Study PIX306

Statistical Analysis Plan

Study Title:	A Randomized Multicenter Study Comparing Pixantrone + Rituximab with Gemcitabine + Rituximab in Patients with Aggressive B-cell Non-Hodgkin Lymphoma Who Have Relapsed after Therapy with CHOP-R or an Equivalent Regimen and are Ineligible for Stem Cell Transplant
Name of Test Drug:	Pixantrone
Indication:	Diffuse large B cell lymphoma (DLBCL), or follicular grade 3 (FG3) lymphoma
Sponsor:	CTI BioPharma Corp. 3101 Western Avenue, Suite 600 Seattle, WA 98121
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
ATC	Anatomic therapeutic chemical
BSA	Body surface area
CHOP-R	Cyclophosphamide, Hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and Prednisone/Prednisolone + the monoclonal antibody Rituximab
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B cell lymphoma
DOR	Duration of overall response
DCR	Duration of complete response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FG3	Follicular grade 3
HLGT	High level group term
HLT	High level term
HR	Hazard ratio
ID	Identification
IDMC	Independent Data Monitoring Committee
IPI	International Prognostic Index
IRC	Independent Radiology Committee
ITT	Intent-to-treat
IWRS	Interactive web response system
LDH	Lactate Dehydrogenase
LLT	Lower level term
LVEF	Left Ventricular Ejection Fraction
m	Meter(s)
mg	Milligram(s)
MedDRA	Medical Dictionary for Regulatory Activities
NHL	Non-Hodgkin Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive disease
PFS	Progression-Free Survival

Abbreviation	Explanation
PR	Partial response
PP	Per-protocol
PK	Pharmacokinetic
PT	Preferred term
R	Rituximab
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCT	Stem Cell Transplant
SGOT (or AST)	Aspartate aminotransferase
SGPT (or ALT)	Alanine aminotransferase
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

1 SCOPE

This document describes all planned statistical analyses and data presentations to be performed for clinical study reports for study protocol PIX306, "A Randomized Multicenter Study Comparing Pixantrone + Rituximab with Gemcitabine + Rituximab in Patients with Aggressive B-cell Non-Hodgkin Lymphoma Who Have Relapsed after Therapy with CHOP-R or an Equivalent Regimen and are Ineligible for Stem Cell Transplant".

This statistical analysis plan (SAP) provides a detailed description of the strategy, rationale, and statistical techniques to be used to assess the efficacy and safety of Pixantrone in the scope of the study. It provides additional details concerning the statistical analyses that were originally outlined in the protocol. The purpose of the SAP is to ensure the credibility of the study findings by specifying the statistical approaches for all data analyses. This SAP will be finalized and signed prior to the core clinical database lock. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the clinical study report as post-hoc supplemental analyses.

The statistical analyses are planned at the following time points:

- The core database lock and analysis will be performed by the responsible CTI statistician after 195 PFS events per Independent Radiology Committee (IRC) have occurred to evaluate the primary objective of the study and safety.
- The first interim analysis of OS (performed by IDMC) is planned at the time of the core analysis. It is estimated that at the time of the core analysis, approximately 165 deaths will have occurred.
- The second interim analysis of OS (performed by IDMC) will be performed when 190 OS events (86%) have occurred.
- The final database lock and analysis will be performed by the responsible CTI statistician at the end of the study (defined as the date when the required OS events have occurred or the study is terminated) for OS, updating PFS, other efficacy and safety as well, when 220 death events are reached.

2 STUDY OBJECTIVES AND HYPOTHESES

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy (as measured by progression-free survival [PFS]) of pixantrone + rituximab (pixantrone + R) compared with gemcitabine + rituximab (gemcitabine + R) in patients with a diagnosis of de novo diffuse large B-cell lymphoma (DLBCL), DLBCL transformed from indolent lymphoma, or follicular grade 3 lymphoma who have relapsed after at least 1 prior chemotherapy regimen and who are currently ineligible for high-dose (myeloablative) chemotherapy and stem cell transplant (SCT).

2.1.2 Secondary Objectives

To compare the two treatment arms with regard to the following secondary endpoints:

- Overall Survival (OS)
- Overall response rate (ORR)
- Complete response (CR) rate
- Safety

2.1.3 Exploratory Objectives

- Assess the duration of overall response between treatments
- Assess the duration of complete response (CR) between treatments
- Determine the proportion of randomized patients who receive a SCT after study treatment

2.1.4 Pharmacokinetic (PK) Sub-Study Objective

- To characterize the PK profile of pixantrone when co-administered with rituximab

An overview summary of the study objectives, the corresponding endpoints, and the section where the detailed analysis method are described is provided in the below Table 1.

Table 1. Overview of Study Objectives, Study Endpoints, and Sections for Analysis Method Information

Objective	Endpoint	Analysis
Primary	Progression-free survival (PFS)	Refer to Section 7.1
Secondary	Overall Survival (OS)	Refer to Section 7.2.1
	Overall response rate (ORR)	Refer to Section 7.2.2
	Complete response (CR) rate	Refer to Section 7.2.3

	Safety	Refer to Section 9
Exploratory	Duration of overall response	Refer to Section 7.3.1
	Duration of complete response	Refer to Section 7.3.2
	Proportion of patients who receive a SCT after study treatment	Refer to Section 7.3.3
Pharmacokinetic (PK) Sub-Study Objective	Pixantrone drug concentration at nominal PK sampling time	Refer to Section 10

2.2 Hypotheses

The hypothesis tests described below are based on intent-to-treat population using the IRC assessment for disease response.

2.2.1 Primary Hypotheses

The primary hypothesis of this study is that the combination of pixantrone + R will result in an improvement in PFS compared with treatment with gemcitabine + R in patients with a current diagnosis of DLBCL (de novo DLBCL or DLBCL transformed from indolent lymphoma) or follicular grade 3 lymphoma on the basis of a tissue biopsy who are not currently eligible for high-dose (myeloablative) chemotherapy and stem cell transplant and who have relapsed after at least 1 prior chemotherapy regimen.

2.2.2 Secondary Hypotheses

In patients with a current diagnosis of DLBCL (de novo DLBCL or DLBCL transformed from indolent lymphoma) or follicular grade 3 lymphoma on the basis of a tissue biopsy, who are not currently eligible for high-dose (myeloablative) chemotherapy and stem cell transplant and who have relapsed after at least 1 prior chemotherapy regimen:

- The combination of pixantrone + R will result in an improvement in OS compared with treatment with gemcitabine + R.
- The combination of pixantrone + R will result in a higher ORR compared with treatment with gemcitabine + R.
- The combination of pixantrone + R will result in a higher CR rate compared with treatment with gemcitabine + R.

