CTI BioPharma Corp.

Protocol PIX306

(PIX-R® Trial)

A Phase 3 Clinical Study of Pixantrone

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

IND 62,678
EudraCT: 2012-001790-86

Amendment 9
July 10, 2017

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July 14, 2017
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14 July 2017
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Sponsor:
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Synopsis

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
Study No.	PIX306
Name of Sponsor	CTI BioPharma Corp.
Phase of Development	3
Investigational Drug	Pixantrone
Study Objectives	***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). ***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 ***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 an SCT after study treatment ***Pharmacokinetics Sub-Study Objective*** (participating sites refer to Section 12 Addendum: Pharmacokinetics Sub-Study) • To characterize the PK profile of pixantrone when co-administered with rituximab
Study Design	This is a randomized, active-controlled, multicenter, phase 3 study evaluating the objectives described above.

	Eligible patients will be randomized to receive up to six 28-day cycles of treatment with pixantrone + R, or gemcitabine + R. Details of the treatment period are presented in Table--1. Patients who complete study treatment or discontinue study treatment for any other reason will participate in the follow-up periods described below. At the time patients experience progressive disease per Modified IWG criteria during Study Treatment, or Early or Intermediate Follow-up, or withdraw consent for study procedures, they enter the Survival Follow-up Period. Patients who begin a subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, will enter the Survival Follow-up Period. Details of assessments in the follow-up periods are found in Table--2. ***Early Follow-up:*** After treatment completion or discontinuation, patients will enter a 24-week follow-up period. ***Intermediate Follow-up***: After completing the 24-week Early Follow-up period, patients will enter an additional 72-week follow-up period. ***Survival Follow-up****:* All patients will be monitored for survival. The sample size for this trial is based on the number of PFS events (per IRC). Approximately 320 patients are planned to be randomized in a 1:1 ratio to one of the two treatment arms to reach the required number of PFS events. The randomization 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, ≥ 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).
Enrollment Period	Approximately 80 months from study initiation
Study Population	Eligible patients are 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 SCT and who have relapsed after at least 1 prior 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) Patients must have received at least one rituximab-containing multi-agent regimen and must have had no progression for at least 12 weeks after last dose of a treatment regimen (see Section 3.4 for details). Patients must have at least one bidimensionally measurable site of disease that has not been previously irradiated: nodal disease ≥ 1.5 cm in short axis or extranodal disease > 1.0 cm in short axis. Lesion must be PET positive if PET scan is

	obtained. Additional requirements include left ventricular ejection fraction (LVEF) ≥ 45% by echocardiogram.
Planned No. of Patients	Approximately 320 patients are planned to be randomized in a 1:1 ratio to one of the two treatment arms. Enrollment will continue until 195 PFS events (per IRC response assessments) occur.
Test Product, Dose, and Mode of Administration	Pixantrone + R: rituximab 375 mg/m^2 IV on Day 1 and pixantrone 50 mg/m^2 IV on Days 1, 8, and 15.
Reference Therapy, Dose, and Mode of Administration	Gemcitabine + R: rituximab 375 mg/m^2 IV on Day 1, and gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15.
Treatment Regimen	**Pixantrone + R**: rituximab 375 mg/m^2 IV on Day 1 and pixantrone 50 mg/m^2 IV on Days 1, 8, and 15. The drug is supplied in vials, each containing 29 mg pixantrone. Regimen is given in 28-day cycles. Up to 6 cycles may be administered. **Gemcitabine + R**: rituximab 375 mg/m^2 IV on Day 1 and gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15. Regimen is given in 28-day cycles. Up to 6 cycles may be administered. Patients who must discontinue pixantrone or gemcitabine due to toxicity may remain on rituximab every 28 days to complete up to 6 total cycles of study treatment. Patients who must discontinue rituximab due to toxicity may remain on gemcitabine or pixantrone to complete up to 6 total cycles of study treatment.
Inclusion Criteria	The study's inclusion criteria include the following: 1. Signed Institutional Review Board or Institutional Ethics Committee-approved Informed Consent Form 2. Age ≥ 18 years old 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 4. Pathology and immunohistochemistry reports documenting the current histological diagnosis according to World Health Organization (WHO) classification must be reviewed by the sponsor or designee prior to randomization 5. Number of prior therapies allowed: a. Patients with de novo DLBCL must have received 1-3 prior regimens for DLBCL b. Patients with follicular grade 3 lymphoma must have received 1-3 prior regimens for follicular lymphoma (any grade) c. Patients with DLBCL transformed from indolent lymphoma must have received 1-4 prior regimens for NHL (any type) *The salvage combination therapy used to achieve a response in*

	preparation for possible SCT (eg, R-ICE, R-ESHAP, or R-DHAP), along with the subsequent high-dose myeloablative therapy (eg, BEAM) and SCT, is counted as a single regimen. *Maintenance therapy with rituximab or similar agents, single-agent corticosteroids, and local radiation therapy are* ***not counted*** *as treatment regimens.* 6. Received a rituximab-containing multi-agent regimen (eg, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R-CHOP]; rituximab, cyclophosphamide, vincristine, prednisone [R-CVP]; or bendamustine-R) 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 8. Not eligible for high-dose (myeloablative) chemotherapy and SCT. Patients not eligible for SCT include those who: a. Relapsed after previous SCT b. Did not respond to a standard salvage regimen c. Did not mobilize an adequate number of stem cells for SCT d. Are unsuitable for SCT due to other medical conditions or age e. Do not wish to undergo SCT f. Have financial issues precluding SCT g. Are considered by the investigator as unsuitable for SCT for any other reason 9. At least 28 days from completion of last NHL therapy to randomization 10. At least one bidimensionally measurable site of disease that has not been previously irradiated: nodal disease ≥ 1.5 cm in short axis or extranodal disease > 1.0 cm in short axis. Lesion must be PET positive if PET scan is obtained. 11. Slides confirming diagnosis of follicular grade 3 lymphoma or DLBCL available for independent histology review 12. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 (Section 8.2) 13. Life expectancy ≥ 12 weeks in investigator's judgment 14. Left ventricular ejection fraction (LVEF) ≥ 45% by echocardiogram and normal serum troponin T 15. Hemoglobin ≥ 8 g/dL (can be post-transfusion) 16. Platelet count ≥ 100×10^9/L; platelet count ≥ 75×10^9/L permitted if documented bone marrow involvement 17. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L; ANC ≥ 1.0×10^9/L permitted if documented bone marrow involvement 18. Serum bilirubin ≤ 1.5 × upper limit of normal (ULN); patients with proven Gilbert's syndrome and bilirubin ≤ 5 × ULN may be enrolled. 19. Aspartate aminotransferase (AST; also called serum glutamic-oxaloacetic

	transaminase [SGOT]) and alanine aminotransferase (ALT; also called serum glutamic-pyruvic transaminase [SGPT]) ≤ 2 × ULN, or ≤ 5 × ULN if elevation is due to hepatic involvement by lymphoma 20. Serum creatinine ≤ 2 × ULN 21. All acute toxicities related to prior treatment recovered to grade ≤ 1, except alopecia 22. Willingness and ability to comply with the visit schedule and assessments required by the study protocol 23. Due to the long retention time of rituximab in B cell-depleted patients, both males and females must agree to use effective birth control. Women of childbearing potential (WOCBP) must use highly effective methods (defined as those resulting in a failure rate of < 1% per year when used consistently and correctly) for the duration of study treatment and for 12 months after last dose of study drug. The contraceptive methods that are considered highly effective are intrauterine devices and hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release).
Exclusion Criteria	The study's exclusion criteria include the following: 1. Any of the following as the only site(s) of disease: palpable lymph nodes not visible on imaging studies, skin lesions, or bone marrow involvement only 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 regimen 3. Prior treatment with a cumulative dose of doxorubicin or equivalent exceeding 450 mg/m² (see Section 8.5 for formula) 4. LVEF < 45% by echocardiogram 5. Active National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 3/4 infection 6. Major surgery ≤ 28 days prior to randomization 7. Known acute or chronic hepatitis B or hepatitis C virus infection 8. Known seropositivity for human immunodeficiency virus (HIV) 9. Current CNS involvement by lymphoma a. Any history or evidence of current leptomeningeal involvement by lymphoma is prohibited. b. Patients with prior localized CNS involvement who have been without recurrence for ≥ 12 months and currently have a negative head MRI may be eligible; please discuss with the Medical Monitor. 10. Any experimental therapy ≤ 28 days prior to randomization 11. Myocardial infarction within the past 6 months 12. New York Heart Association class III or IV heart disease (Section 8.4) 13. Other malignancy within the last 5 years. Exceptions are: a. Curatively treated basal cell/squamous cell skin cancer

	b. Carcinoma in situ of the cervix c. Superficial transitional cell bladder carcinoma d. In situ ductal carcinoma of the breast after complete resection e. Localized, resected and/or low-risk prostate cancer may be eligible; please discuss with the Medical Monitor 14. Any contraindication, known allergy, or hypersensitivity to any study drugs 15. Pregnant or lactating 16. Concomitant therapy with any anticancer agents, immunosuppressive agents, other investigational anticancer therapies. Low-dose corticosteroids for the treatment of non-cancer-related illnesses are permitted 17. Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study procedures or follow-up schedules 18. Severe and/or uncontrolled medical disease that could compromise participation in the study, or any medical or psychiatric condition that, in the opinion of the investigator, would make study drug administration hazardous or obscure the interpretation of data.
Schedule of Treatment and Assessments	• All treatment cycles are 28 days. • Three (3) days is the maximum visit delay allowable for nonmedical reasons (eg, scheduling problems, holidays) during a 28-day treatment cycle. Visit delays > 3 days for nonmedical reasons may be permitted with prior Medical Monitor approval. See Section 3.6 for details of dose adjustments and treatment delays. • Disease response is assessed by imaging every 8 weeks ± 1 week during the Treatment and Early Follow-up periods, and every 12 weeks ± 2 weeks during Intermediate Follow-up. All time points for disease assessment are calculated from Day 1 of Cycle 1. If an assessment is done off schedule, the next assessment should be calibrated as closely as possible back to the original schedule starting at Day 1 Cycle 1. • The EOT visit occurs at 4 to 7 weeks (inclusive) after the last dose of study drug, or before subsequent systemic anticancer therapy is given, whichever occurs first. Rituximab given as maintenance therapy is not allowed prior to the EOT visit per protocol window. • A patient who develops progressive disease per Modified IWG criteria during the Treatment, Early Follow-Up or Intermediate Follow-up periods, or begins subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, enters the Survival Follow-up Period. • A patient who discontinues study treatment without meeting Modified IWG criteria for progression will enter the Early Follow-up period and will continue to have imaging assessments per protocol, until developing progressive disease per Modified IWG criteria or beginning subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, at which point the patient will enter the Survival Follow-up

	period. • A patient who is randomized, but not treated, will immediately enter the Early Follow-Up period. • A patient who withdraws consent for study procedures will enter the Survival Follow-up period. • End-of-Study (EOS) is defined as the date when the required OS events have occurred or the study is terminated. • See Table--1 for screening and treatment details, and Table--2 for information on the follow-up periods.
Criteria for Evaluation	**Efficacy Evaluation** ***Disease Response Assessment*** The Modified IWG 2007 Revised Response Criteria used in this study are detailed in Table--11. Baseline disease assessment of the neck, chest, abdomen, and pelvis is required. Computed tomography (CT) with intravenous (IV) contrast is the preferred imaging modality, but patients intolerant of CT IV contrast may have MRI of the neck, abdomen, and pelvis with noncontrast chest CT (see Section 3.9.1). The imaging method used at baseline must be used throughout the study. All scans obtained during the course of the study will be reviewed by an Independent Radiology Committee (IRC), whose members will be blinded to treatment assignment. Baseline positron emission tomography (PET) is not required, but PET images obtained at baseline or during the study are to be submitted. PET/CT images should not typically be used for lesion measurements, unless the CT images are obtained using optimal CT imaging protocols in a fashion consistent with other study CT imaging time points (ie, similar imaging energies and use of IV contrast). If a PET scan is obtained at baseline, all sites of disease selected as target lesions must be PET positive. An end-of-treatment (EOT) PET scan is required, unless it is geographically unavailable, the patient has progressive disease per Modified IWG criteria, or the patient has started subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy. Regardless of whether serum samples, radiologic material, and other patient data are sent to a central lab or an independent review panel for study purposes, treatment and eligibility decisions must be made by the investigator based on his or her clinical assessment of the patient and interpretation of local labs, radiology assessments, and other tests. ***Survival*** Survival status will be recorded at each scheduled visit during treatment and follow-up periods until the end of the study.
	Safety Evaluation Safety will be assessed in all randomized patients by monitoring and recording all adverse events (AEs), serious adverse events (SAEs), cardiac,

	hematologic and blood chemistry parameters, vital signs, performance status (PS), and any abnormal findings observed during the performance of physical examinations. • Safety measurements • Adverse events • Clinical labs • Physical examinations • Cardiac assessments (serial LVEF evaluations by echocardiogram and serum troponin T)
Statistical Methods and Analyses	The primary efficacy endpoint of the study is PFS, defined as the time from the date of randomization to the date of disease progression or death due to any cause (whichever occurs first). The primary analysis of PFS will use disease progression, assessed by the IRC. The stratified log-rank test will be used for the primary analysis comparing PFS between the two treatment arms based on the intent-to-treat population. The secondary efficacy endpoints are OS, ORR, and CR rate. One hundred ninety-five (195) PFS events are required to detect at least a 35% improvement (ie, HR = 0.65) in PFS with 85% power. Based on updated study projections, it is estimated that approximately 320 patients are needed to reach the 195 PFS events.

Table--1
Screening and Treatment Period

		Screening/ Baseline	Cycle 1			Cycles 2-6			EOT[14]
		Day -28 to Randomi-zation	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	
			Wk 1	Wk 2	Wk 3				
Informed consent		X							
Path sample to central lab; report to sponsor [0]		X							
Medical history and eligibility review		X							
NHL treatment and history, IPI, staging		X							
Randomization ≤ 14 days prior to first dose[1]		X							
Safety Assessment									
CBC with differential[2,3]		X	X	X	X	X	X	X	X
Chemistry panel (including LDH)[2,4]		X	X			X			X
Urinalysis		X							
Vital signs (before drug administration)		X	X	X	X	X	X	X	X
Weight and ECOG PS [3]		X	X			X			X
Physical examination[5]		X	X	X	X	X	X	X	X
Pregnancy test [6](WOCBP only)		X	X			X			
Adverse events [13]		X	X	X	X	X	X	X	X
Concomitant medications [7]		X	X	X	X	X	X	X	X
Cardiac Assessment									
LVEF by echo [8]		X				X[8]			X
ECG		X							X
Serum troponin T[8]		X				X[8]			X
Pharmacokinetics Assessments (participating sites see Section 12.4.1)									
Treatment Administration									
Pix + R	Rituximab 375 mg/m^2 IV		X			X			
	Pixantrone 50 mg/m^2 IV[9]		X	X	X	X	X	X	
Gem + R	Rituximab 375 mg/m^2 IV		X			X			
	Gemcitabine 1000 mg/m^2 IV		X	X	X	X	X	X	

	Screening/ Baseline Day -28 to Randomi-zation	Wk 8 (± 1 Wk)	Wk 16 (± 1 Wk)	Wk 24 (± 1 Wk)	EOT[14]
Disease Assessment					
CT scan [10]	X	X	X	X	
PET scan [11]					X
Bone marrow biopsy with core[12]					X

Table--2
Follow-up Periods

	Early Follow-up[15] (± 1 Week)			Intermediate Follow-up (± 2 Weeks)						Survival Follow-up (± 2 Weeks)	
	FU Wk 8	FU Wk 16	FU Wk 24	FU Wk 36	FU Wk 48	FU Wk 60	FU Wk 72	FU Wk 84	FU Wk 96	Every 12 Wks Until Death or Study Termination	EOS
Adverse events[13]	X										
LVEF by echo[8]			X								
Troponin T[8]			X								
CT scan[10]	X	X	X	X	X	X	X	X	X		
LDH	X	X	X	X	X	X	X	X	X		
Documentation of all subsequent systemic anti-cancer therapy	X	X	X	X	X	X	X	X	X		
Survival	X	X	X	X	X	X	X	X	X	X	X

Abbreviations:
AEs = adverse events
CBC = complete blood count
CR = complete response
CT = computed tomography
DLBCL = diffuse large B-cell lymphoma
ECG = electrocardiogram
ECOG = Eastern Cooperative Oncology Group
EOS = end of study
EOT = end of treatment, at 4 to 7 weeks after last study drug dose, inclusive
FU = follow-up
IPI = International Prognostic Index
IV = intravenous(ly)
LDH = lactate dehydrogenase
LVEF = left ventricular ejection fraction
mg/m^2 = milligrams per square meter
MRI = magnetic resonance
imagingNHL = non-Hodgkin lymphoma
PD = progressive disease
PET = positron emission tomography
PS = performance status
wk(s) = week(s)
R = rituximab
WOCBP = women of childbearing potential.

