Title: A Phase 4, Open–label, Single-Arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

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STATISTICAL ANALYSIS PLAN

A Phase 4, Open-Label, Single-Arm Study of Brentuximab Vedotin in Patients With Relapsed or Refractory System Anaplastic Large Cell Lymphoma

Protocol #: C25006

SAP Version:	Date of Statistical Analysis Plan:
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Approval Signatures

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List of Abbreviations and Definitions of Terms

Abbreviation	Term
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
BMI	body mass index
BUN	blood urea nitrogen
CO_2	carbon dioxide
CR	complete response
CSR	clinical study report
CT	computed tomography
DOR	duration of response
DOCR	duration of response in the subset of patients achieving complete remission
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
GGT	gamma-glutamyl transpeptidase
HLT	High Level Term
CCI	[redacted]
IRF	independent review facility
ITT	intent-to-treat
IV	intravenous; intravenously
IWG	International Working Group
IWRS	interactive web response system
LDH	lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethylauristatin E
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease (disease progression)
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	per protocol
PR	partial response

Abbreviation	Term
CCI	
PT	Preferred Term
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
CCI	
SCT	stem cell transplant
SD	stable disease
SOC	System Organ Class
SPD	sum of the products of the largest diameters
CCI	
TEAE	treatment-emergent adverse event
CCI	
WHO	World Health Organization

1. INTRODUCTION

In general, the purpose of the Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that addresses the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

1.1 Study Design

This single-arm, open-label, multicenter phase 4 clinical study seeks to evaluate the efficacy and safety of brentuximab vedotin as a single agent in adult patients with relapsed or refractory systemic anaplastic large-cell lymphoma (sALCL) who have previously received at least 1 multiagent chemotherapy regimen (CHOP or equivalent multiagent chemotherapy regimens with curative intent). Its primary objective is to determine the antitumor efficacy of single-agent brentuximab vedotin as measured by objective response rate (ORR) in patients with relapsed or refractory sALCL following at least 1 multiagent chemotherapy regimen (CHOP or equivalent multiagent chemotherapy regimens with curative intent).

Brentuximab vedotin will be administered as a single intravenous (IV) infusion over 30 minutes on Day 1 of each 3-week cycle for up to a maximum of 16 cycles and should be administered for a minimum of 8 cycles for patients who achieve stable disease (SD) or better. Overall response will be assessed by independent review facility (IRF) according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma (Cheson 2007)[(1)]. Patients who experience disease progression at any time will be withdrawn from study drug treatment.

Patients may continue on study treatment until disease progression or unacceptable toxicity. Patients will have an End of Treatment (EOT) assessment 30 ± 7 days after receiving their final dose of study drug. Patients who discontinue study treatment with SD or better will have computed tomography (CT) scans done every 3 months for 18 months from EOT or until the sooner of disease progression, death, or study closure. Overall survival (OS) data will be collected every 3 months from EOT for 18 months, then every 6 months thereafter until the sooner of death or study closure. The study will be closed when 50% of the patients have had an OS event or 5 years after enrollment of the last patient, whichever occurs first.

1.2 Study Objectives

1.2.1 Primary Objectives

The primary objective is:

- To assess the antitumor efficacy of single-agent brentuximab vedotin (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall ORR in patients with relapsed or refractory sALCL following at least 1 multiagent chemotherapy regimen (CHOP or equivalent multiagent chemotherapy regimens with curative intent).

1.2.2 Secondary Objectives

The secondary objectives include:

- To determine duration of tumor control, including duration of response, progression free survival (PFS), and complete remission rate (CR) with brentuximab vedotin
- To determine the proportion of patients receiving hematopoietic stem cell transplant (either autologous or allogeneic) after brentuximab vedotin
- To determine overall survival (OS) with brentuximab vedotin
- To assess the safety and tolerability of brentuximab vedotin
- To assess the pharmacokinetics (PK) of brentuximab vedotin
- To determine immunogenicity of brentuximab vedotin

1.2.3 Tertiary/Exploratory Objectives

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2. POPULATIONS FOR ANALYSIS

2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) analysis population includes all patients enrolled in the study.

