Statistical Analysis Plan

Sponsor:	Seattle Genetics, Inc.
Protocol No:	SGN19A-004
PRA Project Id:	SGB1B219-1B219A
Version Date:	30JAN2018
Version Number:	1.0

APPROVALS

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Seattle Genetics, Inc., Protocol SGN19A-004, entitled "An open-label phase 2 study of denintuzumab mafodotin (SGN-CD19A) in combination with RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or RCHP (rituximab, cyclophosphamide, doxorubicin, and prednisone) compared with RCHOP alone as frontline therapy in patients with diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) Grade 3b". Results of the proposed analyses will become the basis of the final clinical study report for this protocol.

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 18 February, 2016 and CRF dated 24 August, 2016. Any further changes to the protocol or CRF may necessitate updates to the SAP.

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 be reflected in amendments to this plan before the database lock, detailed below, or specifically documented in the clinical study report.

The SAP is to be developed in two stages. The purpose is to "finalize" a SAP so that programming can begin 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 will end the study early after Part A, 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). Analyses for the abbreviated CSR will focus on patient disposition, demographics, exposure and safety. Secondary efficacy endpoints will not be calculated or summarized as they pertain to Part B only. Biomarker endpoints will be described in a separate report.

2. STUDY OBJECTIVES

2.1 PRIMARY STUDY OBJECTIVES

- To compare the complete response (CR) rate at the end of treatment (EOT) in treatment-naive patients with high-intermediate or high-risk systemic DLBCL or FL Grade 3b treated with denintuzumab mafodotin plus RCHOP or RCHP versus RCHOP alone (Part B)

- To assess the safety profile of denintuzumab mafodotin administered in combination with RCHOP or RCHP in treatment-naive patients with high-intermediate or high-risk systemic DLBCL or FL Grade 3b (Part A and Part B)

2.2 SECONDARY STUDY OBJECTIVES

- To compare event-free survival (EFS) between study arms (Part B)
- To compare progression-free survival (PFS) between study arms (Part B)
- To compare overall survival (OS) between study arms (Part B)
- To compare the objective response rate (ORR) at EOT between study arms (Part B)
- To compare the duration of objective response (OR) and of CR between study arms (Part B)

2.3 ADDITIONAL OBJECTIVES

- To evaluate the pharmacokinetics (PK) of denintuzumab mafodotin administered in combination with RCHOP or RCHP (Parts A and B)
- To evaluate the incidence of antitherapeutic antibodies (ATA) against denintuzumab mafodotin (Parts A and B)
- To assess denintuzumab mafodotin-mediated pharmacodynamic (PD) effects and potential biomarkers of response to denintuzumab mafodotin in combination with RCHOP or RCHP (Parts A and B)
-

3. STUDY DESIGN

3.1 OVERALL STUDY DESIGN AND PLAN

This is an open-label, phase 2, multicenter study of denintuzumab mafodotin in combination with RCHOP or RCHP compared with RCHOP alone as frontline therapy in patients with DLBCL or FL Grade 3b. This study has 2 parts (Part A and Part B). Part A of the study is a safety evaluation of denintuzumab mafodotin in combination with either RCHOP or RCHP. Results from Part A will be used to determine the regimen (RCHOP or RCHP) to be tested in combination with denintuzumab mafodotin in Part B. Part B is a multicenter study designed to evaluate the antitumor activity and safety of denintuzumab mafodotin in combination with either RCHOP or RCHP compared with RCHOP alone.

In Part A and Part B, lymphoma response and progression will be assessed using the Lugano Classification Revised Staging System (Cheson, 2014) for malignant lymphoma. Diagnostic quality computed tomography (CT) scans (neck, chest, abdomen, and pelvis with intravenous and oral contrast) and positron emission tomography (PET) scans will be performed at baseline and at 5 weeks after the last dose of study treatment; all other EOT evaluations will be assessed 30 to 37 days after the last dose. Follow-up assessments will be performed every 4 months from the last scan until 24 months, then every 6 months until 48 months, and then annually until study