3 SUMMARY OF STUDY DESIGN

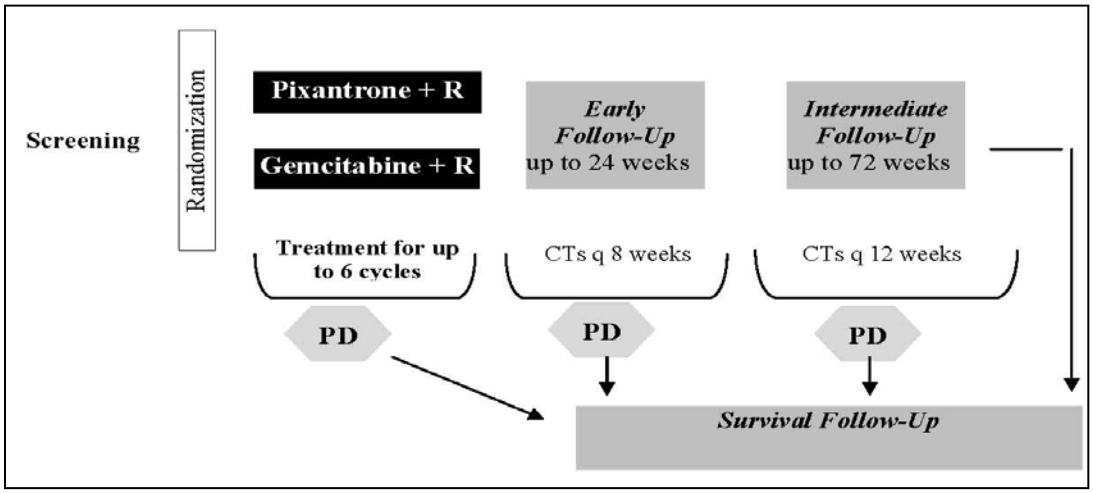
This is a randomized, active-controlled, multicenter, phase 3 study to evaluate the efficacy of pixantrone with rituximab versus gemcitabine with rituximab in patients with a diagnosis of DLBCL (de novo DLBCL or DLBCL transformed from indolent lymphoma), or follicular grade 3 lymphoma on the basis of a tissue biopsy who are not currently eligible for high-dose (myeloablative) chemotherapy and SCT and who relapsed after at least one chemotherapy regimen.

- Patients with de novo DLBCL must have received 1-3 prior regimens for DLBCL
- Patients with follicular grade 3 lymphoma must have received 1-3 prior regimens for follicular lymphoma (any grade)
- Patients with DLBCL transformed from indolent lymphoma must have received 1-4 prior regimens for NHL (any type)

The study will be conducted in North America and Europe.

This study includes screening, treatment, and follow-up periods (Figure 1). Patients will be randomized to the investigational treatment (pixantrone + R) or the control treatment (gemcitabine + R). Treatment will be administered in 28-day cycles.

Figure 1. Study Flow Chart



An Independent Data Monitoring Committee (IDMC) will evaluate the safety of pixantrone. No interim analysis is planned for the primary efficacy endpoint PFS for this study. Two interim efficacy analyses are planned for the secondary efficacy endpoint OS, respectively at the time of core database lock for PFS primary analysis (approximately 165 death events occurring), and at the time of reaching 190 death events.

3.1 Sample Size and Power Calculations

One hundred ninety-five (195) PFS events are required to detect at least a 35% improvement (i.e., HR = 0.65) in PFS with 85% power and a 2-sided alpha of 0.05. Based on results from the study by Pettengell *et al*, it was assumed that the median PFS for the control group is 2.8 months.

Based on updated study projections, it is estimated that approximately 320 patients are needed to reach the required 195 PFS events that are projected to occur approximately 80 months after randomization of the first patient. The actual number of patients enrolled may vary, as actual enrollment may differ from assumptions.

For the secondary endpoint of OS, 220 deaths are planned to have 75% power to detect at least a 30% improvement in OS allowing for 5% drop-offs, or 68% power to detect at least a 28% improvement in OS. Based on the study by Pettengell *et al.*, it is assumed that the median OS for the control group is 7 months.

3.2 Interim Analysis

No PFS interim analysis is planned for this study for the primary objective prior to the core analysis.

Two interim analyses of OS in the ITT population are planned. The first interim analysis of OS is planned at the time of the core analysis to evaluate primary efficacy endpoint for this study. It is estimated that at the time of the core analysis, approximately 165 deaths will have occurred. The second interim analysis is planned to occur when 190 death events are reached. The purpose of the interim analysis is to stop the study early due to superiority of OS. The two OS interim analyses will be performed and reviewed by IDMC. Approach for addressing multiplicity of OS interim and final analyses is provided in Section 7.4.

3.3 Randomization and Blinding

At the screening visit, patients will be assigned a unique screening ID number by the electronic data capture system. Upon the Medical Monitor's confirmation of eligibility, patients will be randomized (1:1) to receive either investigational or control therapy. Randomization will be done by central randomization through interactive web response system (IWRS) and will be stratified by number of prior therapies for DLBCL or follicular grade 3 lymphoma (0-2 vs. ≥3), International Prognostic Index (IPI) score (0-2 vs. ≥3), and length of time from initiation of first-line therapy for DLBCL or follicular grade 3 lymphoma until first relapse (<1 year vs. ≥1 year). Permuted blocks within strata will be used to restrict treatment allocation.

Although this is an open label study, the double-blind procedure was followed in-house (see the PIX306 Treatment Blinding Plan). The sponsor (with the exception of pharmacovigilance, site monitoring, clinical document control, and drug supply personnel) and IRC will remain blinded to study treatment assignment, including study drug administration records, until the core database lock for analysis of the primary efficacy endpoint PFS.

When 195 PFS events per IRC are reached and the core database have been locked for evaluating the primary objective of this study, the clinical database except OS dataset will be unblinded to the sponsor.

The sponsor will remain blinded to OS datasets (although the death contributes to the PFS events in the core locked database will be unblinded to the sponsor) until either if the study can claim OS superiority for the pixantrone + R arm at one of the 2 interim analyses, or after the final analysis which will be performed at the end of the study when 220 death events are reached. Two OS interim analyses will be performed and reviewed by IDMC. Sponsor will have access to the unblinded OS interim analysis results via IDMC after core database lock and all patients complete the study treatment.

To maintain the sponsor's blinding to the OS dataset after the unblinding of the treatment assignment at the time of core locked database analysis, the two interim OS analyses including the generation of the OS analysis dataset will only be performed by external independent statistics organization (Axio) for the IDMC review. The sponsor will neither generate any OS analysis dataset nor perform any OS analyses until after the final database lock when 220 death events are reached.

4 ANALYSIS POPULATION AND ANALYSIS CONVENTIONS

4.1 Intent-to-Treat (ITT) Population

The ITT population (i.e., Full Analysis Set) is defined as all randomized patients regardless of whether subjects receive any study treatment, or receive a different treatment from the treatment they are randomized to. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization by IWRS.

The ITT population is the primary population used for all efficacy analysis.

4.2 Histologically Confirmed Population

The histologically confirmed population will include all randomized patients with DLBCL (de novo DLBCL or DLBCL transformed from indolent lymphoma) or follicular grade 3 lymphoma per WHO guidelines confirmed by the central pathology review committee.

