dose
UNUNK2013	UNFEB2013	2	not recovered/resolved	post 1st dose

Post imputation:

Start date	*Condition end date*	*Severity*	*Outcome*
15FEB2013	UNUNK2013	2	recovering/resolving
31JAN2013*	15FEB2013	2	not recovered/resolved

*Note: This AE would now precede the other AE with the same year after sorting.

Appendix 3 Treatment Emergent Adverse Event Programming Guide

Term	Standard Definition
Treatment emergent	Any newly occurring or worsening AE, where newly occurring means an AE that was not present at baseline. (E.g., if the patient had a grade 1 headache at baseline that resolved and later had another grade 1 headache, that second headache would NOT be considered a TEAE. See below for more algorithm details.) Where: 1. Get first dose date/time of study medication 2. Define baseline/pre-existing AEs as AEs with: • An onset period of ("started before the signing of informed consent", or "started after consent but before the first dose of investigational product". • If the onset period of the AE is missing, then look for AE start date < first dose date or AE start date = first dose date and onset time is 'Started before first infusion or before infusion on any dosing day'. • If AE start date is missing, use AE start date imputation rule (described in Appendix 2). **<AND>** • a stop date that is: ➢ ≥ first dose date **<OR>** ➢ missing with outcome equal to ▪ recovering/resolving (this outcome may or may not have a date with it), or ▪ not recovered/not resolved, or ▪ unknown ▪ *Note: AEs with no outcome and missing stop dates should be queried.* • Note: If the event ended on Day 1 (the day of first dose) it will be considered a baseline event. 3. Define post-baseline AEs as AEs with an onset period of ("started after the first dose of investigational product". If the onset period of the AE is missing, then look for AE start date >= first dose date (from 1) or AE start date = first dose date (from 1) but onset time is NOT 'Started before first infusion or before infusion on any dosing day'. If AE start date is missing, use AE start date imputation rule. 4. Compare post-baseline AEs to baseline AEs using lower level term (LLT). • If terms match from baseline to post-baseline: ➢ compare CTC grades. If post-baseline CTC grade is > baseline CTC grade, then TEAE=YES. If post-baseline CTC grade is <= baseline CTC grade, then TEAE=NO. • If there are no matching terms from baseline to post-baseline, then TEAE=Yes. • If post-baseline AEs are uncoded, then TEAE = Yes. **NOTE: if there isn't enough information (partial dates, onset period flags) to determine TEAE, those events should be counted as TEAE = Yes.**

Appendix 4 CTCAE V4.03 Grading for Laboratory Values

CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 × 10^9/L	<3000 - 2000/mm^3; <3.0 - 2.0 × 10^9/L	<2000 - 1000/mm^3; <2.0 - 1.0 × 10^9 /L	<1000/mm^3; <1.0 × 10^9/L
Investigations	White blood cell increased (leukocytosis)	-	-	>100,000 mm^3	Clinical manifestations of leucostasis; urgent intervention indicated
Blood and lymphatic system disorders	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Investigations	Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x10^9 /L	<800 - 500/mm^3; <0.8 - 0.5 × 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 × 10^9 /L	<200/mm^3; <0.2 × 10^9 /L
Investigations	Lymphocyte count increased	-	>4000 - 20,000 mm^3	>20,000 mm^3	-
Investigations	Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 × 10^9/L	<1500 - 1000/mm^3; <1.5 - 1.0 × 10^9/L	<1000 - 500/mm^3; <1.0 - 0.5 × 10^9/L	<500/mm^3; <0.5 × 10^9/L
Investigations	Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 × 10^9/L	<75,000 - 50,000/mm^3; <75.0 - 50.0 × 10^9/L	<50,000 - 25,000/mm^3; <50.0 - 25.0 × 10^9/L	<25,000/mm^3; <25.0 × 10^9/L
Investigations	Serum amlylase increased	>ULN - 1.5 × ULN	>1.5 - 2.0 × ULN	>2.0 - 5.0 × ULN	>5.0 × ULN
Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated

CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Alkaline phosphatase increased	>ULN - 2.5 × ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Alanine aminotransferase increased	>ULN - 3.0 × ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 × ULN
Investigations	Aspartate aminotransferase increased	>ULN - 3.0 × ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 × ULN
Investigations	Blood bilirubin increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 10.0 × ULN	>10.0 × ULN
Investigations	GGT increased	>ULN – 2.5 x ULN	>2.5 - 5.0 × ULN	>5.0 - 20.0 × ULN	>20.0 × ULN
Investigations	Hemoglobin increased	Increase in >0-2 gm/dl above ULN or above baseline if baseline is above ULN	Increase in >2-4 gm/dl above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dl above ULN or above baseline if baseline is above ULN	-
Investigations	Lipase increased	>ULN - 1.5 × ULN	>1.5 - 2.0 × ULN	>2.0 - 5.0 × ULN	>5.0 × ULN
Metabolism and nutrition disorders	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences

CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Investigations	Creatinine increased	>1 - 1.5 × baseline; >ULN - 1.5 × ULN	>1.5 - 3.0 × baseline; >1.5 - 3.0 × ULN	>3.0 baseline; >3.0 - 6.0 × ULN	>6.0 × ULN
Metabolism and nutrition disorders	Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Metabolism and nutrition disorders	Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Metabolism and nutrition disorders	Hyperuricemia	>ULN – 10 mg/dl (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dl (0.59 mmol/L) with physiologic consequences	>10 mg/dl ; >0.59 mmol/L; life-threatening consequences