Footnotes for Table--1 and Table--2

0 Pathology and immunohistochemistry reports documenting a current diagnosis of DLBCL (de novo DLBCL or DLBCL transformed from indolent lymphoma) or follicular grade 3 lymphoma must be reviewed by sponsor or designee prior to randomization. Tissue slides should be requested during the screening period for central review, but completion of central review is not required prior to randomization and treatment.
1 All screening procedures to determine eligibility must be completed prior to randomization.
2 Chemistry and hematology labs are evaluated locally to direct patient treatment and determine eligibility; samples are also sent to central laboratory for study analysis. Dose delays may require that both local and central labs are redrawn.
3 ≤ 1 day before study drug administration; no time parameter at EOT visit (at 4 to 7 weeks after last study drug dose, inclusive); see Section 8.2 for ECOG PS grades and definitions).
4 ≤ 7 days before study drug administration; no time parameter at EOT visit (at 4 to 7 weeks after last study drug dose, inclusive).
5 Physical examination required ≤ 3 days prior to Day 1 study drug administration for Cycles 2-6 and at EOT (at 4 to 7 weeks after last study drug dose, inclusive). Symptom-directed examination as needed ≤ 1 day before study drug administration on Day 1 Cycle 1 and Days 8 and 15 of all cycles.
6 Pregnancy test (WOCBP only) ≤ 1 day before study drug administration; serum test at screening; urine test permitted at all other time points.
7 If used, colony-stimulating factors must be discontinued ≥ 2 days prior to next scheduled drug administration. If Neulasta (pegfilgrastim) is used, it should be given only after the Day 15 dose.
8 LVEF ≥ 45% by echocardiogram and normal troponin T test results are required for eligibility. LVEF is then done ≤ 7 days before expected Day 1 of Cycles 3 and 5 and at Follow-up Week 24; troponin T samples are obtained before Cycles 3 and 5 and at Follow-up Week 24. Echocardiogram and troponin T need not be repeated, if a dose is delayed for reasons other than abnormal LVEF (see Section 3.10.4).
9 The drug is supplied in vials each containing 29 mg pixantrone.
10 CT with IV contrast of the neck, chest, abdomen, and pelvis. Patients intolerant of IV contrast will have MRI and noncontrast CT (see Section 3.9.1) and the reason for not using contrast specified in source documents. The imaging method used at

Table--2
Follow-up Periods

	Early Follow-up[15] (± 1 Week)			Intermediate Follow-up (± 2 Weeks)						Survival Follow-up (± 2 Weeks)	
	FU Wk 8	FU Wk 16	FU Wk 24	FU Wk 36	FU Wk 48	FU Wk 60	FU Wk 72	FU Wk 84	FU Wk 96	Every 12 Wks Until Death or Study Termination	EOS

baseline must be used throughout the study. All time points for CT/MRI are calculated from Day 1 Cycle 1. If an assessment is done off schedule, the next assessment should be calibrated as closely as possible back to the original schedule starting at Day 1 Cycle 1.

11 PET scan may be obtained alone or in combination with CT scan. PET scan is not required at baseline, but any PET images obtained at baseline or during the study are to be submitted for central review. PET scan is required at EOT visit, unless geographically unavailable, patient has PD per Modified IWG criteria, or patient has started subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy.

12 A bone marrow biopsy (with core) is required at EOT (at 4 to 7 weeks after last study drug dose, inclusive) to confirm a CR, unless a bone marrow biopsy was obtained at baseline and was negative. All bone marrow biopsies obtained during the study should be submitted for local review.

13 For randomized patients, study-drug related AEs and cardiac AEs ≥ grade 3, including LVEF declines, are collected and followed until resolution or no further improvement is expected or EOS, and AEs not related to study drug and cardiac AEs ≤ grade 2 are collected and followed for 30 days after the last dose of study drug, or until no further improvement is expected, or until the patient begins a subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, whichever occurs first.

14 The EOT visit occurs at 4 to 7 weeks, inclusive, after the last dose of study drug is administered (or was scheduled to be administered), or before subsequent systemic anticancer therapy is given, whichever occurs first. Rituximab given as maintenance therapy is not allowed prior to the EOT visit per protocol window. However, even if rituximab is given as maintenance therapy prior to EOT, all EOT procedures, including PET, will be performed. In the unanticipated event that a patient is randomized, but receives no study treatment, no EOT procedures are required and the patient would continue per protocol Section 3.8.1.4.

15 The Early FU Week 8 visit occurs 8 weeks after the last protocol calendar scheduled CT/MRI imaging disease assessment to ensure an 8-week interval between protocol calendar scheduled scans. In the case of CT/MRI imaging done outside the calendar schedule (unscheduled), consult with Medical Monitor for appropriate scheduling of the next CT/MRI.

List of Abbreviations and Acronyms	
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aSCT	autologous stem cell transplant
AST	aspartate aminotransferase
BSA	body surface area
CBC	complete blood count
CDC	clinical document control
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHOP-R	cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab
CHF	congestive heart failure
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CRu	complete response unconfirmed
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTI	CTI BioPharma Corp.
dFdCDP	gemcitabine diphosphate
dFdCTP	gemcitabine triphosphate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EF	ejection fraction
EOS	end of study
EOT	end of treatment

List of Abbreviations and Acronyms	
EPOCH	etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone
ESR	expedited safety report
EU	European Union
FDA	Food and Drug Administration
FDG	2-deoxy-2-[18F]fluoro-D-glucose
FU	follow-up
GCP	Good Clinical Practice
GVHD	graft-versus-host disease
HDC	high-dose chemotherapy
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator brochure
IC_{50}	50% inhibitory concentration
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Radiology Committee
ITT	intent-to-treat
IV	intravenous(ly)
IWG	International Working Group
LDi	longest diameter of a measurable lesion
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin lymphoma
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease

List of Abbreviations and Acronyms	
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PP	per protocol
PPD	product of the perpendicular diameters
PR	partial response
PS	performance status
QA	quality assurance
R	rituximab
R-CVP	rituximab, cyclophosphamide, vincristine, prednisone
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RR	response rate
r/r	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SCID	severe combined immunodeficiency disease
SCT	stem cell transplant
SD	stable disease
SDi	short diameter; the longest diameter perpendicular to the LDi
SGOT	serum glutamic-oxaloacetic transaminase (obsolete, see AST)
SGPT	serum glutamic-pyruvic transaminase (obsolete, see ALT)
SOC	system organ class
SPD	sum of the products of the perpendicular diameters
SSC	Study Steering Committee
SUSAR	suspected unexpected serious adverse reaction
TLS	tumor lysis syndrome
TTP	time to tumor progression
ULN	upper limits of normal
WHO	World Health Organization
wk(s)	week(s)
WOCBP	women of childbearing potential

1 Background and Rationale

1.1 Overview of Relapsed/Refractory Aggressive NHL

Non-Hodgkin lymphomas (NHLs) are the 7th-most-common type of cancer, with an estimated annual incidence of 70,800 new patients in the United States in 2014 [1]. Aggressive NHL comprises 60% of all NHL, and diffuse large B-cell lymphoma (DLBCL) is the most common subtype, accounting for 75% of all aggressive varieties. Regardless of histology, survival for patients with aggressive NHL is brief without intensive chemotherapy or chemoimmunotherapy[2].

Anthracycline-based regimens have long been the standard of care front-line therapy in patients with aggressive NHL, with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) possessing the best combination of efficacy and tolerability[3]. CHOP was the prevailing international regimen until 2006 in the USA and 2007 in Western Europe, when the addition of rituximab made CHOP-R the standard front-line chemotherapy for DLBCL[4].

While a substantial number of patients with aggressive NHL obtain a durable response with anthracycline-containing first-line regimens, 30% to 50% relapse or prove to be refractory to initial therapy. Following relapse to initial therapy, a high-dose myeloablative regimen followed by stem cell transplant (SCT) is a potential curative option for patients who can tolerate the procedure.

However, the 3-year disease-free survival for SCT-eligible patients in first relapse after standard front-line therapy with CHOP-R is only approximately 20%, and the median progression-free survival (PFS) is 6.5 months[5]. A substantial number of relapsed patients do not receive SCT because of comorbidities, advanced age, patient choice, or failure to have a major response to second-line therapy[5, 6]. Eighty-percent of patients who receive second-line therapy experience disease progression. Among patients who are not candidates for SCT or who relapse following second-line regimens, response rates are low, complete remissions are rare, and expected survival is less than 6 months.

There is no standard or consensus treatment for patients with relapsed/refractory aggressive NHL beyond second-line treatment regimens. Retreatment with anthracyclines is generally precluded, due to the risk of cardiac toxicity that increases with the cumulative dose[7]. By the time of first relapse, most patients have received 300 to 400 mg/m^2 doxorubicin-equivalent cumulative dose, and thus are already near the recommended lifetime limit of 450 mg/m^2 (400 mg/m^2 doxorubicin-equivalent if cyclophosphamide or thoracic radiation was previously given)[8].

In the second-line setting for patients who are not transplant eligible, NCCN guidelines recommend single-agent rituximab, lenalidomide, clinical trial participation, or intensive multi-agent regimens (ie, EPOCH, CEPP) if the patient can tolerate the high incidence of grades 3 to 4 toxicities associated with such regimens. For patients who relapse after, or are refractory to, second-line therapy, there is no approved therapy in the US or EU, and NCCN guidelines recommend palliative care or participation in a clinical trial.

The lack of consensus regarding treatment of patients with relapsed/refractory NHL and the paucity of robust data supporting current clinical practices clearly demonstrate a need for controlled trials in this setting to define an effective therapy for the unmet medical need in this patient population. Pixantrone may offer a more effective alternative to the diverse therapies currently in use.

1.2 Pixantrone

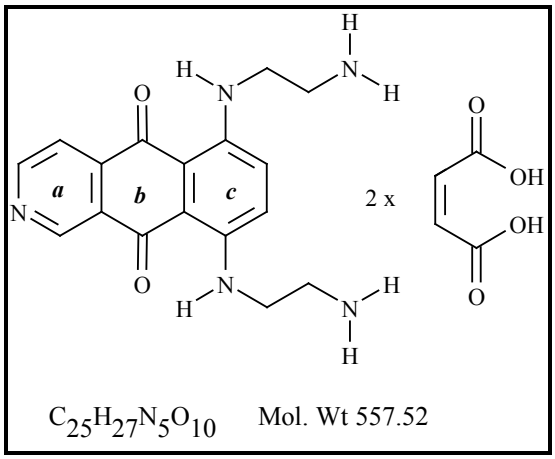
Pixantrone is a novel aza-anthracenedione compound related to anthracyclines and anthracenediones, such as doxorubicin and mitoxantrone, classes of drugs whose antineoplastic activity is due to deoxyribonucleic acid (DNA) intercalation and inhibition of topoisomerase II. Figure--1 illustrates the chemical structure of pixantrone dimaleate.

Pixantrone was designed to improve the efficacy and reduce the toxicity associated with anthracyclines and anthracenediones by increasing the stability of DNA adduct formation, while reducing the potential to form oxygen-free radicals and toxic drug-metal complexes. Pixantrone lacks the 5, 8-dihydroxy-substitution of mitoxantrone, and instead contains a nitrogen heteroatom. The quinone-hydroquinone site responsible for oxygen-free radical generation and iron binding in mitoxantrone and doxorubicin is not present in pixantrone.

Because of this design, pixantrone exhibits physiochemical and DNA-binding properties that are distinct from these agents[9]. Unlike other anthracycline-like agents, pixantrone forms stable DNA adducts through alkylation with specificity for DNA hypermethylated sites[10].

Furthermore, pixantrone cannot bind iron, and consequently does not generate oxygen-free radicals, the putative mechanism linked to the acute cardiac toxicity of other anthracycline-like agents. In addition, pixantrone does not form alcohol metabolites (eg, doxorubinol), which are implicated as important contributors to late-onset cardiac toxicity.

Figure--1
Pixantrone Dimaleate Chemical Structure and Molecular Weight



Multiple nonclinical hematological tumor models demonstrated enhanced antitumor efficacy of pixantrone compared with doxorubicin and mitoxantrone.

Treatment with multiple cycles of pixantrone alone did not cause major myocardial changes, whereas doxorubicin and mitoxantrone induced the expected myocardial toxicity[11]. In animals pretreated with doxorubicin, pixantrone caused significantly less additional myocardial damage than did mitoxantrone or additional doxorubicin.

1.2.1 Pixantrone Clinical Studies

Pixantrone has been evaluated in a total of 407 patients with hematologic and solid-tumor malignancies in single-agent and combination regimens.

Previously, the expression of the pixantrone dose used in clinical and nonclinical studies was based on the drug's salt form (pixantrone dimaleate), which could be confusing when pixantrone is prescribed and dispensed. In previous studies and publications, the dose was expressed as 85 mg/m^2, based on the salt form. This dose is equivalent to 50 mg/m^2 pixantrone (active substance).

In response to a recommendation from the European Medicines Agency, the dose is now expressed as 50 mg/m^2 and refers to the active substance (pixantrone). The expression of the dose as the salt form in historical documents and previous studies will not be corrected.

1.2.1.1 Pixantrone Efficacy: Study PIX301

Protocol PIX301 was the first randomized, controlled study in patients with aggressive NHL who had previously received two or more lines of systemic therapy, such as chemotherapy or chemoimmuno-therapy, which could include SCT following high-dose myeloablative therapy. Patients (N = 140) age 18 years or older with stage III to IV aggressive NHL who had adequate organ function, including left ventricular ejection fraction (LVEF) of 50% or greater, were eligible.

Patients were randomized to pixantrone dimaleate 85 mg/m^2 by 1 hour infusion on Days 1, 8, and 15 of each 28-day cycle for up to 6 cycles, or to physician's choice of a single-agent comparator drug most appropriate for that patient using the standard dose and schedule for that drug. Response and disease progression assessments were standardized to every 8 weeks (± 1 week) through the end of the treatment period and during the 18 month follow-up period.

The primary endpoint of ProtocolPIX301 was the CR/CRu rate at the end of treatment. Twenty percent of pixantrone patients and 6% of comparator patients achieved a CR/CRu (p = 0.021), which met the primary study endpoint. Without additional therapy during follow-up, 3 additional patients receiving pixantrone and 1 control patient achieved a CR/Cru, for final CR/CRu rates of 24% and 7% (p = 0.009).

As shown in Table--3, ORRs were similarly in favor of pixantrone, with 40% of pixantrone patients and 14% of comparator patients (p = 0.001) achieving a response by the end of the study.

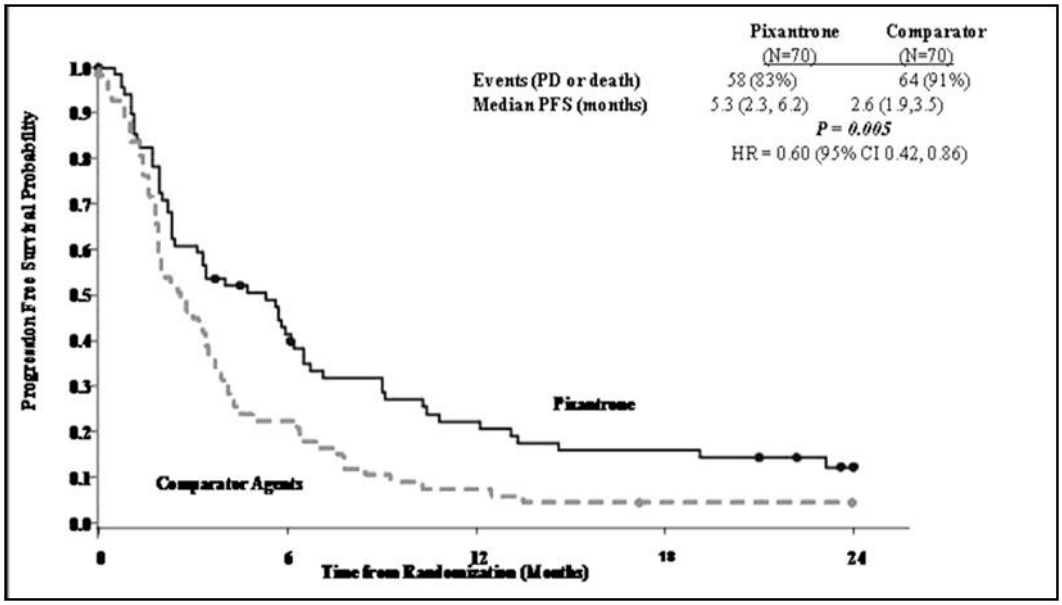
Table--3
Response Rates in Protocol PIX301 Patients, N (%)

	End of Treatment			End of Study (18-month Follow-up)		
	Pixantrone N = 70	**Comparator** N = 70	**P-value**	**Pixantrone** N = 70	**Comparator** N = 70	**P-value**
CR	8 (11%)	0		11 (16%)	0	
CRu	6 (9%)	4 (6%)		6 (9%)	5 (7%)	
CR/CRu	14 (20%)	4 (6%)	0.021	17 (24%)	5 (7%)	0.009
ORR	26 (37%)	10 (14%)	0.003	28 (40%)	10 (14%)	0.001

Source: CSR PIX301 EOS Tables 11.1-1 and 11.1-2 (derived from statistical tables 14.2.1.1, 14.2.1.2, 14.2.5.1, and 14.2.5.2).
Abbreviations:
CR = complete response CRu = complete response unconfirmed EOS = end of study
N = number of patients ORR = overall response rate.

As shown in Figure--2, pixantrone was also associated with a statistically significant increase in PFS (5.3 vs 2.6 months; HR: 0.60, p = 0.005). Overall survival also favored pixantrone, with a median of 10.2 vs 7.6 months (hazard ratio [HR] = 0.79, p = 0.25).

Figure--2
PIX301 Progression-Free Survival (End of Study)



Source: CSR PIX301 EOS Figure 11.1-1 (based on statistical table 14.2.4.1).
Abbreviations:
HR = hazard ratio N = number of patients PD = progressive disease
PFS = progression-free survival.

1.2.1.2 Pixantrone Safety in Clinical Studies

The safety of pixantrone in NHL has been well characterized in 407 patients. Thirteen studies have been conducted in cancer patients: 8 studies were Phase 1, 3 were Phase 2, and 2 were Phase 3. Multiple dose levels, dose schedules, and both single-agent and treatment combinations were studied.

The safety of pixantrone as a single agent has been well characterized in 197 patients. The most common adverse events (AEs) reported for pixantrone-treated patients in single-agent studies were neutropenia (43%), leukopenia (35%), anemia (32%), lymphopenia (32%), nausea (27%), asthenia (24%), pyrexia (22%), vomiting (21%), skin discoloration (20%), diarrhea (18%), and alopecia (17%).

In the safety database, cardiac failure events grade ≥ 3 occurred in 6 of 197 patients (3%) receiving pixantrone as single-agent therapy and in 4 of 210 patients (2%) receiving pixantrone in combination regimens. In Protocol PIX301, the controlled single-agent study, decreased LVEF (defined as a ≥ 10% decrease) was reported in 13 (19.1%) patients in the pixantrone group. Of these, 11 (16.2%) were grade 1 or 2 and 2 (2.9%) were grade 3. In the comparator group, decreased LVEF was reported in 7 patients (10.4%), and all were grade 1 or 2. Independent cardiology review demonstrated that no patient treated with pixantrone developed CHF that was considered typical for anthracyclines, and no grade 4 declines in LVEF were observed.

Assessment of cardiac safety is confounded, since many of the patients in these studies have been heavily pretreated with anthracyclines or anthracenediones, which may manifest latent cardiotoxic effects. It is possible that events identified during pixantrone administration represent late effects attributable to anthracyclines or anthracenediones. Many cardiac events observed in these studies were not typical of anthracycline-associated left ventricular dysfunction and did not exhibit a dose-response relationship with pixantrone.