A patient is considered to be enrolled in the study when enrolled in the interactive Web response system (IWRS). Procedures for completion of the enrollment information are described in the Study IWRS Manual.

The ITT analysis population will be used for the primary efficacy analysis. Secondary and additional efficacy endpoints will also be analyzed using this analysis set.

2.2 Per-Protocol Population

The Per-Protocol (PP) analysis population includes all patients who receive at least 1 dose of brentuximab vedotin and who have measurable disease at baseline, the correct histological cancer type per central pathology review, and no other major protocol deviations that could potentially affect tumor response.

The Per-Protocol analysis population will be used for analyses of the primary efficacy endpoint.

2.3 Safety Population

The Safety analysis population includes all patients who receive at least 1 dose of brentuximab vedotin.

The Safety analysis population will be used for all safety analyses as well as for patient demographics and baseline disease characteristics.

2.4 Pharmacokinetics Population

Patients with sufficient dosing and analyte concentration data will be included in the Pharmacokinetic analysis population.

PK analysis will be performed using PK population.

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3. HYPOTHESES AND DECISION RULES

No applicable.

4. INTERIM ANALYSIS

No formal interim analysis is planned for this study.

5. STATISTICAL METHODOLOGY

Statistical analyses will be primarily descriptive and graphical in nature. For continuous variables, descriptive statistics will be used including n, mean, median, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be used for the analyses. The Kaplan-Meier survival curves will be provided along with their two-sided 95% CIs for time-to-event data.

No formal statistical hypothesis testing will be performed.

5.1 Sample Size Justification

A minimum of 45 patients with relapsed or refractory sALCL will be enrolled in the study. Based on previous study results, with a sample size of 45, observing 31 (69%) objective responses (complete or partial remission) would provide the lower bound of the 95% confidence interval (two-sided) is greater than 53%.

5.2 Randomization and Stratification

This is an open-label, single-arm study. Randomization and stratification are not applicable to this study.

5.3 Unblinding

This is an open-label, single-arm study; investigators and patients will know their individual treatment assignment. Unblinding is not applicable to this study.

5.4 Data Handling

5.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. The relevance of missing sample data will be assessed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

In general, missing data will be treated as missing, and no data imputation will be applied unless otherwise specified.

5.4.2 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but before, the start of study drug administration.

5.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which they were collected.

These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

5.4.4 Justification of Pooling

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis due to the rarity of the disease and potentially limited number of patients at each center.

5.4.5 Withdrawals, Dropouts, Loss to Follow-up

Enrolled patients who do not receive study drug for any reason will not be replaced; however, additional patients may be enrolled to ensure an adequate number of patients with histologically confirmed sALCL in the study.

5.5 Patient Disposition

Patient disposition will be summarized. The disposition of patients includes the number and percentage of patients for each analysis population (ITT population, PP population, safety population, PK population, and biomarker population) in the study.

The number and percentage of patients who completed the study treatment will be summarized. The primary reason for treatment and study discontinuation will also be summarized in this table.

A listing will be presented data concerning patient disposition.

5.6 Demographics and Baseline Disease Characteristics

5.6.1 Demographics

Demographic, baseline characteristics and prior therapies will be summarized using descriptive statistics for safety population.

Demographics to be evaluated will include age at inform consent, gender, ethnicity, race, baseline height, weight, and body mass index (BMI).

The formulation for BMI is:

$BMI = weight/height^2$,

where weight is in kilograms (kg) and height in meters (m).

Baseline characteristics and prior therapies to be evaluated will include disease type, Eastern Cooperative Oncology Group (ECOG) performance status, time from initial systemic ALCL diagnosis to first dose of brentuximab vedotin, anaplastic lymphoma kinase (ALK) status, baseline B symptoms, Ann Arbor Stage at initial diagnosis, and other parameters as appropriate.

No inferential statistics will be generated.

A listing of demographic data will be provided.

5.6.2 Medical History

No table or listing is planned to be produced for general medical history in this study.

5.7 Treatments and Medications

5.7.1 Concomitant Medications

Concomitant medications will be coded by generic term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications from signing informed consent form through 30 days after the last dose of study drug will be tabulated using WHO drug generic term.

Concomitant procedures will not be coded.