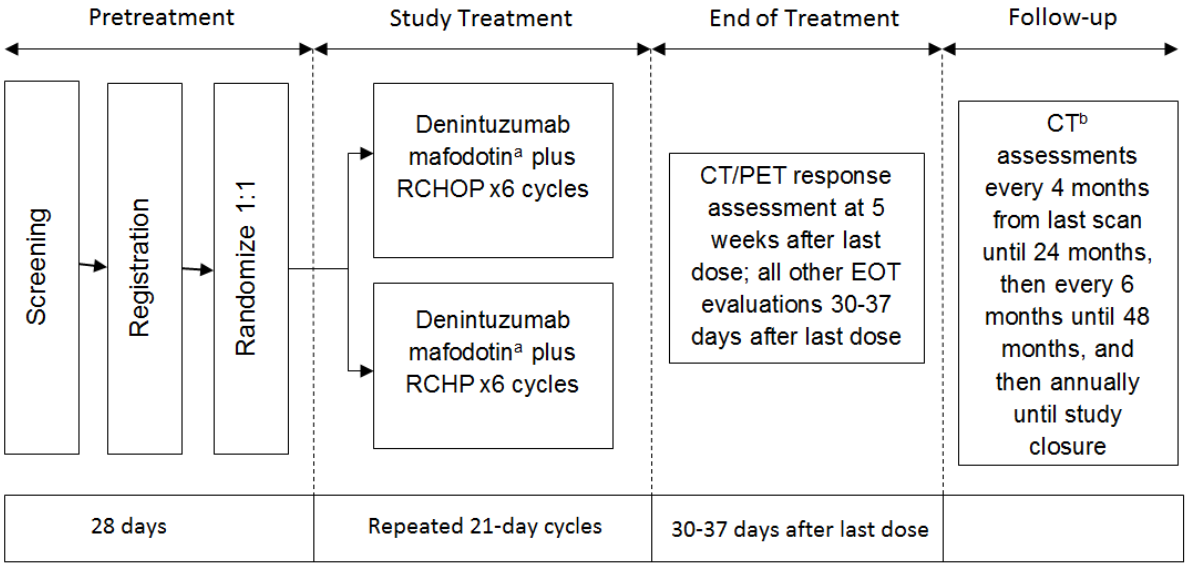
closure. For all follow-up assessments, both PET and CT scans are required until disease is PET negative; responses will then be followed by CT scan only. A CT scan will also be performed at the time of suspected clinical progression. Follow-up assessments will continue until disease progression, initiation of a new anti-cancer treatment, or study closure, whichever comes first. Survival status follow-up will continue until patient death or study closure, whichever comes first.

A schedule of safety and efficacy procedures for the screening and treatment periods for part A and B is provided in Table 18-1 of the protocol. PK, ATA, and biomarker assessments are provided in Table 18-2 (Part A Intense Sampling Schedule), Table 18-3 (Part B Intense Sampling Schedule) and Table 18-4 (Part B Sparse Sampling Schedule) of the protocol

3.1.1 Part A – Safety Evaluation

In Part A of the study, up to approximately 24 patients will be randomized 1:1 to receive denintuzumab mafodotin plus RCHOP or denintuzumab mafodotin plus RCHP to assess safety in these 2 combination regimens. Patient randomization will be stratified by high-intermediate or high-risk disease. Study treatment is up to six 21-day cycles of either RCHOP or RCHP combined denintuzumab mafodotin administered on Day 1 of Cycles 1, 3, and 5. The study schema for Part A is depicted in Figure 1.

Figure 1: Part A Study Schema



a CT = computed tomography; EOT = end of treatment; PET = positron emission tomography; RCHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCHP = rituximab, cyclophosphamide, doxorubicin, and prednisone
b Administered on Day 1 of Cycles 1, 3, and 5
c Follow-up PET and CT scans required until disease is PET negative; responses will then be followed by CT scans of diagnostic quality. Follow-up assessments continue until disease progression, initiation of a new anti-cancer treatment, death, or study closure, whichever comes first. Survival status follow-up until death or study closure, whichever comes first.

The Safety Monitoring Committee (SMC), comprising the study investigators, medical monitor, and biostatistician and Sponsor's medical expert, will periodically monitor the safety of patients at predefined interim safety evaluations and at regular intervals during the treatment period. Formal safety evaluations of cumulative data from both treatment groups will be conducted at the following 6 time points in Part A of the study:

- after 6, 12, and 24 patients have completed Cycle 1
- after 6, 12, and 24 patients have completed EOT

At each interim safety evaluation, the SMC will review the cumulative safety data, including the incidence of dose-delaying toxicities (DDTs) that are associated with denintuzumab mafodotin in combination with RCHOP or RCHP, as well as the rates of adverse events of interest such as peripheral neuropathy (PN) in each treatment group. A DDT is defined as any study treatment-related toxicity that necessitates a delay of >14 days in the start of RCHOP or RCHP treatment in the next cycle. With respect to hematologic recovery, it is recommended that the next cycle of RCHOP or RCHP be given once the patient's absolute neutrophil count recovers to ≥ 1000/μL and the platelet count recovers to ≥ 75,000/μL, as applicable. Upon its evaluation of the data, the SMC will make one of the following recommendations to the Sponsor:

- continue the trial as planned
- modify the dose of denintuzumab mafodotin in subsequently enrolled patients
- temporarily halt enrollment for additional evaluation

If the SMC determines that the risks outweigh the benefits of the study treatment in both combination regimens, no further patients will be enrolled at that dose and schedule.

