Statistical Analysis Plan

NCT Number: NCT05673785

Title: A Phase 2, Single-Arm, Open-Label, Multicenter Study of Brentuximab Vedotin in Combination With Cyclophosphamide, Doxorubicin (Hydroxydaunorubicin), Prednisone (CHP) in the Frontline Treatment of Chinese Patients With CD30-Positive (CD30+) Peripheral T-Cell Lymphomas (PTCL)

Study Number: C25024

Document Version and Date: Version 2.0, 21 Apr 2025

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STATISTICAL ANALYSIS PLAN

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Phase: II

Version: Version 2.0

Date: 21-Apr-2025

Prepared by: [redacted]

Based on: A Phase 2, Single-Arm, Open-Label, Multicenter Study of Brentuximab Vedotin in Combination with Cyclophosphamide, Doxorubicin (Hydroxydaunorubicin), Prednisone (CHP) in the Frontline Treatment of Chinese Patients With CD30-Positive (CD30+) Peripheral T-Cell Lymphomas (PTCL)

Protocol Version: Original

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Approval Signatures

Date	Prepared by: [redacted], Clinical Biostatistics
Date	Approved by: [redacted], Clinical Biostatistics

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Final 1.0	05 Aug 2022	[Not Applicable]
Version 2.0		To correct typos, provide clarity and additional statistical analysis details

TABLE OF CONTENTS

ABBREVIATIONS

A+CHP	Adcetris plus cyclophosphamide, doxorubicin (hydroxydaunorubicin), and prednisone
ADA	antidrug antibody(ies)
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
AITL	angioimmunoblastic t-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK+/-	anaplastic lymphoma kinase positive / negative
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CD30+	CD30-positive
CHP	cyclophosphamide, doxorubicin (hydroxydaunorubicin), and prednisone
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
eCRF	electronic case report form
EOT	end of treatment
FAS	full analysis set
HLT	high level term
IRF	independent review facility
IXRS	interactive voice/web response system
KM	Kaplan-Meier
LTFU	long-term follow up
MMAE	monomethyl auristatin E
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NMPA	National Medical Product Administration
ORR	objective response rate
OS	overall survival
PD	progressive disease/disease progression
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcomes
PT	preferred term
popPK	population PK

Q1	25th percentile
Q3	75th percentile
SAE	serious adverse event
sALCL	systematic anaplastic large cell lymphoma
SAP	statistical analysis plan
SD	stable disease
SMQ	standardised MedDRA queries
SOC	System Organ Class
SOE	schedule of events
TEAE	treatment-emergent adverse event
TTR	time to response
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objectives

The primary objectives are:

- To evaluate ORR (CR and PR) by IRF assessment per Revised Response Criteria for Malignant Lymphoma following the completion of study treatment.
- To evaluate the safety and tolerability of the A+CHP combination.

1.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate CR rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria following the completion of study treatment.
- To evaluate 1-year PFS rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria.
- To evaluate 1-year OS rate.
- To evaluate IRF- and investigator-assessed ORR and CR rate following the completion of study treatment, time to response (TTR), and 1-year PFS rate per 2014 Lugano classification.
- To evaluate duration of response (DOR) by investigator assessment per 2014 Lugano classification.
- To collect serum/plasma concentration-time data to contribute to population PK (popPK) analyses.
- To assess immunogenicity.

1.1.3 Additional Objectives

The additional objectives are:

- To evaluate PFS by investigator assessment.
- To evaluate OS.

1.2 Endpoints

1.2.1 Primary Endpoints

The primary efficacy endpoint is:

- ORR by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria following the completion of study treatment.

The primary safety endpoints are:

- AEs, assessment of clinical laboratory values, and vital signs measurements.