5.7.2 Study Treatments

Brentuximab vedotin will be administered on Day 1 of each 3-week cycle. The dose of brentuximab vedotin is 1.8 mg/kg and is administered by outpatient IV infusion given over approximately 30 minutes. Patients with stable disease or better should receive a minimum of 8 cycles and, all patients will be given the opportunity to complete a maximum of up to 16 cycles of brentuximab vedotin.

Brentuximab vedotin should be administered through a dedicated IV line and cannot be mixed with other medications. Details on the dosing of study drug can be found in the protocol and pharmacy manual.

5.7.2.1 Extent of Exposure

The exposure to study drug will be characterized by duration of treatment, total amount of dose taken in mg, total number of doses taken, number of treated cycles, and average dose per cycle in mg. Dose intensity and relative dose intensity (%) will be derived and summarized.

A treatment cycle is defined as a 3-week period, during which the patient received any amount of brentuximab vedotin (scheduled for a single dose on Day 1 of the 3-week cycle).

The duration of treatment is defined as time from the first study dose to 3 weeks after the last study dose: Duration of Treatment = last dose date + 3 weeks – first dose date. If death occurs less than 3 weeks after the last study dose, duration of treatment is defined as (date of death – first dose date +1 day). If discontinuation of the study drug occurs less than 3 weeks

after the last study dose due to reasons including but not limited to progressive disease (PD), initiating SCT, etc, duration of treatment is defined as (date of EOT – first dose date +1 day). The amount of dose taken in mg for each cycle will be calculated as:

prepared dose in mg × (actual volume / prepared volume).

Dose intensity (mg/week) will be calculated as:

actual total dose administered (mg)/(3 × number of treated cycles).

Relative dose intensity (%) will be calculated as:

100% × (Total dose administered (mg) / Total dose expected (mg)).

where the dose expected for each cycle is the standard lose level (1.8 mg/kg) × the body weight used for the dosing calculation.

All extent-of-exposure data will be summarized as continuous variables for brentuximab vedotin in the safety population.

The number and percentage of patients whose dose was ever modified will be summarized for each type of modification by cycle and overall.

5.8 Efficacy Analyses

All efficacy analysis will use the ITT population unless otherwise specified.

5.8.1 Primary Efficacy Endpoint

The primary endpoint of this study is ORR per IRF in patients with relapsed or refractory sALCL following at least 1 multiagent chemotherapy regimen (CHOP or equivalent multiagent chemotherapy regimens with curative intent).

ORR is defined as the proportion of patients with complete remission (CR) or partial remission (PR) according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma (Cheson 2007). ORR per IRF is based upon the response assessment from an independent review facility.

5.8.1.1 Primary Efficacy Analysis

The ORR per IRF and its two-sided 95% exact confidence interval will be calculated. The primary analysis will be performed using both ITT and per-protocol population.

The maximum percent reduction in the sum of the products of the largest diameters (SPD) of the tumor masses being followed for response assessment per IRF will be graphically displayed.

The ORR per investigator and its two-sided 95% exact confidence interval will also be calculated. The difference of objective responses between assessments by IRF and investigator will be tabulated.

As exploratory analyses, subgroup analyses will be conducted for ORR using age (<65 years, ≥ 65 years) and ALK status of the tumor (ALK +, ALK -). The subgroup analyses will be conducted for IRF assessment and investigator assessment.

5.8.2 Secondary Efficacy Endpoints

Complete remission rate is defined as the proportion of patients with CR according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma (Cheson 2007). CR per IRF is based upon the response assessment from an independent review facility.

Duration of response (DOR) is defined as the time between initial response and documented tumor progression. DOR per IRF is based upon the radiological assessment of measured lesions from an independent review facility. DOR will only be calculated for the subgroup of patients with CR or PR. DOR will also be analyzed in the subset of patients achieving CR.

Progression-free survival is defined as the time from start of study treatment to first documentation of objective tumor progression or to death due to any cause, whichever comes first. PFS per IRF is based upon the radiological assessment from an independent review facility.

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

Another secondary efficacy endpoint is the proportion of patients receiving hematopoietic stem cell transplant (SCT, either autologous or allogeneic) after brentuximab vedotin therapy.