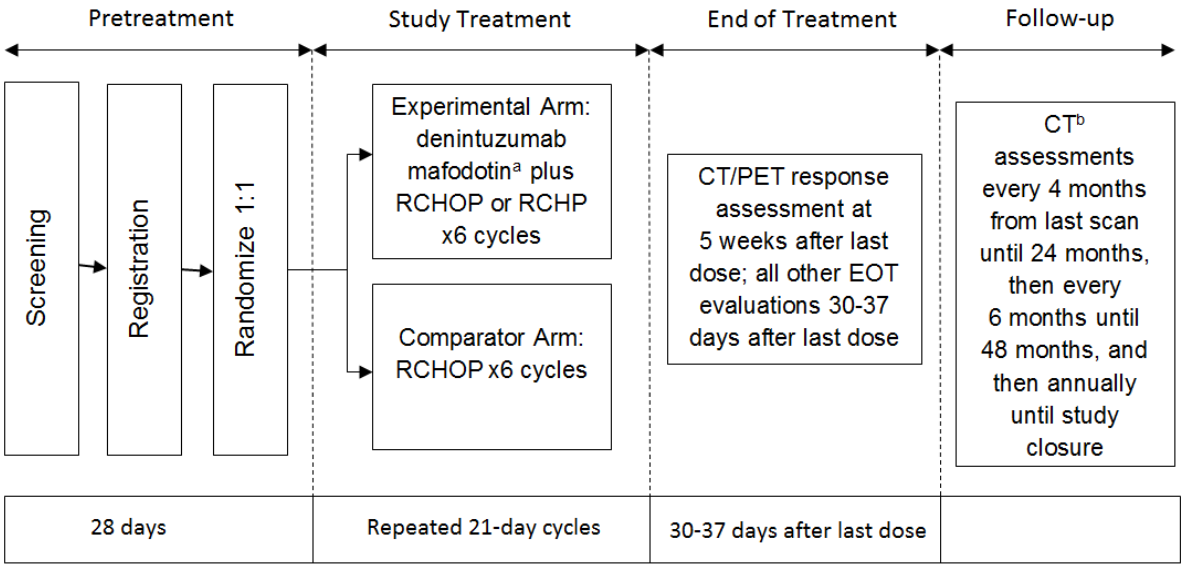
The evaluation of the safety and antitumor activity data at the end of Part A will be used to determine the regimen (RCHOP or RCHP) to be tested in combination with denintuzumab mafodotin in Part B. If Grade 3 neuropathy (sensory or motor) is observed in >20% of patients in the denintuzumab mafodotin plus RCHOP treatment group (n = 12), then that combination will have exceeded the stopping criteria for that regimen, and RCHP may be selected for administration in combination with denintuzumab mafodotin in Part B of the study, with the support of the overall safety and antitumor activity data from both arms.

During the treatment period, the SMC may also recommend conducting additional safety analyses or temporarily halting enrollment until an appropriate evaluation of the cumulative safety data, including review of unanticipated safety issues, has been completed.

3.1.2 Part B – Randomized, Open-Label Phase 2

Part B of the study is a phase 2, randomized, open-label, multicenter study designed to evaluate the antitumor activity and safety of denintuzumab mafodotin in combination with either RCHOP or RCHP (Experimental Arm) compared with RCHOP alone (Comparator Arm). Approximately 136 patients will be randomized 1:1 to either the Experimental or Comparator Arm. Randomization will be stratified by high-intermediate or high-risk disease and by cell of origin (COO). The study schema for Part B is depicted in Figure 2.

Figure 2: Part B Study Schema



d CT = computed tomography; EOT = end of treatment; PET = positron emission tomography; RCHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCHP = rituximab, cyclophosphamide, doxorubicin, and prednisone

a Administered on Day 1 of Cycles 1, 3, and 5

b Follow-up PET and CT scans required until disease is PET negative; responses will then be followed by CT scans of diagnostic quality. Follow-up assessments continue until disease progression, initiation of a new anti-cancer treatment, death, or study closure, whichever comes first. Survival status follow-up until death or study closure, whichever comes first.

The SMC will continue to monitor the safety of the combination of denintuzumab mafodotin and either RCHOP or RCHP at predefined interim safety evaluations and during the treatment period. The SMC will review cumulative safety data at the following timepoints:

- after 10 patients in each arm (N=approximately 20) have completed treatment,
- after 20 patients in each arm (N=approximately 40) have completed treatment, and
- after all patients in both arms have completed treatment.

During the treatment period, the SMC may also recommend conducting additional safety analyses or temporarily halting enrollment until an appropriate evaluation of the cumulative safety data, including review of unanticipated safety issues, has been completed.

3.2 SAMPLE SIZE CONSIDERATIONS

In Part A of the study, up to approximately 24 patients will be enrolled to receive denintuzumab mafodotin with either RCHOP or RCHP (approximately 12 patients per treatment arm). With 12 patients in each arm, the probability of observing at least 1 patient with a clinically relevant adverse event is 72% if the true event rate is 10%. The probability becomes 93% if the true event rate is 20%. In evaluating the grade 3 peripheral neuropathy, the observed incidence rate for patients treated with RCHOP is approximately 10%.