The occurrence of secondary AML or MDS is a well-described complication of chemotherapy regimens containing anthracyclines and other DNA-damaging agents. Relatively few patients treated with pixantrone are long-term survivors, and the relative frequency of secondary AML or MDS cannot be estimated. To date, of the 50 clinical study patients with at least 1 reported treatment-emergent AE in the SOC category of neoplasms, 38 patients had progressive neoplastic disease, 8 had simple complications of the neoplasm (infection or pain), 5 had non-melanoma skin neoplasms or benign tumor (oncocytoma), and 2 (one Grade 3) had tumor lysis syndrome. In addition, 2 safety reports of secondary AML or MDS have been reported, 1 each from ongoing study PIX306 and from an ongoing investigator-sponsored trial. In both cases, the patients had previously received multiple lines of chemotherapies, including agents known to cause secondary MDS or AML.

1.2.2 Pixantrone Nonclinical Photosensitivity Study

Photosensitivity is a potential risk, based on in vitro and in vivo nonclinical data; however, no confirmed cases have been reported in the clinical study program. A study (RTC Study No. 90740) was performed to investigate the acute phototoxicity of pixantrone (BBR2778) in nude rats after IV administration of a single 50 mg/kg dose and subsequent ultraviolet (UV) irradiation. Negative-control (similarly drug treated, but not irradiated) and positive-control rats (treated with lomefloxacin) were included in the test system. In vivo and post mortem examinations of the animals revealed that an inflammatory reaction had occurred in the skins of animals treated with pixantrone compared with nonirradiated controls. The reaction was of lower intensity than that seen in the positive-control lomefloxacin-treated animals. Animals treated with 25 mg/kg pixantrone and UV irradiation had reactions that were limited in severity and/or incidence, and the reactions were restricted to males; these reactions were considered not toxicologically relevant. Thus, under these test conditions, pixantrone may result in an acute phototoxic reaction after a single 50 mg/kg IV dose, but a dose of 25 mg/kg is not expected to elicit a phototoxic reaction.

Given these nonclinical data, as a precaution, patients should be advised to follow sun protection strategies, including wearing sun-protective clothing and using sunblocking agents; these strategies are recommended for patients who are treated with pixantrone. Since most medicinal product-induced photosensitivity reactions are caused by wavelengths in the UVA range, the use of sunscreen that strongly absorbs UVA irradiation is recommended.

1.3 Rituximab

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody that binds to the transmembrane antigen CD20, which is located on pre-B and mature B lymphocytes. The CD20 antigen is expressed on > 95% of all B cell NHLs and on normal B cells, but not on hematopoietic stem cells or plasma cells[(12)].

Treatment with rituximab is generally well tolerated, particularly in terms of adverse hematological effects and serious or opportunistic infections relative to standard chemotherapy. Infusion-related reactions, usually mild-to-moderate influenza-like symptoms, are common with rituximab treatment, but usually decrease in frequency with subsequent infusions. However, approximately 10% of patients

develop severe infusion-related reactions (eg, bronchospasm, hypotension) that are usually reversible with appropriate interventions and supportive care, but there have been fatalities.

Rituximab has been evaluated for treatment of patients with relapsing or refractory aggressive lymphoma. In a study by Coiffier et al[13], patients received 8 weekly infusions of rituximab at 375 mg/m^2 or a single infusion of 375 mg/m^2 followed by 7 weekly infusions of 500 mg/m^2. Five complete responses (CRs) and 12 partial responses (PRs) were observed among the 54 enrolled patients, and no difference was observed between the two doses. The CR rate was 9% and the PR rate was 22%, for an overall response rate (ORR) of 31%. The median time to progression exceeded 246 days. The most frequently reported AEs were mild and related to an infusion syndrome. Nineteen patients had grade 3 related AEs, and only 1 patient had a grade 4 related AE. Two patients (3.7%) withdrew from treatment because of severe adverse events.

Tobinai et al[14] studied 68 Japanese patients with relapsed or refractory aggressive B-cell lymphoma who were treated with rituximab (375 mg/m^2) in 8 consecutive weekly infusions. The ORR for 57 eligible patients was 37%. The median PFS of 53 evaluable patients was 52 days, whereas time to progression of 21 eligible responders was 245 days. Mild-to-moderate infusion-related toxicities were observed frequently at the first infusion, but all of them were reversible.

1.4 Gemcitabine

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis.

The activities of gemcitabine ± R were evaluated in vitro and in severe combined immunodeficiency disease (SCID)/human NHL xenograft models using two t(14;18)+, CD20+ follicular B-cell NHL cell lines; DoHH2, a transformed NHL line; and WSU-FSCCL cells, isolated from the pleural fluid of a patient with indolent NHL[15].

Gemcitabine was cytotoxic to DoHH2 and WSU-FSCCL cells in vitro, and the 50% inhibitory concentration (IC_{50}) was 2- to 3-fold lower in the presence of rituximab. Apoptosis was also enhanced in the presence of rituximab. Clearance of NHL cells from ascites in SCID mice was prolonged by gemcitabine + R when compared with either agent alone. Most importantly, survival of SCID mice bearing human NHL cells was significantly prolonged by the combination of gemcitabine + R. Activity was also demonstrated in a second model, using a transformed human B-cell lymphoma.

Gemcitabine has been evaluated in multiple trials in the relapsed/refractory lymphoma population[16]. It is well tolerated and has demonstrated antitumor activity in patients who have failed conventional regimens. No cross-resistance with other nucleoside analogues has been reported.

A summary of patient populations and their responses in several published studies of gemcitabine + R is provided in Table--4.

Table--4
Chemoimmunotherapy Studies with Gemcitabine and/or Rituximab

Reference	Regimen	Patient Population	Response	AEs
Bernell[17]	Gemcitabine monotherapy	N = 3 r/r high grade NHL	1 CR, 1 PR and 1 SD	Two AEs of grade 4 thrombocytopenia
Savage[18]	Gemcitabine monotherapy	N = 15 r/r patients 14 NHL, 6 DLBCL, 1 Hodgkin disease	1 CR (7.6%) in Hodgkin disease patient, 3 PR and 3SD	33% Grade 3/4 leukopenia; 60% thrombocytopenia; 6.7% anemia
Fossåi[19]	Gemcitabine monotherapy	N = 31 (65% DLBCL)	19% ORR (all PR patients)	11% anemia, 9% neutropenia, 22% thrombocytopenia
Wegner[20]	Rituximab and gemcitabine	N = 7 (5 DLBCL) Elderly patients not eligible for transplant	2 CR (1 in DLBCL). 20% CR in DLBCL and 3 PR (all DLBCL); ORR= 71%	Grade 3/4 leukocytopenia in 4 patients; 1 febrile neutropenia
Coffier[13]	Rituximab	N = 54; 30 DLBCL; 17% untreated	CR 9%, PR 22% ORR 31%	Infusion toxicity
Rothe[21]	Rituximab monotherapy	21 r/r NHL (16/21 resistant to conventional therapy and ineligible for aSCT)	CR 4.8%, PR 33.3% SD 19%, ORR 38.1% refractory pts ORR 43%	Infusion reactions
Palacios[22]	Rituximab-chemo or rituximab monotherapy	N = 36 (25 r/r/ DLBCL, all with prior R-chemo)	53% ORR 38% CR 15% PR	

Abbreviations:
aSCT = autologous stem cell transplant
DLBCL = diffuse large B-cell lymphoma
PR = partial response
RR = response rate
chemo = chemotherapy
NHL = non-Hodgkin lymphoma
pts = patients
r/r = relapsed/refractory.
CR = complete response
ORR = overall response rate, or CR + PR
R-chemo = rituximab chemotherapy

1.5 Combination Chemoimmunotherapy

Currently there is no established standard of care for the treatment of patients with relapsed/refractory DLBCL who are not candidates for SCT. Patients may be ineligible for transplant due to failure to respond to a standard salvage regimen, advanced age, toxicity from prior therapies, and serious comorbidities. For these patients, current National Comprehensive Cancer Network NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[23] recommend a clinical study or single-agent, doublet, or multi-agent regimens, some containing gemcitabine and/or rituximab.

As single agents, gemcitabine with an approximately 20% ORR, and rituximab with approximately a 30% ORR, have demonstrable activity against DLBCL. As these two drugs do not share overlapping toxicities, they have been used in combination.

1.5.1 Rationale for Pixantrone + R Combination

The combination of pixantrone + R was compared with rituximab alone in a small randomized trial in patients with relapsed follicular NHL who were rituximab naïve (AZA302). The combination was well tolerated and was associated with a significantly higher response rate and progression-free survival than rituximab alone. Although single-agent rituximab has only modest activity in patients with aggressive NHL who have had prior rituximab therapy, even when administered as radioimmuno-therapy[24], it is

likely to have additive or synergistic activity with an active agent such as pixantrone or gemcitabine in a combination setting. Since there is minimal overlapping toxicity between cytotoxic agents such as pixantrone or gemcitabine, the potential benefit of added efficacy for this combination outweighs the risks of combining these agents in a setting for which there is no standard therapy.

Pixantrone is highly effective, with tolerable toxicity, in patients with relapsed and refractory aggressive B cell lymphoma when administered on Days 1, 8, and 15 of a 28-day cycle. Weekly dosing of chemotherapeutic agents such as paclitaxel, docetaxel, and doxorubicin decreases toxicity compared with every-3-week dosing without compromising efficacy. Therefore, this schedule was chosen for development of pixantrone as monotherapy in patients with advanced disease following Phase 1 studies using weekly (Days 1, 8, and 15 of a 28-day cycle) or every-3-week schedules. Pixantrone on a weekly schedule had substantial activity in late-stage lymphoma patients, with an acceptable toxicity profile. At the maximum tolerated dose (MTD) of pixantrone, 50 mg/m^2 (equivalent to 85 mg/m^2 pixantrone dimaleate), this schedule resulted in a dose intensity of 37.5 mg/m^2/week. Although it is possible to achieve similar dose intensity on an every-3-week schedule at 104 mg/m^2 with pixantrone, as this dosing regimen was not studied in the relevant patient population as monotherapy, there is limited evidence for safety or efficacy.

Rituximab does not affect metabolism or clearance of small-molecule chemotherapeutic agents and enhances the activity of other anti-B-cell NHL therapeutics. Pixantrone has been used with rituximab on an every-3-week schedule in less heavily pretreated patients with indolent lymphoma, in combination studies on an every-3-week schedule with cyclophosphamide, vincristine, and prednisone, and on an every-4-week schedule with fludarabine and dexamethasone. In each case, efficacy was demonstrated. Because dose intensity is comparable on the weekly and every-3-week schedules, the sponsor believes it is appropriate to use the current schedule, in which both safety and efficacy have been demonstrated in a similar patient population.

1.5.1.1 Potential for Drug-Drug Pharmacokinetics Interactions

Pixantrone is excreted predominantly unchanged by the liver, whereas rituximab is a humanized monoclonal antibody with no known effects on hepatic excretory function. The likelihood of a pharmacokinetic (PK) interaction is extremely low. No unexpected toxicity was observed with the combination of pixantrone + R in a combination study (AZA302).

1.5.2 Rationale for Gemcitabine + R Combination

There are a small number of potentially active drugs not previously employed for patients as third-line therapy for DLBCL. Most patients have been exposed to CHOP-R, and in second line they likely received treatment with a platinate, etoposide, and/or cytarabine, as well as additional alkylating agent therapy. There is no standard of care regimen beyond second-line therapy; potentially active drugs available include gemcitabine, lenalidomide, and bendamustine. Gemcitabine has activity as a single agent[19], and in preclinical studies in lymphoma models demonstrated synergy with rituximab, as described in Section 1.4.

Gemcitabine + R has been suggested as a reasonable therapeutic option in patients with relapsed NHL ineligible for SCT. A study by Wenger et al[20] showed a 72% response rate for the combination of gemcitabine + R in a very limited number of patients. In relapsed/refractory DLBCL patients, the CR rate was 20%. This response rate aligns with rates of 20% to 50% reported with other regimens. Significant variability in the result of these studies can be attributed to small patient numbers, varying exposure to prior rituximab, varying lines of therapy, and some variations in disease subtypes (eg, grade 3 follicular lymphoma, DLBCL, and mantle cell lymphoma).

Although the numbers are limited, in a study by Palacios[22], patients who received an aggressive regimen (R-ESAHP, R-ICE, and R-TT) had a CR rate of 22% and those treated with less-aggressive regimens (R-GEM-Ox, R-mono) had a CR rate of 45%, suggesting that more aggressive regimens do not necessarily lead to better responses. This appears to support the argument that using the least toxic regimen may be most appropriate, and suggests that early treatment with rituximab does not preclude reuse in the salvage setting as patients continued to respond.

Gemcitabine + R combination therapy was evaluated in a small study of elderly patients with high-grade B-cell lymphoma who had relapsed after CHOP therapy, or were medically unfit to tolerate CHOP as first-line therapy[20]. Seven patients were treated with gemcitabine 1000 mg/m^2/week × 3 q 28 days and rituximab 325 mg/m^2 weekly × 4 in the first cycle and on Day 1 of all subsequent cycles. A median of 4 cycles was delivered. Major toxicities were hematologic; the estimated median time to tumor progression was 12 months. R-gemcitabine has been suggested as a reasonable therapeutic option in patients with relapsed NHL who are ineligible for SCT[16].

1.5.2.1 Potential for Drug-Drug Pharmacokinetics Interactions

Gemcitabine is excreted almost entirely in the urine as an inactive metabolite. Rituximab is a humanized monoclonal antibody with a long half-life that has an important impact on the metabolism of other drugs. There is broad clinical experience with co-administration of gemcitabine and rituximab in combination with oxaliplatin (R-GEMOX) as treatment for DLBCL[25]. The likelihood of a clinically important PK interaction is extremely low.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy (as measured by progression-free survival [PFS]) of pixantrone + R compared with 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).

- 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)

Patients must have received at least one rituximab-containing multi-agent regimen and must have had no progression for at least 12 weeks after the last dose of a treatment regimen (see Section 3.4 for details).

Patients ineligible for SCT include those who:

- Relapsed after previous SCT
- Did not respond to a standard salvage regimen
- Did not mobilize an adequate number of stem cells for SCT
- Are unsuitable for SCT due to other medical conditions or age
- Do not wish to undergo SCT
- Have financial issues precluding SCT
- Are considered by the investigator as unsuitable for SCT for any other reason

2.2 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

2.3 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 an SCT after study treatment

Pharmacokinetics Sub-Study Objective
(participating sites refer to Section 12 Addendum: Pharmacokinetics Sub-Study)

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

3 Investigational Plan

3.1 Overall Study Design

This is a randomized, active-controlled, multicenter, phase 3 study evaluating the efficacy of pixantrone + R versus gemcitabine + R 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 currently ineligible for high-dose (myeloablative) chemotherapy and SCT and who relapsed after at least 1 chemotherapy regimen.

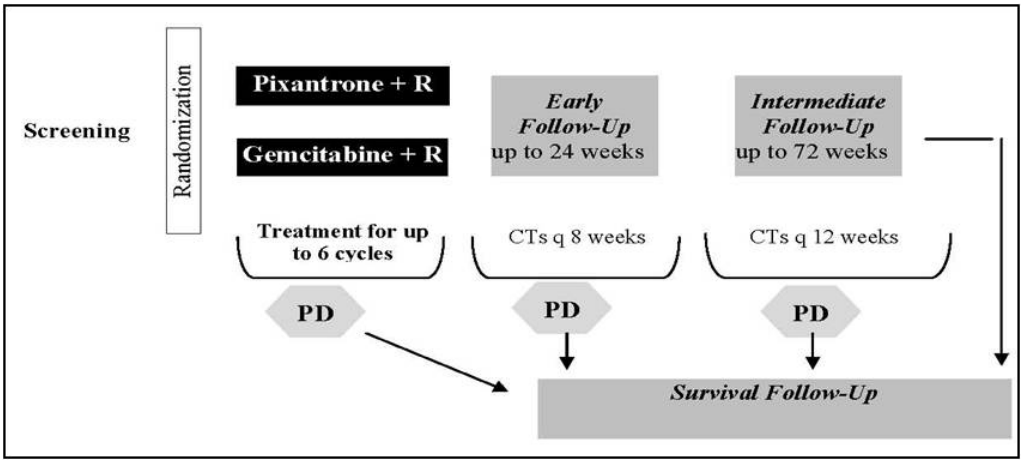
- Patients with de novo DLBCL must have received 1-3 prior regimens for DLBCL
- Patients with follicular grade 3 lymphoma must have received 1-3 prior regimens for follicular lymphoma (any grade)
- Patients with DLBCL transformed from indolent lymphoma must have received 1-4 prior regimens for NHL (any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

The study will be conducted in North America and Europe.

Treatment assignment will be known to investigators, site personnel, and patients, but the sponsor (except as defined in the PIX306 treatment blinding plan) will remain blinded during the study.

This study includes screening, treatment, and follow-up periods (Figure--3). 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--3
Study Flow Chart



Abbreviations:

CT = computed tomography Q 8 = every 8 R = rituximab.

PD = progressive disease per Modified IWG criteria or initiation of subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy

Patients who must discontinue pixantrone or gemcitabine due to toxicity may remain on rituximab every 28 days for up to a total of 6 cycles of study treatment. Patients who must discontinue rituximab due to toxicity may remain on gemcitabine or pixantrone for up to a total of 6 cycles of study treatment.

Disease response will be assessed (Table--1 and Table--2) by CT or MRI at baseline, every 8 weeks ± 1 week during the treatment period and during the Early Follow-up period, then every 12 weeks ± 2 weeks during the Intermediate Follow-up period. If an assessment is done off schedule, the next assessment should be calibrated as closely as possible back to the original schedule starting at Day 1 Cycle 1. Patients with a response (CR or PR) or stable disease (SD) and who the investigator believes are deriving clinical benefit at the time of each assessment will be allowed to continue treatment up to a maximum of 6 cycles. Therapy will be discontinued for progressive disease per Modified IWG criteria, patient refusal to continue, or pregnancy. Therapy may be discontinued for toxicity precluding further treatment, intercurrent illness, or Progressive Disease Due to Symptomatic Deterioration (patients unable to continue study treatment due to progressing lymphoma that does not meet the Modified IWG 2007 Revised Response Criteria for Malignant Lymphoma).