Patients in this population will be analyzed according to the treatment to which they were randomized by IWRS. This population will be used for supportive efficacy analyses.

4.3 Per-protocol (PP) Population

The PP population is defined as all randomized patients who receive any study treatment, undergo at least one post baseline disease assessment or died before the first post baseline scheduled disease assessment, and have no major protocol violations, as defined below.

For the purpose of defining the PP population, the following will be considered to be major protocol deviations that could potentially have an effect on primary efficacy outcomes. Patients who have major protocol violations will be excluded from the PP population.

- Violation of one of the following inclusion criteria:
    - Inclusion 3. Diagnosis of DLBCL (de novo DLBCL, or DLBCL transformed from indolent lymphoma) or follicular grade 3 lymphoma on the basis of a tissue biopsy (based on local investigator assessment)
    - Inclusion 5: Number of prior therapies allowed:
        - Patients with de novo DLBCL must have received 1-3 prior regimens for DLBCL
        - Patients with follicular grade 3 lymphoma must have received 1-3 prior regimens for follicular lymphoma (any grade)
        - Patients with DLBCL transformed from indolent lymphoma must have received 1-4 prior regimens for NHL (any type)
    - Inclusion 6: Received a rituximab-containing multi-agent regimen
    - Inclusion 7: Patients with DLBCL transformed from indolent lymphoma must have had a complete or partial response to a therapy for NHL lasting at least 12 weeks

- Violation of one of the following exclusion criteria:
    - Exclusion 1: Any of the following as the only site(s) of disease: palpable lymph nodes not visible on imaging studies, skin lesions, solitary spleen lesion or bone marrow involvement only.
    - Exclusion 2: Primary refractory de novo DLBCL or primary refractory follicular grade 3 lymphoma, defined as documented progression within 12 weeks of the last cycle of the first-line multi-agent regime
    - Exclusion 9: Current central nervous system involvement by lymphoma.
    - Exclusion 16: Concomitant therapy with any anticancer agents, immunosuppressive agents, other investigational anticancer therapies. Low dose corticosteroid use for the treatment of non-cancer related illnesses are permitted.
- Other
    - Do not have adequate baseline tumor assessment, per IRC.
    - Target lesions not measurable at baseline, per IRC. Measurable lymph nodes and nodal masses must be ≥ 1.5 cm in short axis, and extranodal sites of disease must be > 1.0 cm in short axis. Measurable lesions must always be assessed by imaging.
    - Lack an evaluation of tumor response after randomization, or for whom the first on-study assessment of disease response occurs after Week 18 unless death occurs within Week 18.

Patients in the PP population will be analyzed according to the treatment to which they were assigned at randomization by IWRS and their correct strata if there is miss-stratification. Patients who receive a different treatment from the treatment they are randomized to will be excluded from the PP population.

4.4 Safety Population

The safety population is defined as all randomized patients who receive at least one administration of study drug. The safety population will be analyzed according to the treatment actually received. The safety population will be used for all safety analyses.

4.5 Pharmacokinetic Evaluable Population

The pharmacokinetic evaluable population is defined as all randomized patients who received any dose of study treatment and provided at least one appropriate sample for plasma PK analysis.

4.6 Analysis Conventions

The definitions, algorithms, imputations, and conventions applied in programming of the data for summary tabulations are described in the below several sub-sections.

4.6.1 Definition of Study Drug and Study Treatment

In this study, study drug is referred to Pixantrone or Gemcitabine, and study treatment is referred to Pixantrone + Rituximab or Gemcitabine + Rituximab unless otherwise stated.

4.6.2 Definition of Baseline Value

For any parameter requiring definition of baseline value, baseline value will be defined as the last non-missing assessment prior to treatment with any study therapy unless otherwise stated.

4.6.3 Calculation of Variables

Calculations using dates are to be performed as follows.
Study days are calculated as the difference between the onset date of event of interest and the first dose date. First dose date is defined as the first date when a non-zero dose of study drug administered. A year is defined as 365.25 days, and a month is defined as 30.4375 days. The generalized calculation algorithm for relative day is:

- Study Day is calculated as (event onset day – first dose date) + 1 if event onset day ≥ first dose date and (event onset day – first dose date) if event onset day < first dose date.
- Age (in years) = integer part {(Date of Informed Consent - Date of Birth + 1) / 365.25}.
- Duration of Aggressive NHL (in months) = (Date of Informed Consent - Date of Diagnosis + 1)/ 30.4375.

4.6.4 Missing Data and Outliers

In general, values for missing data will not be imputed unless methods for handling missing data are specified.
No data will be excluded from the analyses, including any outliers.

4.6.5 Partial Dates

Partial dates are those with missing day but month and year are available, or with missing day and month but only year is available. For purposes of analysis and presentation of data in summary tables, partial dates will need to be imputed for some variables, however, all missing and partial dates will be presented "as is" in listings.

AE Partial Dates
For onset date:

- If only day is missing but month and year are available, the missing day will be set to the first day of the month or the first dosing date if they have the same month and year, whichever is later.
- If both day and month are missing but year is available, the missing day and month will be set to 01Jan or the first dosing date if they have the same year, whichever is later.

For resolution date:

- If day and month are missing but year is available, then the imputed day and month will be 31Dec or 30 days after the last dose of study treatment or death date (if patient died) if they have the same year, whichever is earlier.

- If day is missing but the month and year are available, then the imputed day will be the last day of the month or 30 days after the last dose of study treatment or death date (if patient died) if they have the same month and year, whichever is earlier.

Partial Dates for New Anti-cancer Therapy

For purposes of determining censoring for PFS due to receiving new lymphoma-directed therapy prior to disease progression or death, the following rules will be used to handle partial start dates for the new lymphoma-directed therapy. Note that these rules will be applied for PFS as assessed both by IRC review and by local investigators.

Since receiving new lymphoma-directed therapy occurs during the study conduct, the sites should have at least the month information for the start date for the new lymphoma-directed therapy. Both missing day and missing month are unlikely to happen. In the case of missing the start day for the new lymphoma-directed therapy, patient will be censored for PFS analysis only if the year and month of the start date are: a) the same or later than the year and month of the randomization date, AND b) earlier than the year and month of the first occurrence of PD or death, OR the patient did not have PD or death.

4.6.6 Laboratory Data Handling Rule

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed as follows:

- A value that is 1 unit less than the limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of "<x" (x is considered the limit of quantitation). For example, if the values are reported as <50 and <5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively. However, for direct bilirubin, a value of "<0.1" will be treated as 0.05 for calculation of summary statistics.
- A value that is 1 unit above the limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of ">x" (x is considered the limit of quantitation). For example, if the values are reported as >50 and >5.0, then values of 51 and 5.1 will be used for calculation of summary statistics, respectively.
- The limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of "≤ x" or "≥ x" (x is considered as the limit of quantitation).