One criterion for selecting the study treatment for Part B of the study is that the addition of denintuzumab mafodotin, which is another microtubule inhibitor similar to vincristine, to

RCHOP should not cause significant additive neurotoxicity, and Grade 3 peripheral neuropathy should not exceed 20%. With 12 patients in each arm, if the true incidence rate is 15%, the probability of observing at least 3 patients having the event is 26%; if the true incidence rate is 25%, this probability becomes 61%.

In Part B of the study, approximately 136 patients will be randomized 1:1 to each treatment arm (approximately 68 patients per treatment arm). It is assumed that the underlying CR rates for the denintuzumab mafodotin plus RCHOP (or RCHP) treatment group is 88% and RCHOP treatment group is 70%. With a sample size of 136, an 18% improvement in CR rate in the denintuzumab mafodotin plus RCHOP (or RCHP) treatment group would provide approximately 80% power. This calculation is based on a 2-sided chi-squared test with significance level of alpha = 0.1 using EAST 6.3.1.

3.3 RANDOMIZATION

In Part A, following informed consent and screening, patients will be randomly assigned to 1 of 2 treatment regimens combined with denituzumab mafodotin in a 1:1 ratio using a centralized randomization system. Randomization in this part of the study is for the purpose of evaluating the safety of denituzumab mafodotin in combination with RCHOP versus RCHP. Patients will be stratified according to high-intermediate risk (International Prognostic Index ([IPI)] =3 for age >60 years and age-adjusted International Prognostic Index (aaIPI) =2 for age ≤60 years) versus high-risk (IPI =4 or 5 for age >60 years and age-adjusted International Prognostic Index [aaIPI] =3 for age ≤60 years) disease.

In Part B, following informed consent and screening assessments, patients will be randomly assigned to 1 of 2 arms in a 1:1 ratio using a centralized randomization system. Randomization in this part of the study is for the purpose of evaluating the efficacy and safety of denituzumab mafodotin in combination with either RCHP or RCHOP versus RCHOP alone. Randomization will be stratified by the following 2 factors:

- COO by local immunohistochemistry (IHC) assessment per Hans algorithm (germinal center B [GCB] versus non-GCB)
- high-intermediate risk versus high-risk disease based on standard IPI for patients >60 years of age and aaIPI for patients ≤60 years of age

3.4 BLINDING

This is an open label study.

4. STUDY VARIABLES AND COVARIATES

4.1 PRIMARY VARIABLES

4.1.1 Efficacy

- CR rate at the EOT as determined by investigators

4.1.2 Safety

- Adverse events (AEs, type, incidence, severity, seriousness, and relatedness)
- Laboratory abnormalities (type, incidence, and severity)
- Ophthalmologic exams and ocular health surveys

4.2 SECONDARY VARIABLES

4.2.1 Efficacy

Secondary efficacy variables for include: Event-free survival (EFS), Progression-free survival (PFS), Overall survival (OS), Objective response rate (ORR) following the completion of EOT, Duration of objective response and Duration of CR. These variables will not be calculated or presented.

4.3 ADDITIONAL VARIABLES

4.3.1 Pharmacokinetic and Immunogenicity Variables

- Plasma concentrations of denintuzumab mafodotin antibody-drug conjugate (ADC) and released cysteine maleimidocaproyl monomethyl auristatin F (cys-mcMMAF)
- Serum concentrations of rituximab
- Serum denintuzumab mafodin ATA

4.3.2 Biomarker Assessment Variables

Biomarker assessment variables will be defined and summarized in a separate report.

4.4 PREDETERMINED COVARIATES AND PROGNOSTIC FACTORS

Randomization will be stratified by high-intermediate or high-risk disease in Part A, and by high intermediate or high-risk disease and by COO in Part B to insure some level of balance between treatment arms. These stratification factors at randomization will be used as covariates in statistical models for the primary analysis.

5. DEFINITIONS

Age will be calculated with the SAS INTCK function using informed consent date and birth date.

Baseline: Unless otherwise specified, baseline is the last measurement taken prior to first dose of any study drug at Screening and/or Cycle 1 Day 1 visits.

Body Mass Index (BMI) (kg/m^2) = weight (kg) / [height (m)]^2.

Body Surface Area (BSA) (m^2) = (weight (kg) * height (cm)/3600) $^{0.5}$.

Cumulative Dose (mg): is defined as sum of actual doses received for denintuzumab mafodotin, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone, respectively

Dose Intensity, Absolute (ADI): is defined as the actual dose (mg/kg or mg/m^2) per unit of time that the subject received over the entire treatment period, where the treatment time is calculated as:

([Last Cycle day 1 dose date + 21] – first dose date (of any treatment))/7.