3.1.1 Participation in Treatment and Follow-up Periods

Patients may withdraw consent from participation in any phase of the study. Patients may withdraw consent for treatment or withdraw consent for treatment and study procedures. However, unless they have signed a separate written withdrawal of consent, all randomized patients will be followed for survival and safety, as described below.

Randomized patients who complete or discontinue study treatment for any reason, other than progressive disease per Modified IWG criteria, will participate in the follow-up periods, as described below.

At the time patients experience progressive disease per Modified IWG criteria during treatment or during Early or Intermediate Follow-up, begin subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, or withdraw consent for study procedures, they will enter the Survival Follow-up Period.

For randomized patients, study-drug related AEs and cardiac AEs ≥ grade 3, including LVEF declines, are collected and followed until resolution, until no further improvement is expected, or until EOS, whichever occurs first. AEs not related to study drug and cardiac AEs ≤ grade 2 are collected and followed for 30 days after the last dose of study drug, until no further improvement is expected, or until the patient begins a subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, whichever occurs first.

All time points for CT/MRI disease assessment are calculated from Day 1 of Cycle 1 (Table--1 and Table--2). In the case of CT/MRI imaging done outside the calendar schedule (unscheduled), consult with Medical Monitor for appropriate scheduling of the next CT/MRI.

- ***End of Treatment (EOT)*** is defined as the date of the end-of-treatment visit. The EOT visit occurs at 4 to 7 weeks after last study drug dose, inclusive, or before subsequent systemic anticancer therapy, whichever occurs first. Note that rituximab given as maintenance therapy is not allowed prior to the EOT visit per protocol window, but even if rituximab is given, EOT procedures will be obtained per this window. In the unanticipated event that a randomized patient receives no study drug, no EOT procedures are required, and the patient would continue per protocol Section 3.8.1.4.
- ***Early Follow-up***: After treatment discontinuation or completion, patients will enter the 24-week Early Follow-up Period. CT/MRI disease response, survival status, details of subsequent systemic anticancer therapy, including rituximab given as maintenance therapy, and safety will be evaluated every 8 weeks ± 1 week.

- ***Intermediate Follow-up***: After completing the 24-week Early Follow-up Period, patients will enter an additional 72-week Follow-up Period, in which CT/MRI disease response (every 12 weeks ± 2 weeks), survival status, details of subsequent systemic anticancer therapy, including rituximab given as maintenance therapy, and safety will be evaluated.
- ***Survival Follow-up:*** All patients will be monitored for survival status every 12 weeks ± 2 weeks until the end of the study. For any patient who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. Informed consent to obtain these data will be obtained from patients at the time of enrollment.
- ***End of Study (EOS):*** is defined as the date when the required OS events have occurred or the study is terminated.

At the time that 195 PFS events per IRC are reached, patients will be at various stages of the study, including those who have been consented, have been randomized, have started treatment, or are in follow-up. All patients who have consented for enrollment prior to this time will continue on the study per protocol, until EOT, whereupon they will enter Survival Follow-up. All patients in Early or Intermediate Follow-up at this time will subsequently only be followed according to the Survival Follow-up schedule.

The sample size for this trial is based on the number of PFS events per the IRC. Approximately 320 patients are planned to be randomized in a 1:1 ratio to reach the required number of PFS events. The randomization will be stratified by International Prognostic Index (IPI) score (0-2 vs ≥ 3), prior lines of therapy for DLBCL or follicular grade 3 lymphoma (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).

Enrollment will take place in North America and Europe. The expected duration of enrollment is approximately 80 months.

3.1.2 Study Conduct

Regardless of whether serum samples, radiologic material, and other patient data are sent to a central laboratory or independent review panel for study purposes, treatment and eligibility decisions must be made by the investigator, based on his or her clinical assessment of the patient and interpretation of local labs, radiology assessments, and other tests.

Local laboratory tests are required, as needed, for time-limited evaluation windows, per protocol, and to support urgent clinical decisions.

3.1.2.1 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) will meet throughout the study, approximately every 6 months or after 30 additional patients are randomized, whichever occurs first. The first meeting will take place after 25 patients are randomized.

The IDMC's responsibilities include:

- Minimize the exposure of patients to an unsafe therapy or dose.
- Evaluate the toxicity and appropriateness of doses in both arms in order to make recommendations for changes in study if appropriate.
- Advise on the need for dose adjustments because of safety issues.

- Make any other safety associated assessments, including endorsing continuation of the study per protocol.
- Be in charge of the interim OS analyses and release the unblinded OS results to the sponsor after all patients have completed study treatment.

Details on the membership, responsibilities, and working procedures of the IDMC are described in the IDMC Charter, which is provided as a separate document in the study file.

3.1.2.2 Study Steering Committee

The Study Steering Committee (SSC) will be composed of external medical experts, CTI representatives, and selected investigators participating in this study. These investigators will represent all the study investigators.

The SSC will provide advice on modifications as circumstances require, in particular:

- Changes in study design
- Changes in any aspects of study conduct
- One or more SSC representatives may attend the open sessions of the IDMC meetings and be available to clarify issues. The Open Session Minutes of the IDMC meetings, without any treatment arm comparisons, will be shared with the SSC, as requested.

Details on the membership and responsibilities of the SSC are described in the charter, which is part of the study file.

3.1.2.3 Independent Radiology Committee

An Independent Radiology Committee (IRC) will determine the disease responses for all randomized patients according to the modified IWG 2007 Revised Response Criteria detailed in Table--11. The IRC will be blinded to site identifiers, patient treatment arm, and investigator's designation of target lesions.

Investigative sites will be provided with a Site Procedure Manual describing how the imaging portion of the study is to be conducted. The manual will include requirements for the diagnostic evaluations, patient assessment objectives, patient preparation for examination, image media requirements and imaging procedures. The manual will also provide instructions for transferring imaging data for the IRC review.

Images will be read by two radiologists. Any disagreements in the radiological response assessment will be adjudicated by a third radiologist as described in the Image Charter.

The final disease response assessment determined at each imaging evaluation will be determined by an independent oncologist and one of the radiologists who evaluate each patient's clinical, pathologic, and radiologic data.

Details of the IRC operation are described in the Image Charter, which is part of the study file.

3.1.2.4 Central Pathology Review

A central pathology review committee will evaluate biopsy specimens from all randomized patients to confirm the histologic diagnosis of DLBCL (de novo DLBCL, DLBCL transformed from indolent lymphoma) or follicular grade 3 lymphoma per World Health Organization (WHO) classification.

A Site Procedure Manual describing how the pathology portion of the study is to be conducted, including procedures and requirements for obtaining, preparing, processing, and sending biopsy material to the central pathology review committee, will be provided to all investigative sites.

Pathology tissues/images will be read by two pathologists. Disagreements in the disease confirmation will be adjudicated by a third pathologist, as described in the Pathology Charter.

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

The detailed operation and procedures of the central pathology review committee will be described in the Pathology Charter, which is part of the study file.

Bone marrow biopsies (with cores) obtained during the study will undergo local pathology review to confirm a CR.

3.2 Discussion of Study Design

The underlying research hypothesis for this study is that the combination of pixantrone + R is a more effective therapy than 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 SCT and who have relapsed after at least 1 prior chemotherapy regimen.

All patients must have received at least one multi-agent regimen containing rituximab.

In patients with DLBCL who have failed or are not eligible for curative therapy, no therapy has demonstrated improved survival, and thus, there is no standard of care. PIX301, the first randomized study performed in this setting and the predecessor to the current study, compared single-agent pixantrone to the physician's choice of other single-agent therapies in a total of 140 patients (70 per arm). This study demonstrated improvement in the CR/CRu rate, overall response rate, and PFS, for pixantrone compared with control.

3.2.1 Choice of Endpoints

Progression-free survival (PFS) is the primary endpoint, as it reflects the effect of therapy on tumor growth and can be assessed as a surrogate for OS. Unlike the survival endpoint, PFS is not confounded by subsequent systemic anticancer therapy and has been used as a measure of the clinical efficacy of therapy in similar settings. Overall survival (OS) is a secondary endpoint, as a standard endpoint used to measure clinical benefit.

3.2.2 Interim Analysis and OS Analysis

No interim analysis of the PFS primary endpoint is planned for this study. See Section 5 for a description of the OS analysis.

3.2.3 Choice of Dose and Schedule of Pixantrone

The drug is supplied in vials; each vial contains 29 mg pixantrone. (The dose of pixantrone is 50 mg/m^2.)

The choice of pixantrone dose (50 mg/m^2 on Days 1, 8, and 15 in 28-day cycles) is based on preclinical testing and clinical evaluation in phase 1 to 3 studies. The phase 1/2 studies (in which pixantrone doses were expressed in terms of the salt, pixantrone dimaleate) administered dose-dense monotherapy to heavily pretreated patients with lymphoid neoplasia or solid tumors. These studies defined a pixantrone dimaleate dose range of $\geq$ 56 mg/m^2 (with which no grade 3 toxicity was observed) and $\leq$ 112.5 mg/m^2 (with which 50% of patients had grade 3/4 neutropenia). Although some responses were noted at lower dose levels, in patients with relapsed or refractory lymphoma, 84 mg/m^2 pixantrone dimaleate (dose intensity 60.5 mg/m^2/week) was the lowest dose at which durable CRs were seen. This dose choice (which is equivalent to the present dose of 50 mg/m^2 of pixantrone) was confirmed in the phase 2 study, AZA II-01, in patients with relapsed aggressive NHL, and in the phase 3 study, PIX301. Overall, 109 patients have been treated on this dose and schedule.

3.3 Study Population

The target population is 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. All patients must have received a multi-agent regimen containing rituximab.

- 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)

Patients not eligible for SCT include those who:

- Relapsed after previous SCT
- Did not respond to a standard salvage regimen
- Did not mobilize an adequate number of stem cells for SCT
- Are unsuitable for SCT due to other medical conditions or age
- Do not wish to undergo SCT
- Have financial issues precluding SCT
- Are considered by the investigator as unsuitable for SCT for any other reason

The Investigator must ensure that only those patients who meet all of the inclusion (Section 3.3.1) and none of the exclusion (Section 3.3.2) criteria are allowed to enroll in the study. The Investigator should apply no additional criteria to determine patient eligibility.

3.3.1 Inclusion Criteria

The study's inclusion criteria include the following:

1. Signed Institutional Review Board or Institutional Ethics Committee-approved Informed Consent Form
2. Age ≥18 years old
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
4. Pathology and immunohistochemistry reports documenting the current histological diagnosis according to World Health Organization (WHO) classification must be reviewed by the sponsor or designee prior to randomization
5. Number of prior therapies allowed:
   a. Patients with de novo DLBCL must have received 1-3 prior regimens for DLBCL
   b. Patients with follicular grade 3 lymphoma must have received 1-3 prior regimens for follicular lymphoma (any grade)
   c. Patients with DLBCL transformed from indolent lymphoma must have received 1-4 prior regimens for NHL (any type)

   The salvage combination therapy used to achieve a response in preparation for possible SCT (eg, R-ICE, R-ESHAP or R-DHAP), along with the subsequent high-dose myeloablative therapy (eg, BEAM) and SCT, is counted as a single regimen.

   *Maintenance therapy with rituximab or similar agents, single-agent corticosteroids, and local radiation therapy are **not counted** as treatment regimens.*

6. Received a rituximab-containing multi-agent regimen (eg, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [R-CHOP]; rituximab, cyclophosphamide, vincristine, prednisone [R-CVP]; or bendamustine-R)

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
8. Not eligible for high-dose (myeloablative) chemotherapy and SCT. Patients not eligible for SCT include those who:
   a. Relapsed after previous SCT
   b. Did not respond to a standard salvage regimen
   c. Did not mobilize an adequate number of stem cells for SCT
   d. Are unsuitable for SCT due to other medical conditions or age
   e. Do not wish to undergo SCT
   f. Have financial issues precluding SCT
   g. Are considered by the investigator as unsuitable for SCT for any other reason
9. At least 28 days from completion of last NHL therapy to randomization
10. At least one bidimensionally measurable site of disease that has not been previously irradiated: nodal disease ≥ 1.5 cm in short axis or extranodal disease > 1.0 cm in short axis. Lesion must be PET positive if PET scan is obtained.
11. Slides confirming diagnosis of follicular grade 3 lymphoma or DLBCL available for independent histology review
12. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 (Section 8.2)
13. Life expectancy ≥ 12 weeks in investigator's judgment
14. Left ventricular ejection fraction (LVEF) ≥ 45% by echocardiogram and normal serum troponin T
15. Hemoglobin ≥ 8 g/dL (can be post-transfusion)
16. Platelet count ≥ 100×10^9/L; platelet count ≥ 75×10^9/L permitted if documented bone marrow involvement
17. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L; ANC ≥ 1.0×10^9/L permitted if documented bone marrow involvement
18. Serum bilirubin ≤ 1.5 × upper limit of normal (ULN); patients with proven Gilbert's syndrome and bilirubin ≤ 5 × ULN may be enrolled.
19. Aspartate aminotransferase (AST; also called serum glutamic-oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT; also called serum glutamic-pyruvic transaminase [SGPT]) ≤2 × ULN, or ≤ 5 × ULN if elevation is due to hepatic involvement by lymphoma
20. Serum creatinine ≤ 2 × ULN
21. All acute toxicities related to prior treatment recovered to grade ≤ 1, except alopecia
22. Willingness and ability to comply with the visit schedule and assessments required by the study protocol
23. Due to the long retention time of rituximab in B cell-depleted patients, both males and females must agree to use effective birth control. Women of childbearing potential (WOCBP) must use highly effective methods (defined as those resulting in a failure rate of < 1% per year when used consistently and correctly) for the duration of study treatment and for 12 months after last dose of study drug. The contraceptive methods that are considered highly effective are intrauterine devices and hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release).

3.3.2 Exclusion Criteria

The study's exclusion criteria include the following:

1. Any of the following as the only site(s) of disease: palpable lymph nodes not visible on imaging studies, skin lesions, or bone marrow involvement only
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 regimen
3. Prior treatment with a cumulative dose of doxorubicin or equivalent exceeding 450 mg/m² (see Section 8.5 for formula)
4. LVEF < 45% by echocardiogram
5. Active National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 3/4 infection
6. Major surgery ≤ 28 days prior to randomization
7. Known acute or chronic hepatitis B or hepatitis C virus infection
8. Known seropositivity for human immunodeficiency virus (HIV)
9. Current CNS involvement by lymphoma
    a. Any history or evidence of current leptomeningeal involvement by lymphoma is prohibited.
    b. Patients with prior localized CNS involvement who have been without recurrence for ≥ 12 months and currently have a negative head MRI may be eligible; please discuss with the Medical Monitor.
10. Any experimental therapy ≤ 28 days prior to randomization
11. Myocardial infarction within the past 6 months
12. New York Heart Association class III or IV heart disease (Section 0)
13. Other malignancy within the last 5 years. Exceptions are:
    a. Curatively treated basal cell/squamous cell skin cancer
    b. Carcinoma in situ of the cervix
    c. Superficial transitional cell bladder carcinoma
    d. In situ ductal carcinoma of the breast after complete resection
    e. Localized, resected and/or low-risk prostate cancer may be eligible; please discuss with the Medical Monitor
14. Any contraindication, known allergy, or hypersensitivity to any study drugs
15. Pregnant or lactating
16. Concomitant therapy with any anticancer agents, immunosuppressive agents, other investigational anticancer therapies. Low-dose corticosteroids for the treatment of non-cancer-related illnesses are permitted
17. Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study procedures or follow-up schedules
18. Severe and/or uncontrolled medical disease that could compromise participation in the study, or any medical or psychiatric condition that, in the opinion of the investigator, would make study drug administration hazardous or obscure the interpretation of data.

3.3.3 Completion and Discontinuation of Treatment

Patients who receive 6 cycles of pixantrone + R or gemcitabine + R are considered to have completed study treatment.

Patients who must discontinue pixantrone or gemcitabine due to toxicity may remain on rituximab for up to a total of 6 cycles of study treatment.

Patients who must discontinue rituximab due to toxicity may remain on gemcitabine or pixantrone for up to a total of 6 cycles of study treatment.

Study treatment may be discontinued before completion due to:

- Progressive disease per Modified IWG criteria
- Any clinical adverse event, laboratory abnormality, abnormal test result or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not the best interest of the patient
- Progressive Disease Due to Symptomatic Deterioration (patients unable to continue study treatment due to progressing lymphoma that does not meet the Modified IWG 2007 Revised Response Criteria for Malignant Lymphoma).
- Treatment refusal, including withdrawal of consent
- Protocol violation that would jeopardize patient safety
- Patient lost to follow-up
- Pregnancy

Patients who have progressive disease per Modified IWG criteria, begin subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, or withdraw consent for study procedures will enter the Survival Follow-up Period. Patients who complete study treatment, or discontinue study treatment for any other reason (including Progressive Disease Due to Symptomatic Deterioration), will participate in the Early and Intermediate Follow-up periods, as described in Section 3.8.1.4.

Patients may withdraw consent from participation in any phase of the study. Patients may withdraw consent for any of the following: treatment; treatment and study procedures; or treatment, study procedures, and survival follow-up. All randomized patients will be followed for survival and safety, as described in Section 3.8.1.4, unless patients have rendered a separate written withdrawal of consent for survival information.

For any patient who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. Informed consent to obtain these data will be obtained from patients at the time of enrollment.

At the time of the primary endpoint analysis when study recruitment is halted, patients will be at various stages of the study, including those who have been consented, have been randomized, have started treatment, or are in Follow-up. All patients who have consented for enrollment prior to this time will continue on the study per protocol, until EOT, whereupon they will enter Survival Follow-up. All patients in Early or Intermediate Follow-up at the time of primary endpoint analysis will subsequently only be followed according to the Survival Follow-up schedule.

3.4 Study Treatment

The investigational treatment in this trial is pixantrone in combination with rituximab (pixantrone + R). The control treatment is gemcitabine in combination with rituximab (gemcitabine + R).

It is recommended that rituximab be administered prior to the cytotoxic agent.

The dose (in mg) of pixantrone, gemcitabine, and/or rituximab to be administered will be determined by the patient's body surface area (BSA). The BSA should be determined using the institutional standard for BSA calculation.

The investigational drug is supplied in vials that each contain 29 mg pixantrone. (The dose of pixantrone is 50 mg/m^2.)