1.2.2 Secondary Endpoints

1.2.2.1 Secondary Endpoints

The secondary efficacy endpoints are:

- CR rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria following the completion of study treatment.
- 1-year PFS rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma criteria.
- 1-year OS rate.
- ORR and CR rate following completion of study treatment, TTR, and 1-year PFS rate by IRF and investigator assessment per 2014 Lugano classification.
- DOR by investigator assessment per 2014 Lugano classification.
- PK (serum antibody-drug conjugate (ADC) and plasma monomethyl auristatin E (MMAE) concentration time data) to contribute to popPK analyses.
- Immunogenicity status; antidrug antibody (ADA) status, including ADA negative, ADA transiently and persistently positive, ADA titer, and neutralizing antidrug antibody (Nab) negative and positive.

1.2.3 Additional Endpoint(s)

The additional endpoints are:

- PFS by investigator assessment.
- OS.

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

Study C25024 is a phase 2, single-arm, open-label, multicenter study designed to evaluate the efficacy, safety, and PK of A+CHP as frontline treatment of Chinese patients with newly diagnosed CD30+ PTCL. Eligible histologies include ALK-positive sALCL with an International Prognostic Index (IPI) score of ⩾2, ALK-negative sALCL, PTCL-NOS, AITL, EATL, and HSTCL.

Enrollment of approximately 52 patients is planned for the study, including approximately 36 patients with the primary diagnosis of sALCL to mimic the proportion of patients with sALCL in ECHELON-2.

Enrolled patients will receive 6 to 8 cycles of A+CHP, each lasting 21 days, as determined by the investigator and based on patient-specific characteristics, including disease stage and IPI score. Patients will receive study treatment until progressive disease (PD), unacceptable toxicity, or completion of the desired 6 to 8 cycles, whichever occurs first. Patients, including those who discontinue study treatment for any reason other than withdrawal of consent, will have safety follow-up assessments through 30 to 37 days after the last dose of study treatment.

Enrolled patients will undergo radiographic evaluation consisting of fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging and contrast-enhanced computed tomography (CT) scans of the neck, chest, abdomen, and pelvis to monitor and assess disease response. Magnetic resonance imaging (MRI) may be used for patients for whom contrast-enhanced CT scans are contraindicated.

Response will be assessed using Revised Response Criteria for Malignant Lymphoma (Cheson 2007) and the International Working Group 2014 Lugano classification. Radiographic disease evaluation will be conducted at baseline, Cycle 4, and at last cycle of study treatment. During the PFS follow-up period, radiographic disease assessment will be done every 3 months through 24 months after initiation of study treatment and every 6 months thereafter until PD per investigator assessment, initiation of new anticancer therapy to treat residual or PD, death, or study closure, whichever occurs first. The same imaging modality should be used consistently throughout the study to monitor the disease status. Receipt of posttreatment consolidative radiotherapy, posttreatment chemotherapy for the purpose of mobilizing peripheral stem cells, or consolidative autologous or allogeneic stem cell transplantation (SCT) will not be considered PD. Once a patient experiences PD per investigator assessment, the patient will be followed for OS every 6 months until death or study closure, whichever occurs first. All patients will have the opportunity to be followed until 36 months after the last patient's first dose of study treatment. Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective November 2017. Clinical laboratory values and vital signs measurements will be obtained to evaluate the safety and tolerability of brentuximab vedotin in combination with CHP. Blood samples will be collected using a sparse PK sampling scheme at prespecified time points for determination of serum and plasma concentrations of PK and immunogenicity endpoints.

The study will end when the last patient completes their last follow-up visit, which will be 36 months after initiation of study treatment.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable.

3.2 Statistical Decision Rules

The probability of observing ORR by IRF greater than the lower bound of 95% CI (77.7%-87.8%) of global study ECHELON-2 is approximately 83% (i.e., 83% of chance to observe an ORR greater than 77.7%, assuming a true ORR for sALCL and non-sALCL patients is the same as the observed ORR in ECHELON-2).

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

It is anticipated that approximately 52 patients will be enrolled in this study. With a target sALCL patient proportion of 70%, approximately 36 sALCL patients need to be enrolled in the study. In ECHELON-2, the observed ORR was 87.65% for sALCL patients and 71.88% for non-sALCL patients. Assuming a true ORR for sALCL and non-sALCL patients is the same as the observed ORR in ECHELON 2, with a sample size of approximately 52 patients, the probability of observing ORR by IRF greater than the lower bound of 95% CI (77.7%-87.8%) of ECHELON-2 is approximately 83%.