4.6.7 Selection of Data in the Event of Multiple Records in a Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value per visit, whereas a time-to-event analysis would not require 1 value per analysis window but rather 1 value for the study. Unless otherwise noted throughout the rest of this document, when a single value is needed, the following rule(s) will be used:

- If more than 1 assessment occurs during the same nominal visit, select the record closest to the nominal day for that visit.
- If there are 2 assessments that are equidistant from the nominal day, the data of the assessment after the scheduled study day will be used.
- The last measurement will be used if multiple measurements are all taken on the same day.

5 SUBJECT DISPOSITION

5.1 Subject Enrollment

A summary of subject enrollment will be provided by treatment group. The denominator for this calculation will be the number of randomized subjects. Similarly, the number and percentage of subjects randomized in each region and country will be summarized. A by-subject listing for screening failures will be provided by screening identification (ID) in an ascending order with reasons for not being eligible for enrollment to the study.

5.2 Disposition of Subjects

A summary of subject disposition will be provided by treatment group. This summary will present number of subjects:

- randomized (i.e., ITT population)
- treated with study drug (i.e., safety population)
- did not complete the protocol-directed treatment (with summary of reason for not completing)
- discontinued the study (with summary of reasons for study discontinuation)

The denominator for the percentages of subjects in each category will be the number of subjects in the ITT population. No inferential statistics will be generated.

5.3 Protocol Deviations

Protocol deviations will be categorized before database lock by sponsor. The protocol deviations will be summarized by type of deviation based on the ITT population. A listing will be provided for all protocol deviations.

6 DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND MEDICAL HISTORY

6.1 Demographics and Baseline Characteristics

Descriptive statistics (e.g., mean, standard deviation, median, minimum and maximum) will be provided for those variables measured on a continuous scale. The frequency distribution (n and %) will be provided for those variables measured on a nominal scale.

The following demographic and baseline variables will be summarized for patients in the ITT population.

6.1.1 Demographic Variables

Age, age category (< 65 years vs. ≥ 65 years, and 18-64 years vs. 65-84 years vs. ≥ 85 years), gender, race, ethnicity, height, weight, BMI, body surface area (BSA), region and country.

6.1.2 Baseline Disease Characteristic Variables

Histology at baseline (de novo DLBCL, DLBCL transformed from indolent lymphoma, or follicular grade 3 lymphoma) by local and by central assessments, duration of DLBCL or Follicular Grade 3 Lymphoma, NHL Ann Arbor stage at Screening, number of extranodal sites at Screening, IPI at Screening (0-2 vs. ≥3), prior lines of therapy for DLBCL or follicular grade 3 lymphoma (0-2 vs. ≥3; 0-1 vs. ≥2), prior lines of therapy for lymphoma, time from initiation of first-line therapy for aggressive NHL until first relapse (<1 year vs. ≥1 year), prior stem cell transplant (yes vs. no), and reason(s) not a candidate for high-dose chemotherapy or stem cell transplant, ECOG performance status.

6.2 Prior Therapy and Medical History

Prior therapy and medical history are any therapy or diseases that occurred or any medication taken prior to the first day of study drug dosing or prior to the randomization date if patients were never dosed. Prior therapy includes both prior NHL and non-NHL cancer therapies. Both will be summarized for patients in the ITT population by anatomic therapeutic chemical (ATC) class and preferred term using WHO Drug Dictionary, version of 01DEC2010.

For prior NHL therapy, the following will be summarized by the frequency distribution (n and %): number of patients with prior surgeries, number of patients with prior radiation therapies, and number of patients with prior systemic therapy regimens (chemotherapies, steroids, immunotherapy, immunoconjugates, vaccines, etc.) and further by number of prior systemic therapies. Also, the last NHL treatment and response will be summarized by displaying the category of last treatment, duration from last therapy to randomization, and response to the last treatment.

Prior non-NHL therapies will be summarized in a similar manner for number of prior therapies, type of prior therapies, the type of last treatment prior to randomization, and the duration from last therapy to randomization.

Medical history will be summarized as frequency distribution (n and %) by system organ class (SOC) and preferred term (PT) by MedDRA dictionary version 11.1 for patients in the ITT population.

6.3 Cardiac History

Cardiac history will be summarized for patients in the ITT population. The frequency distribution (n and %) of cardiac events will be displayed by event type.

7 EFFICACY ANALYSIS

The efficacy assessment consists of disease response and survival assessment. Disease response will be assessed according to the Modified IWG 2007 Revised Response Criteria in the PIX306 protocol. Efficacy endpoints based on disease response will use the response assessments of the IRC for the primary analysis. The planned tabular summaries and analyses for efficacy endpoints are described below.

7.1 Primary Efficacy Endpoint – Progression Free Survival (PFS)

PFS is defined as the time from the date of randomization to the date of PD or death due to any cause (whichever is first reported). The primary analysis of PFS will be based on disease progression as determined by the IRC.

The PFS event date is either (1) the earliest time when any progression per Modified IWG criteria is observed for a documented progression event; or (2) the date of death if no progression is observed.

Primary Analysis

The following censoring rule will be applied for the PFS primary analysis. Patients will be censored at the last radiological assessment date with evidence of no progression (prior to the new anticancer therapy or prior to the missing tumor assessments if applicable) for those:

- who do not have documented disease progression, or
- who start new anticancer therapy (i.e., chemotherapy, radiation therapy, or oncologic surgical therapy, except for rituximab given as maintenance therapy) before documented disease progression or death, or
- who are lost to follow-up

Patients will be censored on the randomization date for those:

- who do not have adequate baseline tumor assessment, or
- who lack post-baseline disease assessment.

A summary of the event and censoring rules for PFS primary analysis is provided in below Table 2.

Table 2. Event and Censoring Rules for PFS Primary Analysis

Situation	Date of Progression or Censoring	Situation Outcome
Death	Date of death if no progression	Event
Progression documented	Earliest date when any progression per Modified IWG criteria is observed	Event
Do not have documented disease progression	Date of last adequate radiologic assessment	Censored
Start new anticancer therapy (i.e., chemotherapy, radiation therapy, or oncologic surgical therapy, except for rituximab given as maintenance therapy) before documented disease progression or death	Date of last adequate radiologic assessment prior to the new anticancer therapy	Censored
Lost to follow-up	Date of last adequate radiologic assessment	Censored

Table 2. Event and Censoring Rules for PFS Primary Analysis		
Situation	**Date of Progression or Censoring**	**Situation Outcome**
Do not have adequate baseline tumor assessment	Randomization date	Censored
Lack post-baseline disease assessment	Randomization date	Censored

For the primary efficacy analysis, PFS between the 2 treatment arms will be compared based on the ITT population using a stratified log-rank test, stratified by the randomization stratification factors. The actual strata values as documented in the eCRF (if a mis-stratification occurred) will be used in all stratified analyses. If there is insufficient information in a stratum (i.e., if there are ≤5 subjects or there is no informative event in a stratum), that stratum will be pooled with the smallest adjacent stratum for stratified analyses; the smallest stratum is defined as that stratum having the fewest number of subjects or the fewest number of events in case the former is a tie and the adjacent stratum is defined as a stratum having 2 factors of the 3 at the same level. Summary statistics, including median progression free survival time and the corresponding 95% confidence interval based on Kaplan-Meier estimates, will be presented by treatment group. In addition, reasons for events and censoring will be summarized by treatment group. The Kaplan-Meier curve by treatment group will also be plotted.