5.8.2.1 Secondary Efficacy Analysis

5.8.2.1.1 Handling of Censoring for Analysis of Progression-Free Survival

Disease assessment data (PFS and response) should be collected according to the intended schedule of assessment, and the date of PD/response (CR or PR) should be assigned based on the time of the first documentation of PD/response regardless of violations, discontinuation of study treatment, or initiation of a new subsequent anti-cancer therapy.

Patients who discontinue the study treatment with a CR, a PR, or stable disease (SD) will have CT scans performed for assessment of PFS every 3 months for 18 months after the patient's EOT or until the sooner of disease progression (PD), death, or study closure.

PFS will be censored on the date of the last disease assessment documenting absence of PD for patients who are lost to follow-up, withdraw consent, start the subsequently new anti-cancer therapy other than stem cell transplant, or discontinue treatment due to undocumented PD after the last adequate disease assessment. Patients lacking an evaluation of tumor response after their first dose will have their event time censored at 1 day.

If death or PD occurs after a missed visit, then the patient is treated as progressed at the date of death or PD. If PD is documented between scheduled visits, then the date of the documented PD is the date of progression.

5.8.2.1.2 Secondary Efficacy Analysis

CR per IRF will be derived and its two-sided 95% exact confidence interval will be calculated.

DOR per IRF, DOR per IRF in the subset of patients achieving CR (DOCR), PFS per IRF, and overall survival will be estimated using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The 25th percentile, median, and 75th percentile DOR per IRF, DOCR per IRF, PFS per IRF, OS (if estimable) and their two-sided 95% CI will be calculated, along with the minimum and maximum values. The median follow-up based on the reverse Kaplan-Meier will be provided. These endpoints may also be summarized by subgroups of (<65 years, ≥ 65 years) and ALK status of the tumor (ALK +, ALK -).

The investigator assessment of CR, DOR, DOCR and PFS will be analyzed in the same manner.

PFS from the most recent prior treatment before the initiation of the study drug versus PFS from the current study treatment will be presented via Kaplan-Meier plot and water-fall plot. The investigator assessment will be used for this analysis.

The primary analysis for PFS will use the censoring rules defined in Section 5.8.2.1.1. To evaluate the robustness of treatment effects, the following sensitivity analyses are also planned for PFS.

- Patients who start the subsequently new anti-cancer therapy other than stem cell transplant before PD will not be censored, nor be treated progressed at the date of the last disease assessment, until documented disease progression. Patients will be treated as progressed at the date of documented disease progression.

- Patients who start new alternative anti-cancer therapy before PD will be treated as progressed at the date of the last disease assessment. Patients who withdraw inform consent, discontinue from study treatment due to drug related AE or symptomatic deterioration or unsatisfactory therapeutic response will be treated as progressed at the date of the last disease assessment.

In addition, descriptive statistics will be used to present percent of patients receiving stem cell transplantation (SCT) following treatment with brentuximab vedotin.

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5.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analysis

5.9.1 Pharmacokinetic Analyses

The PK of the antibody drug-conjugate (brentuximab vedotin), total antibody, and free payload(MMAE) will be derived from serum or plasma concentration versus time data for all patients who met study inclusion criteria for the PK population (received study drug, and provided evaluable analyte concentration data). Summary statistics of each analyte concentration-time data will be performed. Concentrations of analytes obtained in this study may be combined with those of other studies and be used in population PK analysis. Output of such data may or may not be available at the time of writing the clinical study report (CSR) for this study. Such data may be used in the summary of clinical pharmacology section of regulatory submission that includes information from this study.

5.9.2 Immunogenicity Analysis

All patients who were administered at least 1 dose of brentuximab vedotin will be evaluated for antitherapeutic antibody (ATA) development. A list/table of ATA status will be provided. Antibody neutralizing status (neutralizing or not neutralizing) will also be listed for patients who have positive antibody status.

Immunogenicity information, including ATA and neutralizing ATA, will be summarized in descriptive statistics as applicable.

The relationship between immunogenicity and efficacy and/or safety will be explored.

Immunogenicity analysis will be performed using safety population.