Another rationale to determine the sample size is to ensure the lower bound of the observed 95% CI of ORR by IRF is greater than the threshold response rate of 65%. With a sample size of approximately 52 patients, the desire is to minimally observe 41 responders (CR or PR) in order for the lower bound of the exact 95% CI of ORR by IRF to be greater than 65%. With the same assumption as previously described, the probability of observing at least 41 responders is approximately 83%.

5.0 ANALYSIS SETS

The following analysis sets are defined in the study: full analysis set (FAS), response-evaluable set, immunogenicity analysis set, and PK analysis set. If a patient is not included in an analysis set, that determination should be made before database lock.

5.1 Full Analysis Set

All demographic, efficacy, and safety analyses will be based on the FAS, which is defined as all enrolled patients (ie, those who are entered into the IXRS and have received at least 1 dose of the study treatment).

5.2 Response-Evaluable Set

The response-evaluable set will include a subset of the FAS with measurable disease at baseline and at least 1 postbaseline response assessment. Patients who discontinue due to death before at least 1 postbaseline evaluation will be included in the analyses of response.

5.3 Immunogenicity Analysis Set

The immunogenicity analysis set consists of patients who have received at least 1 dose of any of the study treatments and have had an ADA status assessment at baseline and at least 1 postbaseline sample.

5.4 Pharmacokinetic Analysis Set

PK analyses will be based on the PK analysis set, which includes all patients who are in the FAS with at least 1 PK parameter, are evaluable and are judged by the study team to have adequate dosing records and PK measurements.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Baseline values are defined as the last observed value before the first dose of study treatment.

There is no pre-planned hypothesis testing for this study. Analysis for this study will mostly be descriptive. Two-sided 95% CIs will be presented, where applicable.

Where applicable, variables will be summarized descriptively by study visit. For the categorical variables, the counts and proportions of each possible value will be tabulated. The denominator for the proportion will be based on the number of patients who provided non-missing responses to the categorical variable. For continuous variables, the number of patients with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated. For time-to-event variables, the summary statistics will include median time to event-free survival, 25th and 75th percentiles and number of patients at risk at specified time points.

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

6.2 Disposition of Patients

The disposition of patients includes the number and percentage of patients for the following categories: patients in the FAS, patients in the response-evaluable set, patients in the immunogenicity analysis set, patients in the PK analysis set, patients discontinued from study treatment, and patients discontinued from the study. All percentages will be based on the number of patients treated.

The primary reason for study and treatment discontinuation will also be summarized in this table.

A listing will present data concerning patient disposition.

A by-patient listing of protocol deviations will be provided.

Patient eligibility including inclusion criteria that are not met and exclusion criteria that are met at enrollment will be listed for all enrolled patients.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Demographics and baseline characteristics, including age, gender, ethnicity, race, baseline height, weight, body mass index, and ECOG score, etc., will be summarized using FAS . Disease-specific characteristics, including diagnosis, time from diagnosis, IPI score and other parameters as appropriate will be summarized using FAS. Demographics, baseline characteristics and disease-specific characteristics will also be summarized within the subgroup of patients receiving ≤ 6 cycles of study treatment and the subgroup of patients receiving > 6 cycles of study treatment.

6.3.2 Medical History and Concurrent Medical Conditions

Medical history will be listed for all patients.

6.4 Medication History and Concomitant Medications

6.4.1 Prior Medications

Prior medications are defined as the medication(s) used during screening phase but discontinued prior to the first dose of study treatment. Prior medications will be coded by generic term using World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking prior medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term. Prior medications will also be listed for all patients.

6.4.2 Concomitant Medications

Concomitant medication is defined as a medication where any amount of drug was taken between the first day of study treatment and 30 days after the last dose of study treatment. Concomitant medications will be coded by generic term using World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term. Concomitant medications will also be listed for all patients.
Concomitant procedures will be presented in a data listing.