Dose Intensity, Intended (IDI): is the intended dose of drug (mg/kg or mg/m^2) per unit time. For denintuzumab mafodotin (DM), IDI= assigned DM dose level (mg/kg)/6 weeks..

For the components of RCHP/RCHOP, IDI is the intended dose of drug (mg/kg or mg/m^2)/3 weeks.

Dose Intensity, Relative (RDI): ADI divided by IDI *100.

Dose Modification: is defined as any elimination, delay, reduction, or unplanned dose adjustment

Duration of Treatment (days): is defined as time from the first dose of any treatment to 21 days after the last Cycle day 1 study dose,

[Last cycle day 1 dose date + 21] – first dose date.

If death occurs less than 21 days after the last cycle day 1 dose date, duration of treatment is defined as,

Date of death – first dose date + 1.

Height (cm): Height is reported in centimeters (cm). The following conversion will be used as necessary to convert height measurements collected in inches (in) to cm:

Height (cm) = Height (in) x 2.54

Time Unit Conversion: is defined as follows:

- Weeks = Days/7
- Months= Days/30.4375
- Years = Days/365.25

Time Since Diagnosis (days): is defined as Date of Informed Consent - Date of initial pathologic diagnosis from the disease diagnosis CRF.

Weight (kg): Weight will be tabulated in kilograms (kg). The following conversion will be used as necessary to convert weight measurements collected in pounds (lb) to kg:

Weight (kg) = Weight (lb) / 2.205

AEs of Special Interest:
Improvement of Peripheral Neuropathy(SMQ): is defined for events that are not resolved (defined below) as decrease by at least one grade from worst grade as of the latest assessment.
Improvement of Ocular AEs (SSQ): is defined for events that are not resolved (defined below) as All grade 3 or 4 AEs of interest have improved to grade 2 or better, and all grade 2 AEs of interest have improved to grade 1 or better as of the latest assessment. If multiple preferred terms under the SSQ exist, the preferred terms will be reviewed jointly, eg if one preferred term is improved, but another is not, at a subject level the subject will be counted as not improved.
Resolution of adverse events of special interest: is 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.

Time to onset of treatment-emergent AE (TEAE) of interest(weeks): is defined as the (start date of the AE - first dose date (of any) +1)/7.

Time to onset of Treatment-Emergent Adverse Event of Interest (cycles): is defined as Cycle = x where x:

Day 1 date of cycle x < AE start date <=(min (day 1 of cycle X+1, EOT date, end of study (EOS) date).

6. ANALYSIS SETS

6.1 INTENT-TO-TREAT

The intent-to-treat (ITT) analysis set will include all randomized patients. Patients will be included in the treatment arm assigned at randomization regardless of the actual treatment received. Stratified analyses will be based on the stratification factor as recorded at randomization.

6.2 SAFETY ANALYSIS SET

The safety analysis set will include all patients from Parts A and B who receive any amount of denintuzumab mafodotin or any component of RCHOP or RCHP. Treatment group will be determined using the actual treatment received, regardless of the randomization treatment assignment. In Part B, patients who received any amount of denintuzumab mafodotin will be assigned to the denintuzumab mafodotin in combination with either RCHOP or RCHP actual treatment arm.

7. INTERIM ANALYSES

No formal interim analysis is planned for this study.

An SMC will monitor the trial for safety and will convene regularly during both parts of the study. Members of the SMC will include the study investigators, medical monitor, and biostatistician and Sponsor's medical expert. The primary role of this SMC will be to monitor safety data during Part A.

Formal safety evaluations of cumulative data from both treatment groups will be conducted at predefined interim safety evaluations (for complete details see Section 3.1.1 for Part A)

During the treatment period, the SMC may also recommend conducting additional safety analyses or temporarily halting enrolment until an appropriate evaluation of the cumulative safety data, including review of unanticipated safety issues, has been completed.

An ongoing real-time review of serious adverse events (SAEs) in both parts of the 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 Haematology.

8. DATA REVIEW

8.1 DATA HANDLING AND TRANSFER

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

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1 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).

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (version June 2016 or more recent).

8.2 DATA SCREENING

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

Review of a TFL dry run on the nearly finalized database will allow for further data review prior to finalization. The dry run TFLs 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 Seattle Genetics must approve database lock.

9. STATISTICAL METHODS

All data collected during this study for all subjects will be displayed in data listings, unless otherwise specified. Data listings will be sorted by treatment and subject identifier. Screen failures will be excluded from all tables, with the exception of the Analysis Sets summary table, but will be included in listings. In addition, listings will include all relevant derived variables.

Summary statistics for continuous variables, unless otherwise specified, will include the number of subjects, mean, standard deviation, median, minimum, and maximum values. Continuous variables will generally be presented with the mean, median, Q1, and Q3 to 1 decimal more than individual data, and standard deviation to 2 decimals more than individual data. Data with > 3 decimal places (if any) may not follow this rule. Frequencies and percentages will be used to summarize categorical variables.