A Cox-regression model with a term for treatment arm, adjusted for the randomization stratification factors (actual strata), will be used to quantify the treatment difference in PFS. Hazard ratios and corresponding 95%CIs as estimated from the Cox-regression model will be presented as well.

Sensitivity Analyses

To assess the robustness of the primary PFS results, the following exploratory sensitivity analyses by applying different rules for censoring or defining PD event may be performed if it is necessary based on the IRC assessments:

1. Do not censor for new anticancer therapy. Patients who start new lymphoma-directed therapy prior to progression will not be censored at the start of the new therapy, but will continue follow up until disease progression or death.
2. Consider new anticancer therapy as PD. Patients who start new lymphoma-directed therapy prior to progression will be classified as an event and the start date of the new therapy will be the event date. In case of partial start date (e.g, missing day) of the new anticancer therapy, the 1st day of the month will be imputed.
3. Censor for those who have ≥2 consecutive missing tumor assessments (i.e., >18 weeks after the last on-study tumor assessment for patients who are in or prior to Early Follow-up, or >28 weeks after the last on-study tumor assessment for patients who are in Intermediate Follow-up) before disease progression or death. Patients will be censored at the last adequate radiological assessment date prior to the missing tumor assessment.
4. Censor for patients who discontinue treatment without documented disease progression. Patients will be censored at the last radiological assessment date prior to treatment discontinuation.
5. Worst case: Patients who are missing at least one tumor assessment immediately preceding data cutoff will be classified as events in the Pixantrone+Rituximab arm and will be censored in the

Gemcitabine+Rituximab arm at the date of the last assessment preceding the missing assessments.

6. Censor for SCT. Patients who receive a SCT after study treatment and prior to progression will be censored at the start date of SCT.

Additional sensitivity analyses for PFS based on the IRC assessments may also be performed in the following manners:

1. PFS will be compared between the treatment arms in the ITT population using a stratified log-rank test and adjusted Cox-regression model, considering the strata levels per randomization by IWRS, to assess the effect of mis-stratification.
2. PFS will be compared between the treatment arms in the ITT population using the unstratified log-rank test and unadjusted Cox-regression model

PFS in the histologically confirmed population and in the PP population based on the IRC assessment will be performed as supportive analyses as well as PFS determined by investigators' assessment in the ITT population. The same censoring rule as used for PFS primary analysis should be applied for these three supportive PFS analyses. For the analysis of PFS determined by investigators, censoring due to receiving subsequent anticancer therapy will be based on the investigator assessment of radiographic progression. The same analysis method as used for PFS primary analysis will be used for PFS supportive analyses.

Cox proportional hazard models will also be used to explore the potential influences of baseline stratification factors and other baseline patient characteristics on PFS based on the IRC assessment with event date and censoring date as defined for primary PFS analysis. Beyond the stratification variables, additional baseline subject characteristics include, but are not limited to histology (de novo DLBCL, DLBCL transformed from indolent lymphoma, or follicular grade 3 lymphoma) by local and by central assessments, time since rituximab, absolute leukocyte count, Ann Arbor staging, and time from diagnosis, focusing on those with expected prognostic significance, particularly if these show imbalance between treatment groups. A 2-step selection process will be applied to these baseline patient characteristics to identify the final set of relevant factors. Each prognostic factor will be preliminarily evaluated by including treatment and that factor in the Cox proportional hazard model. Only the variables significant at a 10% level will be considered in building the multivariate model. A backward elimination process will be applied to these variables including treatment, using a 5% level to stay in the model, to identify the final set of relevant factors. Treatment-by-factor interactions may be explored only for the set of factors included in the final model. The estimated hazard ratio and 2-sided 95% confidence interval will be provided.

At the end of the study when 220 death events are reached, PFS updating analysis using will be performed to include additional PFS data collected after core database lock. PFS updating analysis at the end of the study will be limited to the PFS primary analysis as specified in this section, and no PFS sensitivity analysis will be performed for the PFS updating analysis.

7.2 Secondary Efficacy Endpoints

7.2.1 Overall Survival (OS)

OS is defined as the time from the date of randomization to the date of death due to any cause. If a patient is alive or the survival status is unknown by the data cut-off date for analysis, survival will be censored at the date that patient was last known to be alive.

For the two interim analyses and final analysis, primary analysis of OS will be performed in the ITT population using stratified log rank test and adjusted Cox-regression model, stratified by the actual strata values as documented in the eCRF. Medians estimated by KM method, hazard ratios and corresponding 95% CIs from the adjusted Cox-regression model will be presented by treatment arm. A plot of the Kaplan-Meier curves for OS will also be provided by treatment arm.

Supportive analysis of OS in the histologically confirmed population and in the PP population will be performed as well. The same analysis method as used for OS primary analysis in the ITT population will be used for OS supportive analysis.

Additional sensitivity analyses for OS will also be performed:

- OS will be compared between the treatment arms in the ITT population using a stratified log-rank test and an adjusted Cox regression model, considering the strata levels per randomization by IWRS.
- OS will be compared between the treatment arms in the ITT population using the unstratified log-rank test and unadjusted Cox-regression model.

Multivariate Cox proportional hazard model analysis of the overall survival data will be performed as part of the final OS analysis at the end of the study to explore the potential influences of baseline stratification factors and other baseline patient characteristics on OS. Same methods as described for PFS multivariate Cox PH model analysis will be used for OS multivariate model analysis.

A summary of all deaths in the study by treatment arms will be provided to show the number and percentage of subjects in the ITT population who had (1) deaths with any cause including death during follow up, and (2) deaths by primary cause (ie, AE, PD, other).

7.2.2 Overall Response Rate (ORR)

The Overall Response Rate (ORR) is defined as the proportion of patients who achieve a CR or PR without additional anticancer therapy. Patients who discontinue before any response has been observed, or receive additional anticancer therapy before a response has been observed will be considered non-responders.

The primary analysis of ORR will be based on the IRC response assessments in the ITT population. Comparison of the ORRs between the 2 treatment arms will be performed using the exact Cochran-Mantel-Haenszel (CMH) test, controlling for the stratification factors used for randomization with actual strata values as documented in the eCRF (if a mis-stratification occurred). The number and percentage of patients achieving a CR or PR will be presented. The 95% CI for ORR in each arm will be calculated

using Clopper-Pearson method, and 95% CI for the difference in ORR between the 2 treatment arms will also be provided based on the Agresti-Caffo method.

Supportive analysis of ORR in the histologically confirmed population and in the PP population will be performed as well. The same analysis method as used for ORR primary analysis will be used for ORR supportive analysis.

ORR determined by investigators will be analyzed as a supportive analysis in the ITT population using the same analysis method as described above. The discordance between IRC and investigator assessment will be evaluated.