6.5 Efficacy Analysis

6.5.1 Primary Endpoint(s) Analysis

All efficacy evaluations will be conducted using the FAS unless specified otherwise.

The response-evaluable set will be used for the sensitivity analyses of CR rate and ORR, as needed.
For the analysis of AEs, assessment of clinical laboratory values, and vital signs measurements, please refer to Section 6.6 Safety analysis.
The analysis of the primary endpoint and response related secondary endpoints will be conducted when all enrolled patients have had the opportunity to receive 6 to 8 cycles of study treatment and have had EOT assessments. Results will be presented in a CSR. The analysis of the 1-year PFS and OS rate will be performed after all patients have had the opportunity to be followed for a minimum of 12 months. Final analysis of selected endpoints will be performed at the time of study closure.

6.5.1.1 Derivation of Endpoint(s)

ORR is defined as the proportion of patients with CR or PR per IRF following the completion of study treatment (at EOT or the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Patients whose disease response cannot be assessed will be scored as non-responders for calculating the ORR. Any CR or PR that occurs after receipt of subsequent anticancer therapy to treat residual or PD will not be included in the numerator for the ORR calculation (where the FAS will be the denominator).

Note that receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT will not be considered as disease progression or as having started new anticancer therapy.

6.5.1.2 Main Analytical Approach

The ORR and exact two-sided 95% CI using the Clopper-Pearson method (Clopper 1934) will be summarized.

6.5.1.3 Sensitivity Analysis

Sensitivity analysis of primary endpoint will be performed using response-evaluable set.

6.5.1.4 Supplementary Analyses

Not applicable.

6.5.2 Secondary Endpoint(s) Analysis

The secondary endpoints are:

- CR rate by IRF assessment per Revised Response Criteria for Malignant Lymphoma (Cheson 2007) criteria following the completion of study treatment.
- 1-year PFS rate by IRF assessment per Cheson 2007 criteria.
- 1-year OS rate.

- ORR and CR rate following completion of study treatment, TTR, and 1-year PFS rate by IRF and investigator assessment per 2014 Lugano classification.
- DOR by investigator assessment per 2014 Lugano classification.
- PK (serum ADC and plasma MMAE concentration time data) to contribute to popPK analyses.
- Immunogenicity status; ADA status, including ADA negative, ADA transiently and persistently positive.

6.5.2.1 Derivation of Endpoint(s)

CR rate by IRF assessment per Cheson 2007 following the completion of study treatment, defined as the proportion of patients who have achieved a CR by IRF assessment per Cheson 2007 following the completion of study treatment. Any CR that occurs after receipt of subsequent anticancer therapy to treat residual or PD will not be included in the numerator for the CR rate calculation (where the FAS will be the denominator).

The 1-year PFS rate by IRF assessment per Cheson 2007, defined as the proportion of patients alive and progression free at 1 year, will be estimated by the Kaplan-Meier method. PFS, defined as the time from the start of study treatment to the date of first documentation of PD, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or PD, whichever occurs first. PFS will be censored on the date of last radiographic disease assessment for patients without documentation of PD/relapse, subsequent anticancer therapy for residual disease or PD, or death at the time of analysis.

Note that receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT will not be considered as disease progression or as having started new anticancer therapy.

Specifically,

- PFS=(The earliest of the dates of first documented PD, receipt of subsequent anticancer chemotherapy to treat residual disease or death) – Date of start of study treatment + 1.

If PD is not documented, no subsequent anticancer chemotherapy has been initiated and the patient is alive at the time of the data cutoff or study withdrawal, whichever occurs first, PFS will be censored as follows:

- If there is no radiographic post-baseline tumor assessment, PFS will be censored at the date of start of study treatment.
- If there are radiographic post-baseline tumor assessments, PFS will be censored at the most recent tumor assessment before the data cutoff or study withdrawal, whichever occurs first.

Specifically,

- Censored PFS=max(1, (last scan date – date of start of study treatment + 1)), where the last scan is the last CT or PET scan obtained during study.

Full censoring rules are detailed in the table below.