The pixantrone + R regimen (investigational therapy) is given in up to six 28-day cycles, consisting of rituximab 375 mg/m^2 IV on Day 1 and pixantrone 50 mg/m^2 IV on Days 1, 8, and 15 (Table--5).

The gemcitabine + R regimen (control therapy) is given in up to six 28-day cycles, consisting of rituximab 375 mg/m^2 IV on Day 1 and gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 (Table--5).

Table--5
Protocol PIX306 Treatment Regimens

Treatment Regimen		Dosing Schedule
Investigational Therapy	***Pixantrone + R*** Rituximab 375 mg/m^2 IV on Day 1 Pixantrone 50 mg/m^2 IV on Days 1, 8, and 15	Up to six 28-day cycles
Control Therapy	***Gemcitabine + R*** Rituximab 375 mg/m^2 IV on Day 1 Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15	Up to six 28-day cycles

Abbreviations:
IV = intravenous(ly) mg/m2 = milligrams per square meter R = rituximab.

3.4.1 Treatment Assignment

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. The randomization will be stratified by number of prior therapies for DLBCL or follicular grade 3 lymphoma (0-2 vs. ≥ 3), IPI score (0-2, ≥ 3; see Section 8.1), 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).

3.4.2 Treatment Blinding

Treatment assignment will be known to investigators, site personnel and patients, but the sponsor (except as defined in the PIX306 treatment blinding plan) will remain blinded during the study until the core database lock. After the core database lock, the sponsor will remain blinded to OS datasets (although death contributing to the PFS events in the core locked database will be unblinded) until after the final OS analysis. Sponsor will have access to the unblinded OS interim results via IDMC once last patient completes the study treatment.

3.4.3 Treatment Compliance

The investigator or designee should administer study drugs exactly as described. The study medication used, dosages administered, dates, and start and stop times of administration must be recorded as described in the study manual. All treatment visits should comply with the schedule described in Section 3.8, Table--1, and Table--2 of this protocol.

3.4.4 Rituximab Preparation, Storage, and Handling

The current rituximab package insert should be consulted for specific precautions and warnings[26]. Rituximab should be administered at the Investigator's discretion and according to current institutional standards.

Rituximab is a sterile, clear, colorless, preservative-free, liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. Rituximab vials (100 mg [NDC 50242-051-21] and 500 mg [NDC 50242-53-06]) are stable at 2°C to 8°C (36°F to 46°F). Vials should not be used beyond the expiration date stamped on the carton. Rituximab vials should be protected from direct sunlight and should not be frozen or shaken. Rituximab solutions for infusion may be stored at 2°C to 8°C (36°F to 46°F) for 24 hours. Rituximab solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since diluted rituximab solutions contain no preservative, diluted solutions should be refrigerated at 2°C to 8°C (36°F to 46°F). No incompatibilities have been observed between rituximab and polyvinylchloride or polyethylene bags.

The rituximab solution for infusion should be prepared using appropriate aseptic technique. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, and the vial should not be used if particulates or discoloration are observed. The necessary amount of rituximab is withdrawn and diluted to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP or local pharmacopeial equivalent, or 5% Dextrose in water, USP or local pharmacopeial equivalent, and then the bag is gently inverted to mix the solution. The solution should not be mixed or diluted with other drugs. Any unused portion of solution left in the vial is to be discarded.

3.4.5 Pixantrone Handling, Preparation, Administration, and Storage

3.4.5.1 Handling of Pixantrone

Pixantrone is a cytotoxic agent. All work practices must be designed to reduce human exposure to pixantrone. Avoid inhalation, ingestion, contact with the eyes, and contact with skin. Avoid prolonged or repeated exposure. Pixantrone should be handled only by qualified individuals trained in laboratory procedures and familiar with the potential hazards of handling chemicals.

Equipment and supplies used for pixantrone preparation and administration, such as used vials, needles, syringes, and IV bags, should be handled and disposed of as hazardous waste, according to all applicable laws and regulations.

3.4.5.2 Pixantrone Preparation and Administration

The investigational drug is supplied in a vial containing 50 mg pixantrone dimaleate, which is equivalent to 29 mg pixantrone.

Infusion solutions should be prepared and transferred using aseptic technique (see Section 3.4.5.1 on pixantrone handling precautions). Reconstitution to a solution containing pixantrone 5.8 mg/mL is done by adding 5 mL sterile 0.9% Sodium Chloride for Injection, USP/Ph. Eur. or equivalent, aseptically withdrawn from a 250 mL infusion bag. The solution should be agitated for a minimum of 60 seconds to ensure complete dissolution. The color of the reconstituted solution will be dark blue. The reconstituted vial must be used within 24 hours after reconstitution.

The required volume corresponding to the prescribed dose per square meter of BSA is to be aseptically withdrawn and injected back into the 250 mL infusion bag containing normal saline for IV injection (0.9% NaCl, USP, or local pharmacopeial equivalent). The final pixantrone concentration will be < 1 mg/mL (0.4 mg/mL pixantrone for a patient with a BSA of 2.0 m^2).

The diluted solution must be administered as a slow IV infusion over a period of 1 hour (± 10 minutes). To ensure exact drug administration, a chronoinfusor should be used. Pixantrone is compatible with the diluent contained in polyethylene infusion bags. Polyethersulfone 0.2-micron pore-size inline filters should be used.

3.4.5.3 Storage of Pixantrone

Unopened, non-reconstituted vials of pixantrone are to be stored cold at 2°C to 8°C (36°F to 46°F) and protected from light. Diluted or reconstituted pixantrone vials should be protected from freezing.

All temperature excursions beyond 2°C to 8°C (36°F to 46°F) should be documented. The following temperature excursions must be reported to CTI before the vial is used:

- Any excursions above 8°C (46°F) for more than 24 hours
- Any excursions above 25°C (77°F) for any amount of time
- Any excursions below 0°C (32°F) for any amount of time

Contact CTI BioPharma Corp. for information on additional allowable temperature excursions.

Lot/batch numbers within a single patient's dose should not be mixed. Mixing of lot/batch numbers is allowed within a patient's treatment cycle.

Pixantrone contains no preservatives, and each vial is intended for single use. Once prepared, the diluted solution should be used as soon as possible, and in any case, it should be used within 24 hours of reconstitution (including the 1-hour infusion time).

The diluted solution is stable for up to 24 hours at room temperature (< 25°C/77°F) and under normal light exposure while in polyethylene (PE) standard infusion bags. Stability of reconstituted pixantrone solution stored above room temperature has not been evaluated.

3.4.6 Gemcitabine Preparation, Storage, Handling, and Administration

The current gemcitabine package insert must be consulted for specific precautions and warnings[27].

Gemcitabine for injection, USP or local pharmacopeial equivalent, is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g gemcitabine.

The half-life of gemcitabine is influenced by the length of the infusion, and toxicity appears to be increased if gemcitabine is administered more frequently than once weekly, or with infusions longer than 60 minutes.

The recommended diluent for reconstitution of gemcitabine is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution and should be avoided.

To reconstitute, add 5 mL 0.9% Sodium Chloride Injection to a 200 mg vial of gemcitabine or 25 mL 0.9% Sodium Chloride Injection to a1 g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL, which accounts for the displacement volume of the lyophilized powder (0.26 mL for the 200 mg vial, or 1.3 mL for the 1 g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of gemcitabine may be administered as prepared, or it may be further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted gemcitabine is a clear, colorless to light-straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the resulting solution is in the range of pH 2.7 to 3.3. The solution should be visually inspected for particulate matter and discoloration prior to administration, whenever solution or container permits. If particulate matter or discoloration is found, do not administer the drug.

When prepared as directed, gemcitabine solutions are stable for 24 hours at controlled room temperature, 20°C to 25°C (68°F to 77°F). Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur. Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature, 20°C to 25°C (68°F to 77°F), which allows for excursions between 15°C and 30°C (59°F to 86°F).

No incompatibilities have been observed with infusion bottles or polyvinylchloride bags and administration sets.

Caution should be exercised in handling and preparing gemcitabine solutions. The use of gloves is recommended. If gemcitabine solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water, or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, 2 of 3 rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

3.5 Pixantrone Drug Accountability and Disposal

Drug accountability records will be accurately maintained at the study site. The pharmacist or designee must record patient and drug information, as described in the study manual.

The study drug accountability log must be available for inspection by CTI or its designee and is subject to regulatory inspection at any time. The investigator must agree not to destroy or distribute any used or unused drug supplies, unless otherwise directed by CTI or its designee.

At the completion of the study, all unused drugs will be destroyed at the site or returned according to procedures in the study manual.

Investigational products should be stored in a secure area according to local regulations. It is the Investigator’s responsibility to ensure that investigational products are dispensed only to study patients.

Investigational products must be dispensed only from official study sites by authorized personnel according to local regulations.

3.6 Study Drug Precautions, Dose Adjustments, and Delays

Unless otherwise specified, dose modification and delay rules in this section apply to both study arms.

Dose delays may require that both local and central labs are redrawn. Treatment decisions are based on local results. Local labs are required, as needed, for time-limited evaluation windows, per protocol, and to support urgent clinical decisions.

1. There must be at least 7 days between doses of any study medication.
2. There must be at least 10 days between Day 15 of one cycle and Day 1 of the subsequent cycle.
3. Three (3) days is the maximum visit delay allowable for nonmedical reasons (eg, scheduling problems, holidays) during a 28-day treatment cycle. Visit delays > 3 days for nonmedical reasons may be permitted with prior Medical Monitor approval.
4. If Day 1 study drugs of any cycle are delayed ≥ 14 days due to gemcitabine or pixantrone-related toxicity, that drug must be discontinued.
5. If ≥ 28 days have elapsed since the last gemcitabine or pixantrone dose, regardless of the reason, that drug must be discontinued.
6. Only 1 pixantrone dose reduction is permitted for each patient.
7. Once a patient has required a pixantrone dose reduction, the dose remains reduced for all subsequent doses. No re-escalation of pixantrone is permitted.
8. Patients who must discontinue pixantrone or gemcitabine due to toxicity may remain on rituximab every 28 days for up to a total of 6 cycles of study treatment.
9. Patients who must discontinue rituximab due to toxicity may remain on pixantrone or gemcitabine for up to a total of 6 cycles of study treatment.
10. LVEF should be assessed ≤ 7 days before the expected Day 1 of Cycles 3 and 5. Serum troponin T is to be drawn before Cycles 3 and 5 and sent to the central laboratory for batched processing. Echocardiogram and troponin T assessments need not be repeated if a dose is delayed for reasons other than abnormal LVEF.

Photosensitivity is a potential clinical risk, based on in vitro and in vivo nonclinical data (Section 1.2.2). No confirmed cases have been reported in the clinical trial program.

As a precaution, patients should be advised to follow sun-protection strategies, including wearing sun-protective clothing and using sunscreen. Since most medicinal product-induced photosensitivity reactions are caused by wavelengths within the UV-A range, use of a sunscreen that strongly absorbs UV-A is recommended.

3.6.1 Pixantrone Dose Modifications for Hematologic Toxicity

Pixantrone treatment modifications for decreased ANC, neutropenic infection, and decreased platelet counts are shown in Table--6 and Table--7.

Table--6 Pixantrone Dose Modifications for Reduced ANC and Infection	
ANC $\geq 1.0 \times 10^9$/L	No dose change or modification.
ANC ≥ 0.5 to $< 1.0 \times 10^9$/L	▪ On Day 1, delay both drugs up to 14 days until recovery to $\geq 1.0 \times 10^9$/L. ▪ On Day 8 or 15, skip dose.
ANC $< 0.5 \times 10^9$/L	▪ On Day 1, delay both drugs up to 14 days until recovery to $\geq 1.0 \times 10^9$/L. ▪ On Day 8 or 15, skip dose. ▪ When ANC $\geq 1.0 \times 10^9$/L, resume rituximab and restart pixantrone at 41 mg/m^2. No dose reduction is required for patients with bone marrow involvement.
Febrile neutropenia or grade 3/4 neutropenic infection documented after the last administered dose.	Pixantrone dose must be reduced to 41 mg/m^2 for all subsequent doses.

Table--7 Pixantrone Dose Modifications for Platelet Counts	
Platelet count $\geq 50 \times 10^9$/L	No dose change or modification.
Platelet count ≥ 25 to $< 50 \times 10^9$/L with no bleeding	▪ On Day 1, delay both drugs up to 14 days until recovery to $\geq 50 \times 10^9$/L. ▪ On Day 8 or 15, skip dose.
Platelet count $< 25 \times 10^9$/L **or** Bleeding, regardless of platelet levels, if platelet transfusions are readily available	▪ On Day 1, delay both drugs up to 14 days. ▪ On Day 8 or 15, skip dose. ▪ When recovery to $\geq 50 \times 10^9$/L, resume rituximab and restart pixantrone at 41 mg/m^2. No dose reduction is required if there is bone marrow involvement.

3.6.2 Gemcitabine Dose Modifications for Hematologic Toxicity

All patients should receive the full gemcitabine + R dose for Cycle 1 Day 1. Thereafter, gemcitabine dose modifications for hematologic toxicity should follow the guidelines in Table--8.

At the investigator's discretion, a gemcitabine dose can be skipped or decreased. At the investigator's discretion, gemcitabine may be re-escalated after a dose reduction when blood counts have sufficiently recovered.

Table--8 Gemcitabine Dose Modifications for ANC and Platelet Counts	
Day 8 or 15 of Cycle 1 and Day 1, 8, or 15 of Cycles 2-6	**Dose/Schedule**
ANC $\geq 1.0 \times 10^9$/L *AND* platelet count $\geq 100 \times 10^9$/L If bone marrow involvement, platelet count must be $\geq 75 \times 10^9$/L	100% of full dose
ANC 0. 5 to 0.99×10^9/L *OR* platelet count 50 to 99×10^9/L	Reduce gemcitabine dose by 25% (to 750 mg/m^2) until ANC recovery to $\geq 1.0 \times 10^9$/L *AND* platelet count $\geq 100 \times 10^9$/L (If bone marrow involvement, platelet count must recover to 75×10^9/L; then dose may be re-escalated to full dose, at the investigator's discretion.) A second dose reduction (to 500 mg/m^2) is allowed, at the investigator's discretion, if ANC does not recover to $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L. If ANC and platelet count do recover, the dose may be re-escalated, at the investigator's discretion.
ANC $< 0.50 \times 10^9$/L *OR* platelet count $< 50 \times 10^9$/L	Delay gemcitabine treatment, until recovery to ANC $\geq 1.0 \times 10^9$/L ***and*** platelet count $\geq 100 \times 10^9$/L (If bone marrow involvement, platelet count must recover to $\geq 75 \times 10^9$/L.) If no recovery within 14 days, patient must be discontinued from gemcitabine and entered into Follow-up or continued on rituximab alone.

3.6.3 Gemcitabine and Pixantrone Dose Modifications for Nonhematologic Toxicity

1. Unless otherwise specified, dose modification and delay rules in this section apply to both study arms.
2. Grade 1 study drug-related nonhematologic toxicities require no change in treatment.
3. For grade 2 or 1-grade increases from baseline study drug-related nonhaematologic toxicities, treatment with that study drug must be delayed until recovery to grade 1 or baseline at the discretion of the investigator, with retreatment at the same dose level.
4. Any grade 3 or higher nonhaematologic AE related to a study drug requires, at the discretion of the investigator, either discontinuation of treatment or delay of treatment with a 1-level dose reduction (Table--9), until recovery to grade 1 or less, or to baseline. Recurrence of grade 3/4 toxicity at the reduced dose requires that the patient be discontinued from that agent.

The dose levels for pixantrone and gemcitabine are as shown in Table--9.

Table--9
Pixantrone and Gemcitabine Dose Levels

Drug	Dose Level	Dose (mg/m^2)
Pixantrone	1	50
	2	41
Gemcitabine	1	1,000
	2	750
	3	500

Exceptions include a 1-grade increase from baseline, alopecia, grade 3 nausea and vomiting if controlled by supportive measures, central line-related thrombosis, and LVEF declines for pixantrone patients (see below). Gemcitabine, but not pixantrone, can be re-escalated, at the discretion of the investigator, after the AE recovers to grade 1 or less.

5. Patients on pixantrone who have an absolute decrease in LVEF from baseline values of ≥ 16% or an absolute LVEF decrease of ≥ 10% to below institutional limits of normal should have treatment held and the LVEF confirmed with a repeat echocardiogram in 1 to 2 weeks. If the repeat LVEF is within the institutional limits of normal and the absolute decline is ≤ 15% from baseline, resume study drugs. If LVEF is still abnormal, the patient must be discontinued from pixantrone treatment, but may, at the investigator's discretion, continue rituximab treatment for up to a total of 6 cycles.
6. Pixantrone patients who develop congestive heart failure (CHF) during study treatment must be discontinued from pixantrone. The patient may, at the investigator's discretion, continue rituximab treatment for up to a total of 6 cycles.

3.6.4 Rituximab Precautions and Discontinuation

The current rituximab package insert must be consulted for full prescribing information.

The most common adverse reactions from rituximab (incidence ≥25%) observed in clinical trials were infusion reactions, fever, neutropenia, lymphopenia, chills, infection, and asthenia. The incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion. These infusion reactions typically resolved with slowing or interruption of the infusion and with supportive care. The most frequent grade 3 or 4 adverse reaction observed in NHL was cytopenia, including lymphopenia.

Any grade 3/4 adverse reactions to rituximab may require (at the discretion of the investigator and the institutional standard) discontinuation of rituximab, but the patient may, at the investigator's discretion, remain on study and continue to receive the other study drug (pixantrone or gemcitabine) for up to a total of 6 cycles.

3.6.4.1 Cytokine Release Syndrome

Patients should be monitored for cytokine release syndrome for at least 2 hours following the first infusion of rituximab. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients should then be evaluated for evidence of tumor lysis syndrome (TLS), including appropriate laboratory tests and, for

pulmonary infiltration, with a chest x-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms and normalization of laboratory values and chest x-ray findings. At that time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis.

Patients with a high tumor burden, or with a high number (25×10^9/L) of circulating malignant cells, may be at higher risk of especially severe cytokine release syndrome, and should be treated with extreme caution. These patients should be very closely monitored throughout the first infusion.

Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. The syndrome frequently manifests itself within 1 or 2 hours of initiating the first infusion. Cytokine release syndrome may be associated with some features of TLS, such as hyperuricemia, hyperkalemia, hypocalcaemia, hyperphosphatemia, acute renal failure, and elevated lactate dehydrogenase (LDH), and may be associated with acute respiratory failure and death. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest x-ray.