7.2.3 Complete Response (CR) Rate

CR rate is defined as the proportion of patients who achieve a CR without additional therapy. Patients who discontinue before any response has been observed, or receive additional anticancer therapy before a response has been observed will be considered non-responders. CR will be analyzed in the same manner as for ORR.

7.3 Exploratory Efficacy Endpoints

All exploratory efficacy endpoints will be analyzed using the ITT population.

7.3.1 Duration of Overall Response (DOR)

Duration of overall response (DOR) is only defined for CR or PR responders. DOR will be calculated as the time from the date of the first documented CR or PR to the date of first documented evidence of PD (or relapse for patients who experience a CR on this study) or death from any cause. The same rules of censoring used for PFS primary analysis will be used for DOR analysis. DOR will be summarized using Kaplan-Meier methods to present median and corresponding 95% CI and a plot of the Kaplan-Meier curves for DOR will be also provided by treatment group. To test for a treatment difference in duration of response, an unstratified log-rank test will be used. A Cox-regression model with a term for treatment arm will be used to quantify the treatment difference in duration of response and HR with 95% CI from Cox modeling analysis will be reported. Both DOR per IRC assessment and DOR per investigator assessment will be analyzed.

7.3.2 Duration of Complete Response (DCR)

Duration of complete response (DCR) is only defined for CR responders. DCR is defined as the time from the date of the first documented CR to the first documented tumor relapse or death due to any cause. The same rules of censoring used for PFS primary analysis will be used for DCR analysis. DCR will be analyzed in the same manner as DOR. Both DCR per IRC assessment and DCR per investigator assessment will be analyzed.

7.3.3 Proportion of Patients Receiving SCT after Study Treatment

Proportion of patients who receive a stem cell transplant is defined as the percentage of all randomized patients in the ITT population who receive a stem cell transplant after study treatment. The proportion of patients receiving SCT after study therapy will be analyzed using the same statistical method as for ORR.

7.4 Multiplicity

For the efficacy analysis, Pixantrone + Rituximab will be compared with Gemcitabine + Rituximab for all primary and secondary endpoints. The multiplicity arising from the testing of multiple endpoints will be addressed using a closed testing procedure that requires establishing significance in the primary endpoint prior to assessing the significance of secondary endpoints to ensure the overall type I error at 0.05.
The tests hierarchy will reflect the importance of the clinical endpoints in the study, as described below:

- First, the primary hypothesis test for PFS will be performed at the 2-sided 0.05 α-level.
- If the p-value on PFS is significant, the secondary hypothesis of OS will be tested using an overall 0.05 α-level. To be noted that two interim analyses of OS will be carried out using a group sequential procedure. A detailed description of multiplicity adjustment for OS interim and final analyses is provided as below in this section.
- If the hypothesis test of OS is achieved, then the secondary hypotheses of ORR, followed by CR, will be tested at the 2-sided 0.05 α-level. Hypotheses of ORR and CR will be tested only when the p-value on OS is significant either at an interim or at the final OS analysis.

All p-values will be reported in the summary tables regardless of the closed testing procedure, but statistical significance will only be established if the criteria described above are achieved.

The multiplicity of OS analyses will be addressed using group sequential methods, including Rho family alpha spending with a parameter of 7, in order to ensure the overall type I error at 0.05. The interim and final analyses will be implemented as following:

- At the first interim analysis, if the stratified log-rank test p-value for OS is ≤0.007 (assuming 165 events), then the study will claim OS superiority for the pixantrone + R arm.
- At the second interim analysis, the study will claim OS superiority for the pixantrone + R arm if the p-value is ≤0.017 (assuming 190 events).
- At the final analysis, the study will claim OS superiority for the pixantrone + R arm if the p-value is ≤0.048 (assuming 220 events).

The final stopping parameters for both interim analyses will be based on the actual number of events at the time of the data cutoff for the analyses. Table 3 provides the estimated number of deaths, and corresponding stopping parameters based on the potential number of events at each analysis.

Table 3. Stopping Parameters Based on the Potential Number of OS Events

	Number of Deaths	P-value to Reject H_0	Hazard Ratio
Interim OS Analysis #1	165	P ≤ 0.007	0.655
Interim OS Analysis #2	190	P ≤ 0.017	0.706
Final OS Analysis	220	P ≤ 0.048	0.766

7.5 Subgroup Analyses

Subgroup analyses are planned to further explore the primary and secondary endpoints on demographics, baseline characteristics and prognostic factors.

Subgroups based on the stratification factors include:

- IPI score (0-2 vs. ≥ 3)
- Number of prior lines of therapy for DLBCL or follicular grade 3 lymphoma (0 - 2 vs. ≥ 3),
- Time from initiation of first-line therapy for DLBCL or follicular grade 3 lymphoma until first relapse (<1 year vs. ≥1 year)

The actual strata values as documented in the eCRF will be used for the subgroup analyses on the stratification factors.

Depending on the sample size, subgroups may include, but are not limited to:

- Gender
- Age group (<65 years vs. ≥ 65 years)
- Region (North America vs. Europe)
- Number of prior lines of therapy for DLBCL or follicular grade 3 lymphoma (0 - 1 vs. ≥2)
- Ann Arbor Stage (I-III vs. IV)
- ECOG performance status (0-1 vs. ≥ 2)
- Number of extra nodal sites (0 vs. ≥ 1)

The treatment difference for the primary endpoint, PFS, within subgroup will be quantified using a Cox-regression model fit separately for each subgroup category with treatment arm as the predictor variable in the model. The hazard ratio for treatment along with the associated 95% CI and p-value will be reported from this model. Note that p-values from subgroup analysis are provided only for reference purpose and exploratory in nature, thus should not be interpreted for hypothesis testing purpose. Forest plot will be used to display the hazard ratio for treatment and the associated 95% CI for each subgroup category. Additionally, p-values for the treatment by subgroup interaction will be obtained from a Cox-regression model with terms in the model for treatment arm, subgroup variable, and treatment by subgroup interaction.

Subgroup analyses for OS will be performed in a similar manner as described for subgroup analyses of PFS.

Fisher's exact test will be used to compare ORR between the treatment arms within each subgroup. Within each subgroup, the 95% CI for ORR will be calculated using Clopper-Pearson method, and 95% CI for the difference in ORR between the 2 treatment arms will also be provided based on the Agresti-Caffo method. Additionally, p-values for the treatment by subgroup interaction will be obtained from a logistic regression model with terms in the model for treatment arm, subgroup variable, and treatment by subgroup interaction.

Subgroup analyses for CR will be performed in a similar manner as described for subgroup analyses of ORR.