Unless specified otherwise, the tables, figures and listings will be presented by treatment groups and overall.

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

9.1 SUBJECT DISPOSITION

The number of subjects who were screened, enrolled, and/or, randomized in the study and the number and percentage of subjects who were treated with any amount of denintuzumab mafodotin or any component of RCHOP or RCHP, and the number of subjects in each analysis set will be summarized.

Disposition of subjects will be summarized by treatment group and overall for the ITT analysis set. The number and percentage of subjects who are on treatment, off treatment, who complete treatment, who discontinue treatment early, the reasons for discontinuation from the treatment and who are in follow up will be tabulated. All percentages will be based on the number of subjects randomized to the respective treatment group and overall.

9.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized and listed by treatment group and overall for the ITT and Safety analysis set. Demographic and baseline summaries will include age, age group, sex, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status, weight, height, BMI, and BSA. Disease characteristics include diagnosis, time since diagnosis, disease stage, serum lactate dehydrogenase (LDH) levels, extranodal disease involvement, disease transformed from prior Non-Hodgkin lymphoma (NHL) diagnosis, IPI score, aaIPI score, COO, and B-symptoms. CD30 expression will be listed.

Comorbid inflammatory conditions will be listed.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1 and listed.

9.3 PROTOCOL DEVIATIONS AND VIOLATIONS

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. A by-patient listing of important protocol deviations will be presented.

9.4 TREATMENTS

9.4.1 Extent of Study Drug Exposure

Exposure to study drugs denintuzumab mafodotin, RCHOP, or RCHP will be provided separately for each treatment group. Summaries will include the duration of treatment, number of doses received, number of doses eliminated, number of cycles received, number of subjects with at least 1 dose interruption, number of doses interrupted, the reasons for dose interruption, the number of subjects with at least 1 dose decreased for toxicity, the number of doses decreased for toxicity, the number of subjects with at least 1 dose delay, the number of dose delays, the cumulative dose, the relative dose intensity, the number of patients with infusion related or delayed hypersensitivity reaction.

9.4.2 Prior and Concomitant Medications

Verbatim prior and concomitant medications will be coded to preferred name using the World Health Organization Drug Dictionary (WHODRUG, 2016JUNE01 DDE (Enhanced)).

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

Prior cancer related therapies will be listed.

9.5 EFFICACY ANALYSES

Response at the end of treatment visit as assessed using Lugano 2014 will be summarized. Disease response assessments will be listed by patient. Secondary efficacy analyses and variables will not be calculated, as they pertain to part B.

9.6 PHARMACOKINETIC, ANTITHERAPEUTIC ANTIBODY MEASUREMENTS AND BIOMARKERS

The individual plasma concentrations of denintuzumab mafodotin ADC, TAb, and unconjugated drug (cys-mcMMAF) and serum concentrations of rituximab will be summarized with descriptive statistics at each PK sampling time point. Individual PK parameters will be estimated using noncompartmental analysis methods (where data allow), and summarized with descriptive statistics for each dose cohort. Additional PK and PK/PD/biomarker analyses may be conducted and presented in a separate analysis plan and report.

ATA incidence will be summarized by treatment group and overall and ATA results will be listed.

9.7 HANDLING OF DROPOUTS AND MISSING DATA

With the exception of time-related endpoints, missing observations will generally be treated as missing at random and will not be imputed, unless otherwise noted.

For missing or partial start and stop adverse event dates, see Appendix 2 for imputation rules.

Note that the actual value for date (not imputed) will be presented in all data listings and imputed dates will be used for derivations only.

9.8 SAFETY ANALYSES

All safety analyses will be based on the Safety analysis set unless otherwise specified.

9.8.1 Adverse Events and Serious Adverse Events

All adverse events will be coded into system organ class (SOC) and preferred term (PT) using the MedDRA version 19.1 or higher classification scheme, and severity grade using NCI CTCAE Version 4.03.

A treatment-emergent AE (TEAE) is defined as a newly occurring or worsening AE after the first dose of study drug and is defined in Appendix 3. Unless documented as a pre-existing condition, adverse events with unknown start date will be counted as treatment-emergent. Treatment-emergent AEs may or may not have a causal relationship with the study drug being studied. All summaries will include all AEs, unless otherwise specified.

Summary of AEs will be tabulated by treatment group and overall for Part A and B, respectively, and sorted by the highest frequency in the overall group by descending preferred term unless otherwise specified.

Any treatment-related AE summary will include any AE that is deemed related to denintuzumab mafodotin or any component of RCHOP or RCHP. AEs with missing relationship will be considered as related.

Dose modifications include dose elimination, dose reduction, dose delay, and any unplanned dose adjustment.