Patients with a history of pulmonary insufficiency, or those with pulmonary tumor infiltration, may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until TLS and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.

3.6.4.2 Hypersensitivity Reactions and Anaphylaxis

In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting an infusion with rituximab. Infusion-related adverse reactions are usually reversible, with interruption of rituximab infusion and administration of an antipyretic, an antihistaminic, and, occasionally, oxygen, IV saline or bronchodilators, and glucocorticoids. Medicinal products for the treatment of hypersensitivity reactions, such as epinephrine (adrenaline), antihistamines, and glucocorticoids should be available for immediate use during administration of rituximab in the event of an allergic reaction.

Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome.

3.6.4.3 Progressive Multifocal Leukoencephalopathy

Use of rituximab may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that suggest PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (eg, cognitive, neurological, or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since their partners or caregivers may notice symptoms that the patient is unaware of.

If a patient develops PML, the dosing of rituximab must be permanently discontinued.

3.7 Concomitant Medications

Patients may receive all concomitant therapy deemed necessary to provide adequate support, but only study-prescribed investigational agents can be used during the study. Patients may not receive subsequent systemic anticancer therapy or radiotherapy to target lesions while receiving treatment in this study. Low-dose corticosteroids may be used for the treatment of non-cancer-related illness at the discretion of the investigator.

Colony-stimulating factors may be used at the investigator's discretion and according to the institutional guidelines, but must be discontinued at least 2 days prior to the next scheduled study drug administration. If Neulasta (pegfilgrastim) is to be used, it should be given only after the Day 15 dose of each cycle.

Routine prophylaxis with antiemetics is recommended per institutional guidelines. In addition, routine premedication and additional treatments to help prevent or treat hypersensitivity and anaphylaxis to rituximab are recommended (see rituximab package insert), or per institutional guidelines. Routine prophylaxis to prevent TLS by administration with either allopurinol or rasburicase will also be allowed, per the investigator's clinical judgment.

Patients who receive pixantrone and are concomitantly taking medications that are CYP1A2 substrates, such as tricyclic antidepressants or theophylline, should be closely monitored, as pixantrone has the potential to impair metabolism of these agents.

Patients receiving pixantrone must be encouraged to avoid excessive exposure to sunlight and use effective sunblocker agents. Topical sunblocking agents should not be reported as concomitant medications.

All concomitant medications, including routine prophylaxis and premedications, are to be recorded on the electronic case report forms for the study.

In vitro studies with the most common human cytochrome P450 isoforms (including CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4) have shown a possible mixed-type inhibition of CYP1A2and CYP2C8 that may be of clinical relevance. No other significant clinically relevant interactions with CYPP450 isozymes were observed.

Theophylline is primarily metabolised by CYP1A2. When co-administering the narrow-therapeutic index medicinal product theophylline with pixantrone, there is a theoretical concern that this substrate may increase in concentration, resulting in theophylline toxicity. Theophylline levels should be carefully monitored in the weeks immediately following initiation of pixantrone concurrent therapy.

Warfarin is partially metabolised by CYP1A2, and a theoretical concern exists with regard to co-administration of this medicinal product and the effect inhibition of its metabolism might have on its intended action. Coagulation parameters, specifically international normalised ratio (INR), should be monitored in the days immediately following the initiation of pixantrone concurrent therapy.

Amitriptyline, haloperidol, clozapine, ondansetron and propranolol are metabolised by CYP1A2, and therefore a theoretical concern exists that co-administration of pixantrone may increase blood levels of this medicinal product.

Based on in vitro studies, pixantrone was found to be a substrate for the membrane transport proteins P-gp/BRCP and OCT1. Agents that inhibit these transporters have the potential to decrease hepatic uptake and excretion efficiency of pixantrone. Blood counts should be closely monitored when co-administered

with agents that inhibit such transporters, such as cyclosporine A or tacrolimus, commonly used to control chronic graft-versus-host disease (GVHD), and the anti-HIV agents, ritonavir, saquinavir, or nelfinavir.

In addition, caution should be taken when pixantrone is continuously co-administered with efflux transport inducers, such as rifampicin, carbamazepine, and glucocorticoids, as pixantrone excretion maybe increased with a consequent decrease of systemic exposure.

3.8 Visit Schedule and Assessments

3.8.1 Visit Schedule

At randomization, the planned visit schedule according to the Study Schedule (Table--1, Table--2) will be discussed with the patient. All efforts should be made to adhere to this visit schedule. Deviation from the planned visit dates must be avoided in order to ensure that assessments are performed at the predefined time points.

3.8.1.1 Screening Period

Patient consent will be obtained prior to performance of any study related procedures; standard of care procedures applicable to screening obtained within 28 days of randomization can be used for qualification, unless otherwise specified.

Following confirmation of eligibility criteria, patients will be randomized to treatment (Section 3.4.1).

The assessments performed at the screening visit are listed below. Unless otherwise specified, screening assessments can be performed up to 28 days before randomization. All laboratory test values collected as part of the study will be evaluated by the central laboratory as well as by local laboratories. Local laboratory evaluations are used for real-time decisions regarding study eligibility. Local labs are required, as needed, for time-limited evaluation windows, per protocol, and to support urgent clinical decisions.

- Pathology and immunohistochemistry reports documenting a current histological diagnosis of DLBCL (de novo DLBCL or DLBCL transformed from indolent lymphoma), or follicular grade 3 lymphoma according to WHO classification are required and must be reviewed by the sponsor or designee prior to randomization.
- Tissue biopsy slides confirming follicular grade 3 lymphoma or DLBCL should be requested during the screening period and sent as soon as possible for retrospective central pathology review, but completion of central review is not required prior to randomization and treatment. In addition, if a bone marrow biopsy (with core) was performed within 8 weeks of randomization to evaluate bone marrow involvement of disease this should be submitted to the local pathology laboratory for review.
- Medical/cardiac history
- Demographics and baseline disease characteristics
- Physical examination, vital signs, and weight
- Detailed history of primary NHL diagnosis and all prior treatments for NHL
- Adverse events are collected for randomized patients from the time of signing the Informed Consent Form
- Serum HCG (WOCBP only)
- IPI score (Section 8.1), calculated using the screening LDH value and current disease stage
- CBC with differential

- Chemistry panel for central laboratory (includes total bilirubin, alkaline phosphatase, ALT, AST, total protein, albumin, sodium, potassium, calcium, magnesium, phosphorus, glucose, creatinine, LDH, and uric acid). Local chemistry panel is used for eligibility
- Urinalysis
- Cardiac assessment: LVEF by echocardiogram, ECG, and serum troponin T (see Section 3.10.4)
- Concomitant medications
- Baseline disease assessment of the neck, chest, abdomen and pelvis. CT with intravenous contrast is the preferred imaging modality, but patients intolerant of CT IV contrast may have MRI of the neck, abdomen, and pelvis with noncontrast chest CT (see Section 3.9.1). The imaging method used at baseline must be used throughout the study
- Baseline PET is not required; however, if PET scan was obtained within 28 days prior to randomization, images are to be submitted for IRC review
- ECOG performance status (Section 8.2)
- Ann Arbor stage (Section 8.3)

3.8.1.2 Treatment Period

Treatment must be initiated as soon as possible and no more than 14 days after randomization. The treatment period continues until the end-of-treatment visit. Patients will be evaluated through this period for toxicities and adverse events. Assessments to be performed during the treatment period are listed below and are detailed in Table--1.

- CBC with differential ≤ 1 day prior to every study drug administration
- Chemistry panel for central laboratory (includes total bilirubin, alkaline phosphatase, ALT, AST, total protein, albumin, sodium, potassium, calcium, magnesium, phosphorous, glucose, creatinine, LDH, and uric acid) ≤ 7 days prior to study drug administration on Day 1 of each cycle. Local chemistry panel may be used to guide dosing.
- Vital signs prior to study drug administration
- Weight on Day 1 of all cycles for BSA used for dosing should be calculated at least at the beginning of each cycle or by institutional standards.
- Physical examination required ≤ 3 days prior to Day 1 study drug administration for Cycles 2-6. Symptom-directed examination as needed ≤ 1 day before study drug administration on Day 1 Cycle 1 and Days 8 and 15 of all cycles.
- Urine pregnancy test for WOCBP ≤ 1 day prior to study drug administration on Day 1 of all cycles
- Adverse events at each visit day
- Concomitant medications at each visit day
- LVEF by echocardiogram ≤ 7 days before Day 1 of Cycles 3 and 5. Troponin T is obtained before Cycles 3 and 5 (see Section 3.10.4). Echocardiogram and troponin T need not be repeated if a dose is delayed for reasons other than abnormal LVEF.
- ECOG performance status ≤ 1 day prior to study drug administration on Day 1 of each cycle
- Disease assessment by CT/MRI imaging is to be obtained every 8 weeks ± 1 week and must be performed as close as possible to the scheduled dates. Disease assessment time points during the study are to be calculated from Day 1 of Cycle 1. In the case of CT/MRI imaging done outside the calendar schedule (unscheduled), consult with Medical Monitor for appropriate scheduling of the next CT/MRI.

- Pharmacokinetics Assessments (participating sites refer to Section 12 Addendum: Pharmacokinetics Sub-Study)

Routine local laboratory panels and LVEF measurement reports must be reviewed by a qualified health professional participating in the study prior to the next administration of study drug. Dose modifications will be done according to the rules in Section 3.6.

PET scans are not required during treatment, but disease response must be evaluated (per criteria in Section 3.9.6) and reported by the site for all PET images obtained at any time during the study prior to progressive disease per Modified IWG criteria or subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy. All such PET images will be submitted for IRC review.

Regardless of whether serum samples, radiologic material and other patient data are sent to a central lab or independent review panel for study purposes, treatment, and eligibility decisions must be made by the investigator based on his or her clinical assessment of the patient and interpretation of local labs, radiology assessments, and other tests.

Dose delays may require that both local and central labs are redrawn to comply with these time periods.

3.8.1.3 End of Treatment Visit

The ***EOT visit*** is defined as being at 4 to 7 weeks, inclusive, after the last dose of study drug is administered (or was scheduled to be administered), or before subsequent systemic anticancer therapy is given, whichever occurs first. Note that rituximab given as maintenance therapy is not allowed prior to the EOT visit per protocol window. However, even if rituximab is given as maintenance therapy prior to EOT, all EOT procedures, including PET, will be performed. In the unanticipated event that a patient receives no study drug, no EOT procedures are required and the patient would continue per protocol Section 3.8.1.4.

Additional information on AE reporting can be found in Section 3.10.

End of Treatment Procedures

The following assessments should be performed at the EOT visit (at 4 to 7 weeks after last study drug dose, inclusive):

- CBC with differential
- Chemistry panel for central laboratory (includes total bilirubin, alkaline phosphatase, ALT, AST, total protein, albumin, sodium, potassium, calcium, magnesium, phosphorous, glucose, creatinine, LDH, and uric acid)
- Physical examination, vital signs, and weight
- Concomitant medications
- Adverse events
- ECOG performance status
- Measurement of LVEF by echocardiogram
- ECG
- Serum troponin T
- PET scan

- Bone marrow biopsy with core to confirm a CR, unless a bone marrow biopsy was obtained at baseline and was negative

A bone marrow biopsy (with core) is required at EOT (at 4 to 7 weeks after last study drug dose, inclusive) to confirm a CR, unless a bone marrow biopsy was obtained at baseline and was negative. Bone marrow biopsies are submitted for local review.

A PET scan is required at the EOT visit (at 4 to 7 weeks after last study drug dose, inclusive), unless geographically unavailable or the patient has PD per Modified IWG criteria, or the patient has received subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy. If the PET scan cannot be done at EOT, it may be scheduled to coincide with the first early follow-up disease assessment.

Note that rituximab given as maintenance therapy is not allowed prior to the EOT visit. However, even if rituximab is given as maintenance therapy prior to EOT, all EOT procedures, including PET, will be performed.

Out-of-Window PET Scan and Bone Marrow Biopsy

If it is not possible to obtain the EOT PET scan within the protocol-specified window (at 4 to 7 weeks after last study drug dose, inclusive), ongoing attempts should be made to obtain a PET scan for every patient who has not progressed or started subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy (ie, chemotherapy, radiation therapy, or oncologic surgical therapy).

If it is not possible to obtain the EOT bone marrow biopsy (with core) within the protocol-specified window, ongoing attempts should be made to obtain this biopsy from every patient who achieves and remains in CR, and has not started subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy (ie, chemotherapy, radiation therapy, or oncologic surgical therapy).

3.8.1.4 Follow-up Periods

Please see Table--2 for details of the Follow-up Schedule.

Patients who complete or discontinue study treatment will enter the Early Follow-up Period. This includes patients assessed as Progressive Disease Due to Symptomatic Deterioration.

However, a patient enters the Survival Follow-up Period if, during the treatment, Early Follow-up or Intermediate Follow-up periods, he or she:

- Develops progressive disease per Modified IWG criteria
- Receives subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy
- Withdraws consent for study procedures

All randomized patients who withdraw consent will be followed for survival and safety as described below, unless they have rendered a separate written withdrawal of consent.

Study-drug related adverse events and cardiac adverse events ≥ grade 3, including LVEF declines, are collected and followed until resolution or no further improvement is expected or until the end of the study.

Adverse events not related to study drug and cardiac AEs ≤ grade 2 are collected and followed for 30 days after the last dose of the study drug, until no further improvement is expected, or until the patient begins a subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, whichever occurs first.

Early Follow-up

The Early FU Week 8 visit occurs 8 weeks after the last protocol calendar scheduled CT/MRI imaging disease assessment to ensure an 8-week interval between protocol calendar scheduled scans. In the case of CT/MRI imaging done outside the calendar schedule (unscheduled), consult with Medical Monitor for appropriate scheduling of the next CT/MRI.

The Early Follow-up period lasts 24 weeks. Safety evaluation includes measuring LVEF by echocardiogram and obtaining a troponin T sample at Week 24 ± 1 week.

All other assessments, including CT/MRI disease response, LDH, survival status, and details of any subsequent systemic anticancer therapy, including rituximab given as maintenance therapy, are evaluated and recorded every 8 weeks ± 1 week.

Intermediate Follow-up

Patients who complete the 24-week Early Follow-up period then enter the 72-week Intermediate Follow-up period. During Intermediate Follow-up, CT/MRI disease response, LDH, survival status, and details of any subsequent systemic anticancer therapy, including rituximab given as maintenance therapy, are evaluated and recorded every 12 weeks ± 2 weeks.

Survival Follow-up

Patients enter the Survival Follow-up period when one of the following occurs:

- Completes Intermediate Follow-up
- Develops progressive disease per Modified IWG criteria
- Receives a subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy
- Withdraws consent for study procedures
- Completes study treatment and EOT evaluations after 195 PFS events have occurred
- Is in Early or Intermediate Follow-up at the time that 195 PFS events have occurred

The first Survival Follow-up visit should be scheduled 12 weeks (± 2 weeks) from the last study visit. During the Survival Follow-up period, each patient is followed for survival status every 12 weeks ± 2 weeks until death, the end of the study, or the patient withdraws informed consent.

3.9 Efficacy Assessment

An Independent Radiological Committee (IRC) will assess radiographic images obtained during this study based on a prespecified Image Charter.

A Site Procedures Manual will be provided to all clinical sites to facilitate the consistent and quality acquisition of imaging data. All clinical sites and imaging centers will be certified by the independent imaging CRO according to their ability to obtain quality images.

Investigators will assess radiographic images obtained during this study per protocol based on the modified IWG criteria; decisions regarding treatment and eligibility must be made by the investigator based on his or her assessments.

3.9.1 Disease Assessment by Imaging

All patients are required to have scans of the neck, chest, abdomen, and pelvis at the evaluation time points specified in Table--1. At each evaluation time point, every target and non-target lesion must be evaluated. Detailed procedures for assessment and measurement of disease are found in Section 8.6. The method used to assess measurable disease at baseline must be used at all subsequent evaluations. Once a patient is assessed by the investigator as having PD as defined by the Modified IWG criteria, no further CT or PET scans or disease response assessments are required by the study.

CT with IV contrast is the preferred anatomic imaging modality. Patients who have an allergy to iodinated contrast media will have magnetic resonance imaging (MRI) of the neck, abdomen and pelvis and noncontrast CT of the chest. Excluded from MRI examination are patients with contraindicated implants, allergy to gadolinium, and acute or chronic severe renal insufficiency (glomerular filtration rate < 60 ml/min). If a patient cannot have a contrast CT or MRI, noncontrast CT scan of the neck, chest, abdomen, and pelvis must be obtained.

PET/CT images should not typically be used for lesion measurements, unless the CT images are obtained using optimal CT imaging protocols in a fashion consistent with other study CT imaging time points (ie, similar imaging energies and use of IV contrast). Lesions should be measured with CT/MRI imaging per the above paragraph. Chest X-ray, other radionuclide scans, and ultrasonography may not be used to evaluate measurable disease.

3.9.2 PET Scans

PET scans obtained alone or in combination with CT scan (PET/CT) should be acquired from the skull base to the upper thighs following standard imaging protocols.

A baseline PET scan is not required, but if obtained within 28 days prior to randomization, images are to be sent to the IRC for review and all sites of disease chosen as target lesions must be PET-positive. If a baseline PET scan is not done, all lesions are assumed to be PET-positive.

Any unscheduled PET scans obtained during treatment or follow-up periods must be evaluated for disease response (per criteria in Section 3.9.6), reported by the site, and be sent to the IRC for review.

A PET scan is required at EOT, unless not geographically available and/or the patient has progressive disease per Modified IWG criteria, or has received subsequent systemic anticancer therapy. Rituximab given as maintenance therapy is not allowed prior to the EOT visit per protocol window. However, even

if rituximab is given as maintenance therapy prior to EOT, all EOT procedures, including PET, will be performed.

If it is not possible to obtain the EOT PET scan within the protocol-specified window (at 4 to 7 weeks after last study drug dose, inclusive), ongoing attempts should be made to obtain a PET scan for every patient who has not progressed or started subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy (ie, chemotherapy, radiation therapy, or oncologic surgical therapy). As per the Modified IWG criteria, a PET scan (and bone marrow) at EOT is required for determination of CR at EOT (and subsequent time points). If no PET scan (and bone marrow) is available at EOT, PR is the best possible response assessment at and after EOT until such time as the PET scan and bone marrow are obtained. Disease response assessments at time points after EOT are based solely on CT/MRI findings, within these limitations.