Situation	Date of Progression or Censoring	Outcome
No baseline and/or post baseline tumor assessment	Day following date of start of study treatment	Censored
No documented progression	Date of last radiographic tumor assessment (or the date of start of study treatment in the absence of a post-baseline radiographic tumor assessment)	Censored
PD documented between scheduled visits	Date of radiologic tumor assessment demonstrating PD	Event
Treatment discontinuation for undocumented progression after the last radiographic tumor assessment	Date of last radiographic tumor assessment or the date of start of study treatment in the absence of a post-baseline radiographic tumor assessment	Censored
New anticancer therapy to treat residual disease initiated prior to documented progression, including palliative radiotherapy (excludes post-treatment chemotherapy given for stem cell mobilizations, excludes consolidative autologous or allogeneic SCT and excludes post-treatment consolidative radiotherapy)	Start date of new anticancer therapy	Event
Post-treatment consolidative radiotherapy, post-treatment chemotherapy given for stem cell mobilizations, consolidative autologous or allogeneic SCT	Date of last radiographic tumor assessment or the date of start of study treatment in the absence of a post-baseline radiographic tumor assessment	Censored
Death before first PD assessment	Date of death	Event
Death between radiographic tumor assessment visits	Date of death	Event
Death or progression after more than one consecutively missed radiographic tumor assessment	Date of last radiologic tumor assessment prior to missed visits or the date of start of study treatment in the absence of a post-baseline radiographic tumor assessment prior to missed visits	Censored

The 1-year OS rate, defined as the proportion of patients alive at 1 year, will be estimated by the Kaplan-Meier method. OS is defined as the time from the start of study treatment to the date of death due to any cause. OS will be censored on the last known alive date at the time of analysis.

TTR by IRF assessment per 2014 Lugano classification, defined as the time from the date of first study treatment administration to the date of first documented objective response (CR or PR) by IRF assessment per 2014 Lugano classification for responders.

ORR, CR rate, 1-year PFS by IRF and investigator assessment per 2014 Lugano classification will be defined as previously described in a similar fashion.

TTR by investigator assessment per 2014 Lugano classification will also be defined similarly as TTR by IRF assessment.

DOR by investigator assessment per 2014 Lugano classification, defined as the time between the first documentation of objective tumor response (CR or PR) by investigator assessment and the first subsequent documentation of objective tumor progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or PD, whichever occurs first. Censoring in the analysis of DOR will be the same as for PFS. The analysis will include responders only.

6.5.2.2 Main Analytical Approach

CR rate by IRF assessment per Cheson 2007, ORR and CR rate by IRF and investigator assessment per 2014 Lugano classification will be analyzed in a similar fashion as the primary endpoint.

The 1-year PFS rate by IRF assessment per Cheson 2007 will be estimated by the Kaplan-Meier method with the associated 95% CIs when estimable. The 95% CI for the Kaplan-Meier estimation is calculated using the exponential Greenwood formula via log-log transformation of the survival function.

The 1-year OS, 1-year PFS rate by IRF and investigator assessment per 2014 Lugano classification will be analyzed in a similar fashion.

TTR by IRF and investigator assessment per 2014 Lugano classification will be summarized with the associated 95% CIs for responders.

DOR by investigator assessment per 2014 Lugano classification will be summarized using the Kaplan-Meier method with the associated 95% CIs when estimable. The analysis of DOR will only include responders. Censoring in the analysis of DOR will be the same as for PFS.

6.5.2.3 Sensitivity Analysis

The response-evaluable set will be used for the sensitivity analyses of CR rate by IRF assessment per Cheson 2007 and 2014 Lugano classification, and ORR by IRF assessment per 2014 Lugano classification.

6.5.2.4 Supplementary Analyses

Not applicable.

6.5.3 Additional Efficacy Endpoints

The additional efficacy endpoints are:

- PFS by investigator assessment
- OS

6.5.3.1 Derivation of Endpoint(s)

The definition is the same as previously described in the secondary endpoint section.

6.5.3.2 Main Analytical Approach

Kaplan-Meier curves depicting PFS will be generated. Additionally, median PFS and probability of PFS from 3 months to the end of the follow-up period will be reported at 3-month intervals when estimable. The two-sided 95% CI for the median and 3-month intervals will be calculated using the exponential Greenwood formula via log-log transformation.