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5.11 Safety Analyses

Safety evaluations will be based on the incidence, severity, seriousness, type of adverse events (AEs), treatment- emergent adverse events (TEAEs), and clinically significant changes, or abnormalities in the subject's physical examination, vital signs, weight and clinical laboratory results. Exposure to study drug and reasons for discontinuation will be tabulated. Total dose, duration of treatment and dose modifications will be summarized.

These analyses will be performed using the safety population.

5.11.1 Adverse Events

5.11.1.1 Adverse Events

Overall summary of TEAEs will be presented. TEAEs will be tabulated by primary System Organ Class (SOC), High Level Term (HLT), and Preferred Term (PT). All AEs will be listed for each patient.

A TEAE is defined as any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of study medication. AEs will be tabulated according to the most recent version (Version 16.0or higher) of the Medical Dictionary for Regulatory Activities (MedDRA) by SOC, HLT, and PT and will include the following categories:

- TEAEs
- Study drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher drug-related TEAEs

The most commonly reported TEAEs (i.e., those events reported by ≥ 10% of all patients) will be tabulated by SOC and PT. TEAEs leading to study drug dose modification will be summarized in the same manner.

TEAEs will be also summarized by SOC, HLT, PT and intensity.

Infusion-related TEAEs will be summarized by PT.

5.11.1.2 Serious Adverse Events

The number and percentage of subjects experiencing at least 1 treatment-emergent serious adverse event (SAE) including study drug-related SAEs, will be summarized by MedDRA primary SOC, HLT, and PT.

In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment-emergent status).

5.11.1.3 Deaths

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment-emergent status). On-study death is defined as a death that occurs between the first dose of study drug and 30 days after the last dose of study drug.

5.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

TEAEs leading to study drug discontinuation will be tabulated by SOC, HLT and PT.

A by-subject listing of AEs resulting in discontinuation of study drug will be presented.

5.11.1.5 Adverse event of special interest (AESI)

Peripheral Neuropathy (PN) as AESI will ALSO be summarized. Peripheral Neuropathy (PN) is defined by the peripheral neuropathy standardised MedDRA query (SMQ) broad search. The incidence of treatment-emergent PN and treatment-emergent drug-related PN will, each, be summarized by PT and severity. Time-to-onset, time-to-resolution or improvement of PN events will be summarized using summary statistics (mean, median, range, etc). The number of patients with PN resolution or improvement at EOT and at last follow-up will be counted. Patients with ongoing PN events will be summarized by the maximum grade.

Treatment-emergent peripheral neuropathy (SMQ) events by PT will also be plotted to show grade changes where applicable. Treatment-emergent peripheral neuropathy will further be categorized by peripheral sensory neuropathy and peripheral motor neuropathy.

5.11.2 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a nonnumeric qualifier

(e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used.

The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, platelet count, leukocytes with differential, and neutrophil (absolute neutrophil count [ANC]),
- Serum chemistry: blood urea nitrogen (BUN), creatinine, bilirubin (total), urate, lactate dehydrogenase (LDH), phosphate, gamma-glutamyl-transferase (GGT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, sodium, potassium, calcium, chloride, carbon dioxide (CO_2), and magnesium

Descriptive statistics for the actual values of clinical laboratory parameters (hematology and serum chemistry) will be presented at baseline and over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Summary statistics for change from baseline of clinical laboratory parameters will also be presented.

Shift tables for laboratory parameters will be generated based on changes in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade from baseline to the worst post-baseline value.

5.11.3 ECG

A listing of ECG results will be provided for each patient by visit.

5.11.4 Vital Signs

The actual values of vital sign parameters, including seated (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral temperature, when available, will be summarized over time.

5.11.5 Other Safety Assessments

5.11.5.1 ECOG Performance Status

ECOG status will be summarized.

5.11.5.2 Concomitant Medications

All medications taken during the course of the study will be recorded. Concomitant medications will be summarized by the WHO generic term.

6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Not applicable

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.2 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Subject populations are defined in Section 2.

Baseline values are defined in Section 5.4.2.

Treatment-emergent AEs are defined in Section 5.11.1.1.

8. REFERENCES

1. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. Journal of Clinical Oncology 2007;25(5):579-86.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	18-Jun-2021 14:28 UTC