3.9.3 Disease Assessment Definitions

3.9.3.1 Measurable Disease

Measurable sites of disease are defined as clearly bidimensionally measurable lymph nodes, nodal masses and extranodal sites of lymphoma. Measurable lymph nodes and nodal masses must be ≥ 1.5 cm, and extranodal sites of disease must be >1.0 cm in short axes. Measurable lesions must always be assessed by imaging.

3.9.3.2 Nonmeasurable Disease

Nonmeasurable disease includes other lesions or sites of disease that are not bidimensionally measurable, such as positive bone marrow, peripheral blood, bone lesions, mucosal lesions in the GI tract, effusions, and peritoneal/bowel wall thickening.

Table--10 Disease Assessment Definitions	
Node/Nodal disease	A lymph node lesion
Extranodal disease	A non-nodal lesion in a solid organ such as the liver, spleen, kidneys, lung, etc
LDi	Longest diameter of a measurable lesion (nodal or extranodal)
SDi	Short diameter is the longest perpendicular diameter to the LDi
PPD	Product of the perpendicular diameters (applies to a single lesion). SDi × LDi = PPD
SPD	Sum of the products of the perpendicular diameters (applies to a group of lesions). The SPD is the sum of all target lesions' PPDs
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive or relapsed disease
Nadir	The lowest value, whether at baseline or any other study time point.

3.9.4 Selection of Nodal and Extranodal Target Lesions

One to six bidimensionally measurable nodal or extranodal sites of disease (Section 3.9.3.1 and Section 8.6.1) should be selected at baseline as target lesions. Measurable lesions representative of all affected organs should be included, and sites of disease should be chosen from as disparate regions of the body as possible. If measurable nodal disease is present in the mediastinum or retroperitoneum, at least one lesion from that region should be included as a target lesion.

Measureable lesions in a previously radiated site cannot be considered target lesions.

If a baseline PET scan was done, nodal and extranodal lesions selected as target lesions must be PET positive.

All measurements of target lesions are based on SDi and LDi (Table--10).

3.9.5 Selection of Non-Target Lesions

Up to six sites of disease may be selected at baseline as non-target lesions. If more than six sites of nodal and extranodal disease are measurable, additional sites may be followed as non-target lesions. Lesions present at baseline and clearly abnormal by CT/MRI but negative by PET scan should be followed as non-target lesions. Other nonmeasurable disease may be followed as non-target lesions.

At each disease assessment, non-target lesions are individually visually assessed as absent, stable, increased, or decreased (see Section 8.6.3).

3.9.6 Criteria for Response

The modified IWG 2007 Revised Response Criteria used in this study are detailed in Table--11. See Table--10 for definitions of terms and abbreviations. Disease response assessments at time points prior to EOT are based on all criteria, with the exception of bone marrow and PET scan results. Bone marrow

and PET assessments are only scheduled per protocol at EOT and are required to assess CR status at and after EOT. If not obtained at EOT, bone marrow (Section 3.9.7) and PET assessments (Section 3.9.2) may be subsequently obtained and used to assess CR status at that time. CR assessments at and after EOT require the bone marrow and PET results obtained at EOT.

Regardless of the size on CT/MRI, a nodal lesion that is PET negative may be compatible with a CR. Extranodal lesions, however, must be absent for a CR.

Progressive disease includes any new FDG-avid lesion compatible with lymphoma or recurrent FDG-avidity in a preexisting lesion that is ≥ 1.5 cm for nodal disease and > 1.0 cm in any axes for extranodal disease and has unequivocally progressed. Increased FDG-avidity in a previously unaffected site can only be considered progressive disease after confirmation by CT or MRI scans obtained within 2 weeks of the PET scans. Lesion size confirmation must be obtained using optimal CT or MRI imaging in a fashion consistent with other study CT or MRI imaging time points (ie, similar imaging energies and use of IV contrast). If progression per PET scan is later confirmed by CT scan, the date of PD is considered the date the increased avidity was noted on PET scan. Once a patient is assessed as having PD by imaging criteria, no further CT or PET scans or disease response assessments are required by the study.

All scans must be complete per protocol to determine the disease response. In the case of a patient with incomplete baseline imaging, subsequent response assessments are limited to either “Unknown” or “Progressive Disease”. In a patient with complete baseline imaging, but incomplete or inadequate imaging at one or more subsequent time points, response assessments at time points with missing data are limited to either “Unknown” or “Progressive Disease”.

Some patients may be unable to continue study treatment due to progressing lymphoma that does not meet the Modified IWG 2007 Revised Response Criteria for Malignant Lymphoma. In patients who are determined to have “Progressive Disease due to Symptomatic Deterioration”, or otherwise are withdrawn from treatment, study-specified imaging will continue to be obtained and disease response assessed, unless the patient withdraws consent for this imaging. Date of progressive disease per Modified IWG criteria must be reported if assessed prior to initiation of subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy.

After a patient is assessed as having PD per Modified IWG criteria or starts subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, no further CT or PET scans or disease response assessments are required by the study.

See Sections 8.6.2 and 8.6.3 for detailed instructions regarding the lesion assessments necessary to evaluate responses according to these criteria.

Table--11
Modified IWG 2007 Revised Response Criteria for Malignant Lymphoma
Assessment of response is compared with baseline; assessment of PD is compared with nadir.
See text section 3.9.6 for further details regarding response assessments in the case of incomplete imaging at protocol-scheduled time points.

Response[a]	Evaluation	Criteria
CR All criteria are required.[b]	Target Nodal Lesions	Nodal sites < 1.5 cm in LDi and SDi. A nodal lesion of any size is permitted if PET negative.
	Target Extranodal Lesions	Absent (0 × 0 cm)
	Non-Target Lesions	Regression to normal**.** A nodal lesion of any size is permitted if PET negative.
	Spleen/Liver	Prior enlargement has regressed to normal
	New Lesions	None
	PET [b]	No evidence of residual disease.
	Bone Marrow [b]	If bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat biopsy; if indeterminate is immunohistochemistry negative
	LDH	Normal
PR All criteria are required ***and*** criteria for PD or CR are NOT met	Target Lesions	At least a 50% decrease in SPD of all target lesions combined
	Non-Target Lesions	Absent, normal, regressed or stable (no increase)
	Spleen/Liver	Any enlargement has decreased, regressed to normal, or is stable (stable enlargement)
	New Lesions	None
	PET	N/A
	Bone Marrow	N/A
	LDH	N/A
SD	Criteria for PD, PR or CR are NOT met.	
PD At least one criteria is met *(cannot be LDH alone)*	Target Lesions (at least one of these criteria is met)	At least a 50% increase in SPD (sum of all target lesions)
		Individual target lesion(s) must be abnormal in size in any axes (≥ 1.5 cm for nodal disease, > 1.0 cm for extranodal disease) *AND* the LDi or SDi has increased by ≥ 50% *OR* the PPD has increased by ≥ 50%
	Non-Target Lesions	Unequivocal progression
	Spleen/liver	Unequivocal increase
	New Lesions	A new node ≥ 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis Assessable disease of any size unequivocally attributable to lymphoma
	PET	A new FDG-avid lesion compatible with lymphoma Recurrence of FDG-avidity in a preexisting lesion(s) that is ≥ 1.5 cm for nodal disease and > 1.0 cm for extranodal disease in any axes and has unequivocally progressed
	Bone Marrow	New or recurrent involvement
	LDH	Elevated

Table--11
Modified IWG 2007 Revised Response Criteria for Malignant Lymphoma

Assessment of response is compared with baseline; assessment of PD is compared with nadir.
See text section 3.9.6 for further details regarding response assessments in the case of incomplete imaging at protocol-scheduled time points.

Response[a]	Evaluation	Criteria

[a]Cheson B, Pfistner B, Juweid M et al.[28].
[b] PET and bone marrow are required evaluations at EOT only and are required to assess CR status. If not obtained at EOT, bone marrow (Section 3.9.7) and PET (Section 3.9.2) may be subsequently obtained to assess CR status at that time. CR assessments during FU (after EOT) require the bone marrow and PET results obtained at or after EOT in order to assess CR status.

3.9.7 Bone Marrow Biopsy

A bone marrow biopsy (with core) is required at EOT to confirm a CR, unless it was obtained within 8 weeks prior to randomization and was negative. All bone marrow biopsies obtained during the study should be locally assessed and recorded on the CRF.

If it is not possible to obtain the EOT bone marrow biopsy within the protocol-specified window (at 4 to 7 weeks after last study drug dose, inclusive), ongoing attempts should be made to obtain this biopsy from every patient who achieves and remains in CR, and has not started subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy (ie, chemotherapy, radiation therapy, or oncologic surgical therapy).

3.9.8 Efficacy Endpoints

Disease response will be assessed according to the Modified IWG 2007 Revised Response Criteria in Table--11. Efficacy analyses will use the response assessments of the IRC. All obtained CT, MRI, and PET scans, and LDH and bone marrow evaluations will be locally assessed by the investigator during the conduct of the study for the purpose of eligibility and disease response assessment.

3.9.8.1 Primary Endpoint

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of PD or death due to any cause (whichever occurs first) in the intent-to-treat (ITT) population. Patients with no documented progression or death before data cutoff will be censored at the date of the last adequate radiological assessment (defined as the last radiological assessment or set of radiological assessments sufficient to allow IRC disease response assessment per PIX306 Modified IWG 2007 Revised Response Criteria).

Patients who receive high-dose therapy and SCT or other subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, without evidence for relapse will be censored for the PFS analysis at the last radiologic adequate assessment date prior to the start of a new therapy.

3.9.8.2 Secondary Endpoints

Overall survival (OS) is defined as the time from randomization until death due to any cause. If the patient is alive or the survival status is unknown, the date of death will be censored on the date the patient was last known to be alive.

Overall Response Rate (ORR) is defined as the proportion of patients who achieve a CR or PR without additional therapy.

Complete Response (CR) rate is defined as the proportion of patients who achieve a CR without additional therapy.

3.9.8.3 Exploratory Endpoints

Duration of Overall Response **(CR, PR)** will be calculated from the date of initial documentation of response to the date of first documented evidence of PD (or relapse for patients who experience a CR on this study) or death. Responders without disease progression or relapse will be censored at the date of their last disease assessment.

Duration of Complete Response **(CR)** will be calculated from the date of initial documentation of a CR to the date of first documented evidence of relapse or death. Responders who do not relapse will be censored at the date of their last disease assessment.

Proportion of patients who receive a stem cell transplant is defined as the percentage of all randomized patients who receive a stem cell transplant after study treatment.

3.10 Safety Assessments

Safety will be assessed by monitoring and recording adverse events, serious adverse events (SAEs), cardiac, hematologic and blood chemistry parameters, vital signs, performance status (PS), and any abnormal findings observed on physical examinations. Refer to Table--1 and Table--2 for the timing of assessments.

Regardless of whether serum samples, radiologic material and other patient data are sent to a central laboratory or independent review panel for study purposes, treatment and eligibility decisions must be made by the Investigator based on his or her clinical assessment of the patient and his or her interpretation of local labs, radiology assessments, and other tests.

3.10.1 Adverse Events

3.10.1.1 Definition of an Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence, or worsening of a preexisting medical condition, in a patient who has signed the Informed Consent Form. For randomized patients, AEs are collected and reported from the time of signing the Informed Consent Form.

An AE does not necessarily have a causal relationship with the study drug. An AE can be any unfavorable and unintended sign, including an abnormal laboratory finding, or a symptom or concomitant disease temporally associated with the use of the study drug, whether considered related to study drug or not.

Progression of the disease under study is not an AE. However, signs and symptoms of progressive disease are captured as AEs on this study.

Progressive/relapsed disease is not an AE, unless it is the primary cause of death. Signs and symptoms associated with disease progression may be recorded as secondary AE terms.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination or evaluation of the patient. The investigator will evaluate changes in physical signs, laboratory values, or results of other diagnostic procedures to determine if an AE has occurred. (To prevent bias, patients should not be questioned regarding the specific occurrence of one or more AEs.)

The NCI-CTCAE, version 4.0, will be used to assess the severity of any AEs and other symptoms. A copy of these criteria is provided in the study manual.

Abnormalities observed during the study, including a cardiac evaluation, that meet any of the criteria below should be reported as AEs or SAEs, as appropriate:

- Any laboratory or other test result, including cardiac, that is clinically significant or requires active intervention, retesting, or ongoing medical monitoring
- Meets the definition of an SAE
- Requires discontinuation or delay of study drug administration
- Requires that the patient receives specific corrective therapy
- Additionally, clinically significant changes noted during physical examinations, electrocardiograms, x-rays and any other safety assessments, whether or not these procedures were required by the protocol, should be recorded on the appropriate eCRFs.

3.10.1.2 Reporting Adverse Events

All AEs are collected and recorded in eCRFs from the time of Informed Consent for randomized patients.

Study-drug related AEs and cardiac AEs grade ≥ 3, including LVEF declines, are collected and followed until resolution or no further improvement is expected, or until the end of the study.

Adverse events not related to study treatment and cardiac AEs ≤grade 2 are collected and followed for 30 days after the last dose of the study drug, until no further improvement is expected, or until the patient begins a subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, whichever occurs first.

All identified AEs must be recorded and described on the appropriate eCRFs. SAEs for randomized patients must have a corresponding AE recorded with a logical match to the event term or description. The following information should be captured for all AEs: date of onset and resolution, CTCAE grade of the event, whether considered serious, the investigator's assessment of causal relationship to study drug (see Section 3.10.1.3 for criteria), and outcome of the event. If concomitant treatment is given for the AE, this information should be captured on the appropriate eCRF. If the AE is an abnormal local laboratory value or test result, this information should also be captured on the appropriate eCRF.

When recording AEs, the diagnosis of the underlying illness or disorder should be used as the event term or description on the eCRF. Symptoms of the illness or disorder should not be reported as separate AEs, unless related to progressive relapsed disease. Progressive relapsed disease is not an AE or SAE event

term, unless it is the primary cause of death. All AEs ongoing at the time of death that are not the primary cause of death will remain "unresolved" on the eCRFs.

It is expected that wherever possible the clinical, rather than the laboratory, term for the AE will be used by the reporting investigator (eg, *anemia* versus *low hemoglobin value*).

If an AE results in early termination of the patient's study treatment period, *AE* should be selected as the reason for discontinuation on the End-of-Treatment eCRF. However, if the AE that resulted in early termination was a sign or symptom of progressive disease, *progressive/relapsed disease* should be selected as the reason for discontinuation on the End-of-Treatment eCRF.

The investigator shall supply the sponsor and Ethics Committee with any additional information requested, notably for reported deaths of subjects.

For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported (see Section 3.10.2 for SAE guidelines); AEs occurring in this time period that do not meet the definition of an SAE do not need to be reported.

3.10.1.3 Criteria for Assessing Causality of Adverse Events

The following definitions should be used to assess the causal relationship between study drug administration and an AE.

Definite

There is a reasonable causal relationship between the study drug and the event, and the event occurred within a plausible time relationship to drug administration, and the event cannot be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event responds to withdrawal of study drug (dechallenge) and recurs with rechallenge (if clinically feasible to rechallenge and if rechallenge is allowable per Section 3.6 Dose Adjustments and Delays).

Probable

There is reasonable causal relationship between the event and the study drug, the event occurred within a plausible time relationship to drug administration, the event is unlikely to be attributed to the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event follows a clinically reasonable response on withdrawal of study drug.

Possible

There is a reasonable causal relationship between the event and study drug, the event occurred within a plausible time relationship to study drug administration, but the event could also possibly be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. Dechallenge information is lacking or unclear.

Unlikely

There is a temporal relationship of the event to study drug but not a reasonable causal relationship, **or** there is no temporal relationship to study drug administration or the condition under study, concurrent disease, other drugs or chemicals, **or** other circumstances provide a plausible explanation for the event.

Unrelated

There is no temporal relationship between the event and study drug administration (too early or late or study drug not administered). There is no reasonable causal relationship between the event and the study drug. The condition under study, concurrent disease, other drugs or chemicals, or other circumstances provides a plausible explanation for the event.

3.10.2 Serious Adverse Events

3.10.2.1 Definition of a Serious Adverse Event

A serious adverse event is an adverse event that meets any of the criteria below.

1. Results in death.
2. Is life-threatening: in the view of the investigator, the event placed the patient at immediate risk of death. This does not include an AE that, had it occurred in a more severe form, might have caused death.
3. Requires inpatient hospitalization or prolongation of an existing hospitalization (see Exceptions below).
4. Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
5. Is a congenital anomaly/birth defect.
6. Is an important medical event that is not fatal, life threatening, or requiring hospitalization, but may be considered serious if, based on appropriate medical judgment, the event jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above (1-5).
7. Cancer/overdose: All cases of new cancers and drug overdose (defined as accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important) must be reported immediately using the SAE form. Determination of seriousness will be reached in consultation with the Safety Physician, CTI Global Pharmacovigilance US Headquarters or designee.

If either the investigator or sponsor believes an AE is serious, the event must be considered serious and will be evaluated by the sponsor, using the current Investigator's Brochure, for expedited reporting (21 CFR 312.32(a)).

Exceptions

Hospitalizations not reported as SAEs include admissions for:

- Planned, nonlife threatening medical/surgical procedures
- Routine health assessments requiring admission for health status documentation (eg, routine gastroscopy, colonoscopy)
- Other life circumstances that have no bearing on health status and requiring no medical/surgical intervention (eg, lack of housing, family circumstances)
- Administration of study medication

3.10.2.2 Reporting Serious Adverse Events

SAEs are collected and recorded from the time of signing the Informed Consent Form.

For screened patients who are not randomized, only SAEs occurring between the time of signing the Informed Consent Form and determination of screen failure are reported (see Section 3.10.2 for SAE guidelines).

For randomized patients, all SAEs that occur through 30 days after the last treatment should be reported immediately to the sponsor or designee. All study-drug related SAEs occurring through the end of the study must be reported immediately to the Sponsor.

All SAEs for randomized patients must have a corresponding AE recorded on the eCRF with an exact match to the event term or description.

An SAE form should be completed for any event for which doubt exists regarding its seriousness.