OS will be analyzed in a similar fashion as PFS.

6.5.3.3 Sensitivity Analysis

Not applicable.

6.5.4 Subgroup Analyses

Analyses will be performed for the primary endpoint on, but not limited to, the following subgroups (with at least 10 patients in each subgroup), as applicable:

Subgroup	Group Definition
Baseline disease diagnosis	sALCL, non-sALCL
ECOG performance status	0, 1, 2
Gender	female, male
Age	< 65 years, ≥ 65 years
Cycles of study treatment received	≤ 6 cycles, > 6 cycles

6.6 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's clinical laboratory results and vital signs using the FAS.

6.6.1 Adverse Events

Adverse events (AEs) will be summarized by descending 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.

Treatment-emergent adverse events (TEAEs), defined as any AE that occurs after administration of the first dose of study treatment and up through 30 days after the last dose of study treatment, will be tabulated. Unless documented as a pre-existing condition, AEs with unknown start date will be counted as treatment emergent.

A listing of deaths and TEAEs resulting in study treatment discontinuation will be provided. All reported AEs will be listed along with the date of onset, date of resolution (if resolved), CTCAE grade, and relationship to study treatment.

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening.**
- Requires inpatient **hospitalization or prolongation of an existing hospitalization**.
- Results in **persistent or significant disability or incapacity**.
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**.

Refer to protocol Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

Summary information (the number and percentage of patients) by System Organ Class, High Level Term, and Preferred Term will be tabulated for the following categories:

- TEAEs.
- Study treatment related TEAEs.
- Brentuximab vedotin related TEAEs.
- CHP related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher study treatment related TEAEs.
- Grade 3 or higher brentuximab vedotin related TEAEs.
- Grade 3 or higher CHP related TEAEs.
- TEAEs leading to study treatment discontinuation.
- TEAEs leading to brentuximab vedotin discontinuation.
- TEAEs leading to CHP discontinuation.
- TEAEs leading to study treatment modification.
- TEAEs leading to brentuximab vedotin modification.
- TEAEs leading to CHP modification.
- SAEs.
- Study treatment related SAEs

- Brentuximab vedotin-related SAEs
- CHP related SAEs
- AESI: AEs of peripheral neuropathy identified by the MedDRA SMQ broad "Peripheral neuropathy"

Additional analyses of peripheral neuropathy may also be presented.

In addition, infusion-related reactions will be summarized by Preferred Term.

6.6.1.1 Deaths

The total number of deaths, deaths that occur within 30 days of last study treatment, deaths that occur more than 30 days after last study treatment, primary cause of death and relationship to disease will be summarized and listed.

6.6.1.2 Laboratory Data

Clinical laboratory data (hematology and serum chemistry) as listed below will be summarized.

Hematology	Serum Chemistry	
Hematocrit	Albumin	Creatinine
Hemoglobin	Alkaline phosphatase	Gamma glutamyl transferase
Leukocytes with differential	Alanine aminotransferase	Glucose
Neutrophils (ANC)	Aspartate aminotransferase	Lactate dehydrogenase
Platelet count	Bilirubin (total)	Phosphate
	Blood urea nitrogen	Potassium
	Calcium	Sodium
	Chloride	Urate

All laboratory results through the end of treatment visit will be presented in standardized units. Both observed data and changes from baseline for chemistry and hematology will be summarized with descriptive statistics. Mean laboratory values over time will be plotted for key laboratory parameters.

In addition, shift tables for laboratory parameters will be generated based on changes in NCI CTCAE, version 5.0 grade from baseline to the worst postbaseline value.

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

6.6.1.3 Electrocardiograms

Electrocardiogram results will be presented in a listing.

6.6.1.4 Vital Signs

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs measurements (eg, blood pressure, heart rate, and body temperature) and body weight over time will be tabulated by scheduled time point when available.