8 EXPOSURE TO STUDY TREATMENT

Exposure analyses will be based on the actual dose administered (in mg) and normalized by body surface area (BSA, in m^2) per the CRF pages. Treatment exposure and dose modification, dose reductions, dose delays, skipped doses and dose interruptions, and dose discontinuation will be summarized in the safety population separately for pixantrone and gemcitabine as follows:

- Treatment duration (in weeks) defined as the time from the first study drug(s) dose date to the last day of study treatment;
- Number of cycles and doses administered (median, mean, range);
- Number and percentage of patients with at least 1 dose modification;
- Number and percentage of patients with at least 1 dose reduction (with summary of reason for dose reduction);
- Number and percentage of patients with at least 1 dose delay (with summary of reason for dose delay);
- Number and percentage of patients with at least 1 dose skipped (with summary of reason for dose skipped);
- Number and percentage of patients with at least 1 dose interruption (with summary of reason for dose interruption);
- Number and percentage of patients with at least 1 dose discontinuation (with summary of reason for dose discontinuation).

Study drug compliance to pixantrone and gemcitabine will be summarized in the safety population using descriptive statistics as follows:

- Cumulative normalized dose will be calculated as the sum of all administered doses in mg/m^2;
- Weekly dose intensity (mg/m^2/week) will be calculated as the cumulative dose divided by the (treatment duration (in weeks) +1).
- Percentage of protocol dose will be calculated as the cumulative normalized dose divided by the total normalized dose as planed per protocol × 100%. The planned dose per protocol is: for pixantrone 50 mg/m^2 IV on Days 1, 8, and 15 for each cycle of 28 days, and for gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 for each cycle of 28 days, for a total of 6 cycles. Thus, the total normalized dose as planed per protocol is 900 mg/m^2 for pixantrone, and 18,000 mg/m^2 for gemcitabine.

Number and percentage of patients within each percentage of protocol dose categories of ≥ 90%, < 90% to 80%, < 80% to 70%, and < 70% will be summarized.

Similar summary will also be provided for rituximab by treatment arm.

9 SAFETY ANALYSIS

The safety analyses will be performed using the safety population. Safety analyses include treatment emergent adverse events, cardiac assessments, clinical labs, vital signs, ECOG performance status, and any abnormal findings observed during the performance of physical examinations.

9.1 Adverse Events (AE)

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or subject who has received an investigational product and that does not necessarily have a causal relationship with this treatment. Progression of disease is not an AE.

Analysis of AEs will be based on Treatment-Emergent Adverse Events (TEAEs). An AE is considered a TEAE if it meets one of the following criteria:

- AE start date on or after the treatment start date and within 30 days after the permanent discontinuation of the study treatment;
- AE with a relationship to study drug of "Possible", "Probable", or "Definite" as assessed by the investigator regardless the AE start date;
- AE with a missing start date but with an end date after the first study drug dose date;
- A continuing AE diagnosed prior to the start of treatment and worsening in severity grade, or non-serious AEs at baseline which become serious, or AEs resulting in treatment discontinuation after the start of treatment.

9.1.1 Adverse Event Dictionary

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 11.1. System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be attached to the clinical database.

9.1.2 Adverse Event Severity

The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.0. The severity grade will be categorized as:

- Grade 1 (mild)
- Grade 2 (moderate)
- Grade 3 (severe)
- Grade 4 (life threatening), or
- Grade 5 (fatal)

A missing severity grade will be considered as missing and will not be imputed.

9.1.3 AE Partial Date Handling

All AEs with partial onset or stop dates will be identified and the partial dates will be imputed per the rule specified in Section 4.6.5.

9.1.4 AE Analysis

A overall summary of TEAEs by treatment arms will show the number and percentage of subjects who (1) had any TEAE, (2) had any Grade 3/4 TEAE, (3) had any pixantrone -related TEAE, (4) had any gemcitabine-related TEAE, (5) had any rituximab-related TEAE, (6) had any Grade 3/4 pixantrone -related TEAE, (7) had any Grade 3/4 gemcitabine-related TEAE, (8) had any Grade 3/4 rituximab-related TEAE, (9) had any treatment-emergent serious AE (SAE), (10) had any pixantrone-related SAE, (11) had any gemcitabine-related SAE, (12) had any rituximab-related SAE, (13) discontinued from study drug due to an TEAE, (14) dose interruption due to an TEAE, (15) dose reduction due to an TEAE, (16) death due to TEAEs.

Summaries (number and percentage of subjects) of TEAEs (by SOC and PT) will be provided by treatment arms using the safety population as follows:

- TEAEs
- TEAEs by CTCAE Grade
- Grade 3/4 TEAE
- Pixantrone /gemcitabine -related TEAEs
- Rituximab-related TEAEs
- Treatment-emergent serious AE (SAEs)
- Pixantrone/gemcitabine -related SAEs
- TEAEs leading to pixantrone/gemcitabine dose reduction
- TEAEs leading to pixantrone/gemcitabine dose interruption
- TEAEs leading to permanent discontinuation from pixantrone/gemcitabine
- TEAEs leading to death
- TEAE by outcome

Multiple events will be counted once only per subject in each summary. A TEAE will be counted as a related TEAE if the causal relationship to study drug has been marked as one of the following on the CRF: “Definite”, “Probable”, and “Possible”. Also, if the causal relationship is missing, the TEAE will be counted as a related TEAE in summary tables. For data presentation, SOC and PT will be sorted by decreasing frequency based on treatment arm pixantrone + rituximab. For summaries by severity grade, the most severe event will be selected. In addition to the presentation by SOC and PT, each summary will also be presented by PT only, ordered by decreasing frequency based on treatment arm pixantrone + rituximab. Summary of TEAE will also be presented by SOC only, ordered by decreasing frequency based on treatment arm pixantrone + rituximab.

As part of the SAE analysis, a summary of on-treatment deaths in the study by treatment arms will be provided to show the number and percentage of subjects in the safety population who had (1) on-treatment deaths, and (2) deaths by primary cause (ie, AE, PD, other). On-treatment deaths are defined as deaths that occur on treatment and within 30 days of last dose of study therapy.

In addition to the by-treatment summaries, data listings will be provided for the following:

- TEAEs leading to death
- TEAEs leading to permanent discontinuation from pixantrone/gemcitabine
- SAEs (with a variable indicating whether the event is treatment-emergent)
- All Deaths

Relative day from first dose date will be provided for each AE in the listings. If the AE onset date is after the first dose date, the relative day will be calculated as (AE onset date - first dose date + 1); however, if the AE onset date is prior to the first dose date, the relative day will be calculated as (first dose date – AE onset date).

9.2 Clinical Laboratory Measurements

Hematology and Chemistry laboratory measures for analysis are collected via central lab. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities using the safety population.

Data for a few selected laboratory tests will be summarized by visit using descriptive statistics. Summaries of numeric laboratory data will be based on observed data and will be reported using SI units. The rule to handle laboratory data that are less than the lower limit of quantitation or above the upper limit of quantitation is given in Section 4.6.5 when generating summary of numeric laboratory data by visit. Descriptive statistics of change and percent change from baseline in hematological and serum chemistry laboratory values will be presented by visit.

Applicable hematological and serum chemistry laboratory data will be programmatically graded according to CTCAE, Version 4.03 severity grade [grade laboratory results as Grade 0, mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life threatening (Grade 4)]. Grade 0 includes all values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (i.e., increased, decreased) will be presented separately.