Summary of AEs include the following:

- Pre-existing AEs
- All TEAEs
- All Adverse Events
- Treatment-related AEs
- Denintuzumab mafodotin-related AEs
- RCHOP/RCHP-related AEs

- Serious AEs
- Serious treatment-related AEs
- Serious DM-related AEs
- Serious RCHOP/RCHP-related AEs
- AEs leading to dose modifications of DM
- AEs leading to dose modifications of any component of RCHOP/RCHP
- AEs leading to dose eliminations of DM
- AEs leading to dose eliminations of any component of RCHOP/RCHP
- AEs leading to dose delays
- AEs leading to dose delays of DM
- AEs leading to dose delays of any component of RCHOP/RCHP
- Denintuzumab mafodotin-related AEs leading to dose delays of DM
- AEs leading to dose reductions of DM
- AEs leading to dose reductions of any component of RCHOP/RCHP
- AEs leading to dose interruption or dose being stopped early of DM
- AEs leading to dose interruption or dose being stopped early of any component of RCHOP/RCHP
- AEs leading to treatment discontinuation
- Dose-delaying toxicities AEs
- Infusion-related reaction AEs
- Delayed hypersensitivity reactions AEs
- AEs with outcome of death
- Grade 3-5 TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum CTCAE grade

When AEs are counted by subject, subjects will be counted only once within each SOC or PT. When AEs are summarized by subject and CTCAE grade, a subject will be summarized based on the most severe AE for that SOC or PT. If CTCAE grade is missing, it will remain and be displayed as missing.

All AEs recorded on the CRF and captured in the database will be presented data listings. Dose-delaying toxicities, SAEs, and AEs leading to treatment discontinuation will be listed separately.

9.8.2 Adverse Events of Special Interest

Adverse Events of Interest include PN and ocular toxicity events. Neuropathy events will be identified by the broad search MedDRA SMQ (Standardized Medical Dictionary for Regulatory Activities Queries, sensory and motor). Ocular AEs (corneal, eye symptom, and blurry vision AEs) will be identified using three sponsor specified queries (SSQ) defined in Appendix 4. All outputs defined for ocular AEs of interest will be presented separately for each SSQ. For definitions of resolutions and improvement, see Section 5.

Peripheral Neuropathy (PN) and Ocular AEs will be summarized separately by descending preferred term (unless otherwise specified) as follows:

- Pre-existing AEs of interest
- Treatment-Emergent AEs of interest
- Treatment-Related AEs of interest
- DM Related AEs of interest
- RCHP/RCHOP Related AEs of interest

AEs of special interest will also be presented by maximum severity.

Time to onset (weeks and cycles), as well as resolution and improvement of AE events will be summarized.

Maximum severity relationship between the 3 Ocular SSQs will be summarized. Duration from Grade 3 or 4 corneal AEs to Grade 2 or better, duration from Grade 2 or 3 eye symptom AEs to Grade 2 or better, and duration from Grade 2 or 3 blurry vision AEs to Grade 2 or better will be summarized using the Kaplan-Meier method. Subjects without improvement to desired grade or better will be censored at the date of their last ocular exam.

AEs of Peripheral Neuropathy and Ocular AEs will be listed separately.

9.8.3 Deaths

The total number of deaths, deaths within 30 days of last dose, deaths after 30 days of last dose, as well as relationship to disease, will be summarized by treatment arm and total. Cause of death will be summarized by preferred term. Deaths and AEs with outcome of deaths will be listed.

9.8.4 Laboratory Data

All safety laboratory data will be converted to standard units by conversion programming.

The worst observed post-baseline value in CTCAE 4.03 will be summarized. Subjects with at least 1 on-study measurement for each laboratory parameter will be included, regardless of whether or not a baseline assessment is present.

All lab results will be listed.

9.8.5 Vital Signs

All vital sign results will be listed.

9.8.6 Physical Examinations, ECGs, ECOG, and Other Observations Related to Safety

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

Electrocardiogram (ECG) and ECOG assessments will be listed.

9.8.7 Ocular Examinations and Visual Function Survey

Ocular exams and visual function survey results will be listed.

Additionally, the visual function survey will be scored according to the VFQ-25 scoring manual, and scores will be summarized by visit and treatment arm.

10. VALIDATION

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

11. REFERENCES

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.

Collett D (1994). Interval-censored survival data. Modelling survival data in medical research. Boca Raton, Fla., Chapman & Hall/CRC: 237-251.