6.6.1.5 Eastern Cooperative Oncology Group Performance Status

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

6.6.2 Other Safety Analysis

Additional and unplanned safety analyses may be performed as the study is conducted. Those additional analyses, if deemed necessary, will be presented in a listing and documented in the CSR.

6.6.3 Extent of Exposure and Compliance

Treatment administration will be summarized by treatment agent and total using the FAS. Summary statistics for duration of therapy (weeks) and the number of cycles per patient will be presented, as well as the number and percentage of patients who were treated at each cycle and completed each cycle. Cumulative dose (mg), intended dose intensity (IDI), absolute dose intensity (ADI) and relative dose intensity (RDI) will be described. The number and percentage of patients whose dose was ever modified will be summarized by modification type, cycle and overall (i.e. overall drug administrations for a patient). A similar summary will also be provided based on doses.

Duration of treatment for IV-administered treatments is defined as time from the first study dose to 21 days after the last study dose [(last dose date +21) – first dose date]. If death occurs less than 21 days after the last study dose, duration of treatment is defined as [date of death – first dose date +1].

Duration of treatment for prednisone is defined as the time from first study dose to 21 days after the Day 1 dose date of the last cycle [(last cycle Day 1 date +21) – first dose date]. If death occurs less than 21 days after the Day 1 dose date of the last cycle, duration of treatment for prednisone is defined as [date of death – first dose date +1].

IDI is defined as the intended dose of drug (e.g. mg/kg) per unit of time. For example, for brentuximab vedotin this is (1.8 mg/kg)/3 weeks=0.6. For prednisone, IDI is defined as 500 mg/3 weeks=166.67 mg/week.

ADI is defined as the actual dose (e.g. mg/kg) per unit of time that the patient received over the entire treatment period. For prednisone, ADI is defined as the total actual dose in mg per unit of time that the patient received over the entire treatment period.

RDI is defined as the percent of the intended dose intensity over the entire treatment period: RDI=ADI/IDI * 100

Example 1:
For brentuximab vedotin, consider a patient treated for three cycles. The second dose was delayed for one week, and for the third cycle the infusion was not completed and the patient received less than the full dose, as represented in the following table:

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

ADI (per week):

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

RDI:

=0.45/0.6 * 100 =75%

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

PK concentrations will be summarized using the PK analysis set. Serum ADC and plasma MMAE will be summarized with descriptive statistics at each PK sampling time point. Any additional PK and PK/PD analyses may be performed and presented in a separate report.

6.7.1 Pharmacodynamic Analysis

Not applicable.

6.7.2 Immunogenicity Analysis

Immunogenicity will be summarized using the immunogenicity analysis set. Descriptive statistics will be used to summarize patients in the following categories: ADA negative, transiently ADA positive, persistently ADA positive, low or high ADA titer, and Nab positive or negative. The effect of immunogenicity on PK, safety, and efficacy may be examined if appropriate.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.8.1 PRO Analysis

Not applicable.

6.8.2 Health Care Utilization Analysis

Not applicable.

6.9 Other Analyses

Not applicable.

6.10 Interim Analyses

No interim analysis is planned for this study.

6.11 Data Monitoring Committee/Internal Review Committee

No steering committee, data safety monitoring committee, or clinical endpoint committee will be convened for this study.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

SAP Section	Impacted Text	Change	Rationale for Change
	List of Abbreviations	Add new ones and delete unused ones	To provide clarity
5.0, 5.3, 6.4.2, 6.5.3.2	ANALYSIS SETS, Immunogenicity Analysis Set, Concomitant Medications, Main Analytical Approach	Modify the tense and adjust between singular and plural forms	Wording modification
6.6.1	Adverse events	Add SAE definition and infusion-related reactions summary	To provide clarity and additional statistical analysis details
6.6.1.3	Electrocardiograms	Electrocardiogram results will be listed	Correct typos
6.6.3	Extent of Exposure and Compliance	Add by dose summary	To provide clarity
9.2.4	End-of Treatment Response Assessment Definition	Clarify the end of treatment response assessment definition	To provide additional statistical analysis details
9.2.5	Determination of Missing 2 or More Than Assessment	Clarify the definition of missing 2 or More Than Assessment	To provide additional statistical analysis details