A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥1 grade in the period from the first dose of study treatment to 30 days after the last dose of study treatment. If baseline data are missing, then any graded abnormality (i.e., an abnormality that is Grade ≥1 in severity) will be considered treatment-emergent. Assessment of treatment-emergent laboratory abnormality should include all laboratory data collected during the study including data from unscheduled visit. For all summaries of laboratory abnormalities, the denominator is the number of subjects in the safety population. Summary (number and percentage of subjects) of baseline, last post-baseline grade, and worst post-baseline treatment emergent laboratory abnormalities will be provided by treatment arms. Subjects will be categorized according to the most severe abnormality grade. Shift tables will be presented by showing change in CTCAE severity grade from baseline to the worst grade post baseline.

9.2.1 Hematology

The hematology measurements to be analyzed are: leukocytes(white blood cell), hemoglobin, platelet count, neutrophil count, lymphocyte count.

Numeric value of white blood cell, hemoglobin and platelet count will be summarized by visit using descriptive statistics. In the event of multiple records in an analysis window, rule described in Section 4.6.6 should be applied.

9.2.2 Chemistry

The following clinical chemistry measures will be analyzed: sodium, potassium, creatinine, glucose, bilirubin (total), albumin (total), protein (total), ALT/SGOT, AST/SGPT, alkaline phosphatase, calcium, phosphate (phosphorus), magnesium. Summaries of the worst CTCAE grade will be presented for all gradable serum chemistry tests. Worst CTCAE grade for sodium, potassium, calcium, magnesium, and glucose will be summarized in either direction of abnormality (i.e., abnormally low or high).

9.2.3 Hy's law

The number and percentage of subjects who met the Hy's law criteria (defined as AST or ALT > 3xULN, Total Bilirubin > 2xULN, and ALP < 2xULN at the same visit) will be tabulated.

9.3 Cardiac Assessments

Cardiac assessments will be evaluated based on the following clinical data and lab measures.

Cardiac TEAE
Cardiac TEAEs with the preferred terms in the Standardised MedDRA Queries (SMQs) of Cardiac Arrhythmias, Cardiac Failure, Ischaemic Heart Disease, and Embolic and Thrombotic Events will be summarized by SOC and PT for each treatment group. CTC grade 3 or 4 Cardiac TEAEs will be similarly summarized. Additionally, the incidence and prevalence of each Cardiac TEAE with 4-week intervals from baseline will be presented by treatment arm. Incidence and prevalence will also be presented for grade 3 or 4 Cardiac TEAEs.

Electrocardiogram (ECG)
The number and percentage of patients with an abnormal ECG will be summarized at baseline and at end of treatment. A shift table summarizing changes from Baseline to end of treatment will be provided.

Echocardiogram (ECHO)
The number and percentage of patients with an abnormal overall echocardiogram assessment will be summarized by scheduled visit. Change from baseline to each scheduled visit in overall echocardiogram assessment will be summarized by shift table.

Change from baseline in LVEF measurements will be summarized descriptively by scheduled visit.
In addition, the number and percentage of patients with any post-baseline LVEF values fall in categories defined as below will be presented:

- 40%≤ LVEF≤ 50%, or ≥10% ~ <20% absolute decrease from baseline
- 20%≤ LVEF≤ 39%, or ≥20% absolute decrease from baseline
- LVEF < 20%

Serum Troponin T
The number and percentage of patients with a high serum *Troponin T* value will be summarized by scheduled visit. Change from baseline to each scheduled visit in *Troponin T* assessment will be summarized by shift table.

9.4 Vital Sign Measurements

The number and percentage of subjects with abnormal vital sign measurements on study (on or after the first day of treatment and within 30 days after the last dose of study drug) will be summarized by treatment group. The vital sign abnormality criteria are defined as below:

Systolic blood pressure
- < 85 mm Hg
- ≥ 140 - < 160 mm Hg
- ≥ 160 mm Hg

Diastolic blood pressure
- < 50 mm Hg
- ≥ 90 - < 100 mm Hg
- ≥ 100 mm Hg

Weight Gain from Baseline
- ≥ 5% - < 10% increase
- ≥ 10% - < 20% increase
- ≥ 20% increase

Weight Loss from Baseline
- ≥ 5% - < 10% decrease
- ≥ 10% - < 20% decrease
- ≥ 20% decrease

9.5 ECOG Performance Status

The frequency distribution (n and %) in ECOG performance status will be summarized by scheduled visit for each treatment group. Shift table will be used to summarize the ECOG performance status change from baseline to each scheduled visit.

9.6 Number of Transfusions

The frequency distribution (n and %) will be displayed for number of patients with transfusions on study (on or after the first day of treatment and within 30 days after the last dose of study drug) by treatment group.

9.7 Concomitant Medication

Concomitant medications are defined as any medications meeting one of the following criteria:
- Starting on or after the first dose of study drug up to 30 days post the last dose, or
- Starting before and continuing after the first dose of study drug up to 30 days post the last dose
- Missing both start and stop dates
- Having a start date prior to the last dose of study drug and missing the stop date

The partial dates handling method used for AE summaries will be used for concomitant medication summaries (Section 4.6.4).
Concomitant medications will be coded into Anatomical-Therapeutic-Chemical classification (ATC) codes using WHO Drug Dictionary, version of 01DEC2010.

Summaries of the number and percentage of subjects who used concomitant medications will be presented in a table by ATC class and preferred drug name based on the safety population. Subjects will only be counted once within each preferred drug name if multiple drug use. The summary tables will be sorted by descending frequency of drug preferred name.

9.8 Follow-Up Therapy

Follow-up therapies are any therapies received after last study drug administration and prior to survival follow-up or end of study. Number and percentage of patients who had follow-up therapy, time from last dose to follow-up therapy, and type of follow-up therapy will be summarized by treatment group.

9.9 Subgroup Analysis of Safety

Overall TEAEs, grade 3/4 TEAEs, SAE, and Cardiac TEAEs will also be summarized by subgroups as appropriate. Subgroups may include, but are not limited to, baseline IPI score (0-2 vs. ≥ 3), the number of prior lines of therapy for DLBCL or follicular grade 3 lymphoma (0 - 1 vs. ≥ 2), region (North America vs. Europe), gender and age group (<65 years vs. ≥ 65 years). The actual strata values as documented in the eCRF will be used for the subgroup analyses on the stratification factors.

10 PHARMACOKINETIC (PK) ANALYSIS

The PK sub-study of this trial is being conducted to characterize the PK profile of pixantrone when co-administered with rituximab. Rituximab is co-administered with pixantrone on Day 1 of each 28-day cycle; therefore, plasma samples for PK analysis (7 samples per patient) will be collected relative to the Day 1 dose of pixantrone in one of the six treatment cycles for each participating patient. It was planned to enroll approximately 20 patients into the PK sub-study from approximately 20 selected sites. The detailed method for PK data analysis including population PK modeling and summary of blood concentrations of pixantrone at each nominal time point will be described in a separate PK report. Descriptive summary statistics may be provided for PK concentration data by sampling time.

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