APPENDIX 1 GLOSSARY OF ABBREVIATIONS

Term	Definition
aaIPI	age-adjusted International Prognostic Index
ADC	antibody-drug conjugate
ADI	absolute dose intensity
AE	adverse event
ATA	antitherapeutic antibody
BMI	body mass index
BSA	body surface area
BMI	body mass index
BSA	body surface area
CI	confidence interval
CMR	complete metabolic response
COO	cell of origin
CR	complete response
CRF	case report form
CRO	Clinical Research Organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
cys-mcMMAF	cysteine maleimidocaproyl monomethyl auristatin F
DDT	dose-delaying toxicity
DLBCL	diffuse large B-cell lymphoma
DM	denintuzumab mafodotin
DMP	Data Management Plan
DOCR	duration of complete response
DOR	duration of objective response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EFS	event-free survival

EOS	end of study
EOT	end of treatment
FcγR	Fc-gamma receptor
FL	follicular lymphoma
GCB	germinal center B cell
IDI	Intended dose intensity
IHC	immunohistochemistry
IPI	International Prognostic Index
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetics
PFS	progression-free survival
PMR	partial metabolic response
PN	peripheral neuropathy
PT	preferred term
RCHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RCHP	rituximab, cyclophosphamide, doxorubicin, and prednisone
RDI	relative dose intensity
SAE	serious adverse event
SAP	statistical analysis plan
sCD19	soluble CD19
SGN-CD19A	denintuzumab mafodotin
SMC	Safety Monitoring Committee
SMQ	Standardized Medical Dictionary for Regulatory Activities

	QueriesMedDRA Query
SOC	system organ class
SSQ	sponsor derived query
TEAE	treatment-emergent adverse event
TFLTFLs	tables, figures, and listings
US	United States
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. Eg, 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 any study treatment (DM or any component of RCHP/RCHOP) 2. Define baseline 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 any study treatment". If the onset period of the AE is missing, then look for AE start date < first dose date (from bullet #1) or AE start date = first dose date (from bullet #1) but onset time relative to Rituximab is 'Started before first infusion or before infusion on any dosing day'... If AE start date is missing, use AE start date imputation rule. <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 any study treatment". If the onset period of the AE is missing, then look for AE start date > first dose date (from bullet #1) or AE start date = first dose date (from bullet #1) but onset time relative to Rituximab 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.

Term	Standard Definition
	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 TEAE = Yes or . then include in output. I.e., only exclude TEAE= No for "Treatment-emergent" outputs.

APPENDIX 4 OCULAR AES OF INTEREST SSQ DEFINITION

Preferred Terms for SSQ **Corneal Adverse Events**		
Acquired corneal dystrophy	Corneal epithelium defect	Keratitis interstitial
Allergic keratitis	Corneal erosion	Keratitis sclerosing
Atopic keratoconjunctivitis	Corneal exfoliation	Keratoconus
Bowman's membrane disorder	Corneal hypertrophy	Keratopathy
Corneal abrasion	Corneal infiltrates	Keratorhexis
Corneal abscess	Corneal irritation	Limbal hyperaemia
Corneal bleeding	Corneal lesion	Limbal stem cell deficiency
Corneal cyst	Corneal oedema	Limbal swelling
Corneal decompensation	Corneal opacity	Macrocornea
Corneal defect	Corneal perforation	Microcornea
Corneal degeneration	Corneal pigmentation	Neurotrophic keratopathy
Corneal deposits	Corneal scar	Photokeratitis
Corneal diameter decreased	Corneal striae	Punctate keratitis
Corneal diameter increased	Corneal thickening	Terrien's marginal degeneration
Corneal disorder	Corneal thinning	Topography corneal abnormal
Corneal dystrophy	Dellen	Ulcerative keratitis
Corneal endothelial cell loss	Detached Descemet's membrane	Vital dye staining cornea present
Corneal endotheliitis	Iridocorneal endothelial syndrome	Deposit eye[a]
Corneal epithelial microcysts	Keratic precipitates	Ocular toxicity[a]
Dry eye[b]	Keratitis	Slit-lamp tests abnormal[a]
a Broad Terms		b only if LLT is "Keratoconjunctivitis sicca"

Preferred Terms for SSQ **Eye Symptom Adverse Events** (Preferred Terms for Blurry Vision Adverse Events are labeled with *)		
Abnormal sensation eye	Excessive eye blinking	Oscillopsia
*Acute Myopia	Eye disorder	Photalgia
Amaurosis	Eye irritation	Photophobia

Amaurosis fugax	Eye pain	Photopsia
Asthenopia	Eye pruritis	Presbyopia
*Blindness	Eyelid pain	Saccadic eye monement
*Blindness day	Foreign body sensation in eyes	Scintillating scotoma
*Blindness transient	Halo vision	Tunnel vision
*Blindness unilateral	Hypoaesthesia eye	*Vision blurred
Chloropsia	Lacrimal disorder	*Visual acuity reduced
Colour blindness	Lacrimation decreased	*Visual acuity reduced transiently
Colour blindness acquired	Lacrimation increased	Visual brightness
Contact lens intolerance	Loss of visual contrast sensitivity	*Visual impairment
Cyanopsia	Meibomian gland discharge	Vitreous floaters
*Diplopia	Meibomian gland dysfunction	Xanthopsia
Dry eye[a]	*Myopia	Xerophthalmia
Dysmetropsia	*Night blindness	
Erythropsia	Ocular discomfort	
a if the LLT is “Keratoconjunctivitis sicca”, the event will be categorized as corneal SSQ		