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value, and minimum and maximum values will be presented to the same number of decimal places as the measured value. If the measured value is large (eg, > 100), fewer decimal places may be displayed.
- CIs will be presented using the same number of decimal places as the parameter estimate.
- Percentages will be rounded to one decimal place.
- All p-values reported will be 2-tailed and rounded to 3 decimal places prior to assessment of statistical significance. If a p-value is less than 0.001 it will be reported as "<0.001". If a p-value is greater than 0.999 it will be reported as ">0.999".
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) rounded to 1 decimal place.
- 1 year = 365.25 days. Year is calculated as (days/365.25) rounded to 1 decimal place.

9.2.2 Definition of Baseline

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

9.2.3 Definition of Visit Windows

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).

9.2.4 End-of Treatment Response Assessment Definition

Per protocol, response assessment at EOT visit is not required if a patient has response assessment at last cycle of treatment. For analysis purposes:

- If EOT visit response assessment is not performed, the EOT response assessment is defined as the first response assessment after the last dose and before long-term follow up (LTFU);
- If EOT visit response assessment is performed, the response at EOT is the better response between the EOT assessment and first assessment after the last dose and before LTFU.

9.2.5 Determination of Missing 2 or More Than Assessment

Censoring rules for PFS events after more than one consecutively missed radiographic tumor assessment:

- If a patient missed 2 or more scheduled scans in a row and then had a PFS event immediately after, then this is not an event and the patient should be censored at the last adequate response assessment prior to the first of the missed scans.

The PFS censoring and event date options depend on the presence and the number of missing tumor assessments (TAs). An event occurring immediately after two or more missing assessments is censored at the last adequate tumor assessment prior to the first of the missed scans.

An exact rule to determine whether there are 2 or more missing TAs is therefore needed. This rule is based on the interval between the post-baseline last tumor assessment (LTA) date and the event date. The scheduled date of tumor assessments (in days from first IV treatment date) can be found in the following table.

Schedule for derived post-baseline tumor assessment and time windows

Assessment Schedule	Visit #	Target Day	Lower Bound (LB)	Upper Bound (UB)
Cycle 4 Day 15-21	1	78	64	99
Cycle 6 Day 15-21	2	120	100	141
Cycle 8 Day 15-21	2	162	142	265
EOT	2	Last dose date + 30	Last dose date + 1	265
Month 9	3	273	266	319
Month 12	4	365	320	410
Month 15	5	456	411	502
Month 18	6	547	503	593
Month 21	7	639	594	684
Month 24	8	730	685	821
Month 30	9	913	822	1004
Month 36	10	1095	1005	1187
Month 42	11	1278	1188	1369
Month 48	12	1461	1370	1552
Month 54	13	1643	1553	1734
Month 60	14	1826	1735	1917
Month 66	15	2008	1918	2100
Month 72	16	2191	2101	2282
Month x		Floor (x * 30.4375)	Floor {(x-3) * 30.4375} + 1	Floor {(x+3) * 30.4375}

Patients have the choice to receive up to 6 or 8 cycles of treatment, so they either have a cycle 6 TA or cycle 8 TA. If the TA is performed at the last cycle of treatment, then the EOT visit TA is optional. Thus, the derived EOT visit window could be overlapped with the derived visit window for Cycle 4 day 15-21, Cycle 6 day 15-21, or Cycle 8 day 15-21.

The rules that determine the flag of 2 or more missing TAs are described as below:

- When LTA is not available, if PFS event date > EOT UB, then missing flag = 'Y';
- When LTA is in Visit 1 (in Cycle 4 day 15-21 derived time window and not in EOT derived time window), if PFS event date > Visit 3 UB, then missing flag = 'Y';
- When LTA is in Visit 2, if PFS event date > Visit 4 UB, then missing flag = 'Y';
- When LTA is in Visit *X*, if PFS event date > (Visit *X*+2) UB, then missing flag = 'Y'.

9.3 Analysis Software

SAS version 9.4 (or higher) will be used for all analyses.

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