Within 24 hours of the time that the study personnel learn of an SAE, a paper SAE Report Form, with a corresponding AE recorded in the source documents and AE eCRF, must be completed and the SAE form sent to the Pharmacovigilance (PVG) Department. An SAE report should be completed and faxed or emailed to the PVG Department at:

Fax (US Only): 1-508-416-2654
Fax (outside the US): +44 870 7107157
Email: safety@aptivsolutions.com

A narrative outlining the details of the SAE, treatment, and outcome are to be included on the SAE form. The narrative must state whether there is a reasonable possibility that study drug caused the event (see Section 3.10.1.3). Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event, should be submitted by revising the SAE Report Form as soon as the information becomes available.

In addition, investigators must follow the policies of their IRB/EC regarding IRB/EC notification of SAEs.

Source documents should be submitted only in English. If source documents are not in English, the investigator must summarize the source documents, providing a complete English narrative that includes a description of the event as it evolved the results of all diagnostic procedures performed, treatments administered, and outcome of the event.

Pregnancy

Pregnancy is not considered an SAE. However, if a patient becomes pregnant or causes a pregnancy, this must be reported to the sponsor or designee immediately on the pregnancy reporting form. The investigator must obtain written authorization (medical records release) from a female partner of a male subject prior to obtaining follow-up.

The investigator must follow the pregnancy either to term or termination and will collect data on both maternal and fetal outcome. All pregnancy outcomes will be recorded on the Pregnancy Report Form. Normal outcomes will be communicated to the Sponsor within 30 calendar days of birth/delivery. Abnormal pregnancy outcomes and/or any AE for the child or fetus (including miscarriage) will also be recorded in the AE eCRF and on the SAE Report Form. The associated SAE Report Form should be sent to the Sponsor per the procedure and timelines described in Section 3.10.2.2, Reporting Serious Adverse Events.

Deaths

Every death that occurs from the time of signing the Informed Consent Form until 30 days after completing protocol treatment must be reported as an SAE. Death alone is not an AE; it is an outcome of an AE and should be accompanied by a corresponding AE term for the event that led to the outcome of death. Special considerations include the following:

- Progressive/relapsed disease is not an AE, except when it is a cause of death.
- Sudden death, or death due to unexplainable cause(s), should be reported as an SAE, while follow-up is pursued to determine the cause.
- Deaths that occur after 30 days following administration of the last dose of the study drug and are unlikely or unrelated to the study drug do not need to be reported as SAEs, but are captured only on the Death Information eCRF.

3.10.3 Expedited Safety Reports

In accordance with local regulations, CTI will notify investigators of all SAEs that are unexpected and definitely, possibly, or probably related to study drug in the form of an expedited safety report (ESR). An unexpected AE is an AE not described in the current Investigator Brochure (IB), or an AE that occurs with a specificity or severity inconsistent with the current IB.

Upon receiving such notice, the investigator must review and retain the notice with the Investigator's Brochure and submit the ESR as required by the site's local IRB. Where required by local regulations or where there is a central IRB/IEC for the study, the sponsor or designee will submit the ESR to the appropriate IRB/IEC. The sponsor, investigator, and IRB/IEC will determine if the Informed Consent Form requires revision. In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by CTI or its designee to the relevant competent health authorities in all concerned countries according to the local regulations (either as expedited and/or in aggregate reports).

Other important findings that may be reported by the sponsor or designee as an ESR include increased frequency of a clinically significant expected SAE, an SAE considered associated with a study procedure that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or the sponsor's decision to end or temporarily halt the clinical study for safety reasons.

The IB will be updated periodically to include new and relevant safety information. Until an AE is identified in the IB, it is considered unexpected, regardless of whether the AE has been the subject of a previous ESR.

3.10.4 Laboratory Evaluation

All laboratory test values collected as part of the study will be evaluated by a central laboratory, with the exception of urine pregnancy tests after the screening period.

The investigator will use local laboratory evaluations to facilitate real-time decisions about study treatment administration, eligibility, dose modifications, and for evaluation of signs and symptoms. If any clinical intervention results from local laboratory tests, the test result and local laboratory normal ranges for that test will be reported on the appropriate eCRF.

The central laboratory troponin T result should be used to determine eligibility. A local laboratory result may be used if the central laboratory turnaround time (approximately 5 days) would delay randomization. After baseline, serum troponin T samples are stored at the central laboratory for batch processing. The central laboratory will complete troponin T testing within 1 year of the end of study, at which time results will be provided to the investigator and any remaining specimens will be destroyed.

Dose delays may require that both local and central labs are redrawn. Treatment decisions are based on local results. Complete blood count (CBC) with differential is required within 1 day of every administration of study drug (Days 1, 8 and 15 of all cycles); chemistry panel is required within 7 days of Day 1 of all cycles; and a pregnancy test for WOCBP is required within 1 day of Day 1 of all cycles.

Regardless of whether serum samples, radiologic material and other patient data are sent to a central laboratory or independent review panel for study purposes, treatment decisions must be made by the investigator based on his or her clinical assessment of the patient and his or her interpretation of local laboratory results, radiology assessments, and other tests.

3.10.4.1 Cardiac Assessment

Cardiac assessments during the treatment period are described in Table--1, and Table--2 shows assessments during Follow-up. Routine ECG is performed, collected, and analyzed at baseline and at EOT.

The LVEF of all patients will be evaluated by echocardiogram during the screening period; ≤ 7 days before the expected Day 1 of Cycles 3 and 5, at EOT, and at Follow-up Week 24. Echocardiograms will be reviewed at the investigational site.

Serum troponin T is evaluated at baseline, before cycles 3 and 5, at EOT, and at Follow-up Week 24 (Section 3.10.4).

The echocardiogram and troponin T test before Cycles 3 and 5 need not be repeated if a dose is delayed for reasons other than abnormal LVEF. Cardiac-related SAEs ≥ CTCAE grade 3 that occur through the end of the study should be immediately reported to the sponsor or designee. Cardiac adverse events ≥ CTCAE grade 3, including LVEF declines, are collected and followed until resolution or no further improvement is expected, or until the end of the study.

3.10.5 Vital Signs and Physical Examination

Vital signs will be obtained prior to every study drug administration. Physical examinations are performed during screening and ≤ 3 days before study drug administration on Day 1 of Cycles 2-6. A symptom-directed examination may be done as needed ≤ 1 day prior of study drug administration on Day 1 of Cycle 1 and on Days 8 and 15 of all cycles. Vital signs and physical examination are also performed at the EOT visit.

3.10.6 ECOG Performance Status

ECOG performance status (Section 8.2) will be assessed ≤ 1 day before Day 1 of all cycles and at EOT (at 4 to 7 weeks after last study drug dose, inclusive).

3.11 Pharmacokinetics Assessments (for participating sites)

PK samples will be collected from approximately 20 patients (see Section 12 Addendum: Pharmacokinetics Sub-Study).

4 Data Management

The CTI Clinical Data Management Department or its designee will prepare guidelines for data entry and data handling, which will include procedures for data verification and electronic edit checks. The complete data management process will be described in the Data Management Plan.

4.1 Data Collection

An electronic data capture (EDC) system will be used for this study. Designated site personnel will enter subject data required by the protocol directly into electronic case report forms (eCRFs). Personnel will not receive access to the EDC system until they have completed all training requirements. The EDC system will provide an automatic audit trail of all changes made to the clinical database.

4.2 Data Entry and Quality Control

Data items will be entered directly from source documents by designated site personnel using single data entry. Concomitant medications entered into the database will be encoded using the WHO Drug Reference List. Adverse events, coexisting disease, and other data items will be encoded using the *Medical Dictionary for Regulatory Activities* (MedDRA) terminology.

CTI staff or designees will review the data on a periodic basis to ensure validity, accuracy, and completeness. Data suspected to be discrepant or incomplete will be questioned using data queries. Data queries resulting from these reviews will be sent to the study sites via the EDC system. The staff at the study sites will respond to the queries; these responses will be reviewed by CTI staff or designee.

This study will be conducted using in-house blinding procedures. The official clinical database will not be unblinded for the primary endpoint analysis until data review has been completed, protocol violations have been identified, the data have been declared clean, and a detailed Statistical Analysis Plan has been written and approved.

5 Statistical Analysis

The statistical analyses of the data from this study will be the responsibility of Biostatistics at CTI. If, after the study has begun, changes are made to the Statistical Analysis Plan stated below, these deviations will be listed with an explanation as to why they occurred in the Statistical Analysis Plan and/or CSR for this study, as appropriate.

The study analyses planned are planned to be performed as defined at the following time points:

- The core analysis will be performed after 195 PFS events have occurred to evaluate the primary and secondary objectives of the study, with the exception of OS.
- The first interim analysis of OS will be performed after approximately 165 OS events (75%) have occurred and confirmation of 195 PFS events.
- The second interim analysis of OS will be performed when 190 OS events (86%) have occurred.

- The final analysis will be performed at the end of the study, when the required number of OS events have occurred.

5.1 Hypotheses

The hypothesis tests described below will be performed on the intent-to-treat population using the IRC assessments of disease response.

5.1.1 Primary Hypothesis

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.

5.1.2 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.

5.2 Variables/Time Points of Interest

5.2.1 Primary Efficacy Variable

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of disease progression or death due to any cause (whichever occurs first). The progression date is the earliest time any progression is observed. Patients with no documented progression or death before the data cutoff will be censored at the date of the last adequate radiological assessment.

5.2.2 Secondary Efficacy Variables

Overall survival (OS) is defined as the time from randomization until death due to any cause.

Overall response rate (ORR) is defined as the proportion of patients who achieve either a CR or a ***partial response (PR)*** without additional therapy. The primary analysis of ORR will be based on disease response as determined by the IRC.

Complete response (CR) ***rate*** is defined as the proportion of patients who achieve a complete response without subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy.

5.2.3 Exploratory Efficacy Variables

Duration of overall response is defined as the time from first documented response to the first documentation of disease progression, relapse or death due to any cause.

Duration of complete response is defined as the time from first documented complete response to the first documentation of relapse or death due to any cause.

Proportion of patients who receive a stem cell transplant is defined as the percentage of all patients randomized who receive a stem cell transplant after study treatment.

5.2.4 Safety Variables

Safety will be assessed for randomized patients by clinical and/or statistical review of all safety parameters, including adverse events and laboratory values. The safety analysis will focus on overall AEs, grade 3 and grade 4 AEs, SAEs, treatment-related SAEs and AEs, AEs that lead to treatment discontinuation, deaths, and cardiotoxicity as measured by echocardiography and troponin T.

5.3 Statistical Methods

5.3.1 Analysis Populations

5.3.1.1 Intent-To-Treat (ITT) Population

The ITT population is defined as all randomized patients. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization.

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

5.3.1.2 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 central pathology review.

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

5.3.1.3 Per-Protocol (PP) Population

The PP population is defined as all randomized patients who undergo at least one post baseline disease assessment and have no major protocol violations. Patients in this population will be analyzed according to the treatment that they actually received.

The PP population will be used as a supportive efficacy analysis.

5.3.1.4 Safety Population

The safety population is defined as all randomized patients who receive at least one dose 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.

5.3.2 Efficacy Evaluation

5.3.2.1 Progression-Free Survival

The primary analysis of PFS will use disease progression assessed by the IRC. The progression date is the earliest time when any progression per Modified IWG criteria is observed. Patients will be censored at the last adequate radiological assessment date if they are alive with no documented progression before data cutoff. Last adequate radiological assessment is defined as the last radiological assessment or set of radiological assessments sufficient to allow IRC disease response assessment per PIX306 Modified IWG 2007 Revised Response Criteria. Patients who receive subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, without evidence of progression, will be censored at the last adequate radiological assessment date prior to the start of the new therapy. Table--12 provides the event and censoring rules for the primary analysis of PFS.

Table--12
Event and Censoring Rules for Progression-Free Survival Analysis

Situation	Date of Progression or Censoring	Situation Outcome
No post-baseline disease assessment	Day 1	Censored
Progression documented	Earliest date when any progression is observed	Event
No progression	Date of last adequate radiologic assessment with evidence of no progression	Censored
Received any subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy, before progression of disease or death	Date of last adequate radiologic assessment prior to the start of the subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy	Censored
Death	Date of death if no progression	Event
Lost to follow-up	Date of last adequate radiological assessment showing no progression	Censored

The comparison of the treatment effect on PFS will be performed with a log-rank test stratified by IPI score (Section 8.1), prior lines of therapy for DLBCL and follicular grade 3 lymphoma, and length of time from initiation of therapy for DLBCL or grade 3 follicular lymphoma until first relapse. The Kaplan-Meier product-limit method will be used to estimate the distribution of PFS. Summary statistics (median, 95% confidence interval) and PFS curves will be presented by treatment group.

Sensitivity analyses will be performed to evaluate the robustness of the PFS result and will include PFS, as determined by investigator assessments, and PFS based on other analysis populations. The detailed methodology for these analyses is displayed in the Statistical Analysis Plan.

5.3.2.2 Overall Survival

Overall survival (OS) is defined as the time from the date of randomization to the date of death due to any cause. If the patient is not known to have died, survival will be censored at the date the patient was last known to be alive. The comparison of the treatment effect on OS will be performed with a stratified log-rank test, as described for PFS. The primary analysis of OS will be performed at the end of the study, although two interim analyses of OS are also planned (see Section 5.4 for the details).

5.3.2.3 Overall Response Rate (ORR) and Complete Response (CR) Rate

ORR will be based on disease response as determined by the IRC. Comparison of the ORRs between the two treatment arms will be performed using the exact Cochran-Mantel-Haenszel (CMH) test, controlling for IPI score (Section 8.1), number of prior lines of therapy for DLBCL or follicular grade 3 lymphoma, and length of time from initial therapy for DLBCL or follicular grade 3 lymphoma until first relapse. The number and percentage of patients achieving a PR or better will be presented. The 95% confidence interval of the difference in response rates between the two treatment arms will also be provided. The CR rate will be analyzed using the same method as for the ORR.

5.3.2.4 Exploratory Efficacy Variables

Exploratory efficacy variables will be analyzed using descriptive statistics. A 95% confidence interval will be calculated for each endpoint. The detailed analysis of these secondary endpoints will be discussed in the Statistical Analysis Plan.

5.3.2.5 Multiplicity

The hypotheses tests will follow a closed-step-down procedure 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 these analyses is provided in Section 5.4.
- If the hypothesis test of OS is achieved, then the secondary hypotheses of ORR, followed by CR, will be tested at the remaining 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.

5.3.2.6 Subgroup Analyses

Subgroup analyses will be performed for primary and secondary endpoints, as appropriate. The subgroups will include the number of prior treatment regimens for DLBCL and follicular grade 3 lymphoma, length of time from initiation of therapy for DLBCL or follicular grade 3 lymphoma until first relapse, and IPI score (Section 8.1). The subgroups may also include, but are not limited to, gender, age, race, Ann Arbor Stage (Section 8.3), time between first and second-line regimens, the number of prior lines of therapy for DLBCL or follicular grade 3 lymphoma (0 - 1 vs. ≥ 2) and prior SCT. Cox regression model will be performed as well. The detailed subgroup analyses will be addressed in the Statistical Analysis Plan.

5.3.3 Safety Evaluation

The assessment of safety will be mainly on the frequency of adverse events and on the number of laboratory values that fall outside of predetermined ranges.

Adverse events, including SAEs, in each treatment group will be summarized by presenting the number and percentage of patients having any AE, an AE in each body system, and individual events according to MedDRA dictionary. CTCAE grades and relatedness to study drug will be summarized, as appropriate.

Laboratory data will be summarized by presenting shift tables using CTCAE grades. Summary statistics of value and change from baseline will be performed for each visit.

5.3.4 Pharmacokinetics Analysis

The analysis of PK data (collected at participating sites) will be performed as described in Section 12 Addendum: Pharmacokinetics Sub-Study.

5.4 Interim Analysis

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

The first interim analysis of OS 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 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 2 OS interim analyses and reviews will be performed by IDMC.

Using group sequential methods, including Rho family alpha spending with a parameter of 7, if the 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 first interim analysis. 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). 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--13 provides the estimated number of deaths, and corresponding stopping parameters based on the potential number of events at each analysis.

Table--13
Stopping Parameters Based on the Potential Number of Events

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

5.5 Power and Sample Size Determination

One hundred ninety-five (195) PFS events are required to detect at least a 35% improvement (ie, HR = 0.65) in PFS with 85% power and a 2-sided alpha of 0.05. Based on results from a recent study by Pettengell et al.[29], it is 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.[29], it is assumed that the median OS for the control group is 7 months.

6 Ethical Considerations

6.1 Informed Consent

The investigator is responsible for obtaining written informed consent from each patient (or the patient's legally authorized representative) before any study-specific screening or other procedures are performed and before any study drug is administered.

Patients meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the investigator must exercise no selectivity with regard to offering eligible patients the opportunity to participate in the study. Potential patients, or the legally authorized representatives of potential patients, will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previous adverse reactions, the investigational status of the study drug, and other factors that are part of obtaining proper informed consent. Patients will be given the opportunity to ask questions of a qualified health care professional trained on the study, as well as adequate time to consider whether they wish to participate.

Informed consent will be documented by the use of a written Informed Consent Form that includes all elements required by regulations and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. The form is to be signed and dated by the patient or the patient's legally authorized representative and by the person who administered the consent process. A copy of the signed form will be given to the person who signed it and the original will be maintained with the patient's medical records. The date and time that informed consent was obtained must be recorded in source documents. The informed consent process must be documented at the site in the patient's file.

If an amendment to this protocol changes the schedule, scope, or activity of patient participation or increases the potential risk to patients, the protocol amendment and a revised informed consent document must be submitted to the IRB for review and approval before use. Patients currently enrolled in the study who could be affected by the protocol amendment must again give consent using the revised document. This includes all patients in the Follow-up periods of the study if new information about the study drugs or procedures increases the risk patients incur by participation in the treatment period. All patients enrolled after the approval date of the protocol amendment must sign and date the revised informed consent form.

For any subject who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. Informed consent to obtain these data will be obtained from subjects at the time of enrollment.

6.2 Institutional Review Board/Ethics Committee Approval

An appropriately constituted Institutional Review Board (IRB)/Ethics Committee (EC) that complies with the requirements of 21 CFR Section 56 and appropriate Good Clinical Practice (GCP) regulations must provide initial and continuing review and approval of this clinical study. Before enrolling any patients, investigators must transmit the investigator's brochure, protocol, and consent form to their IRB/EC for review and approval, and notification of IRB/EC approval must be received by CTI before any investigational supplies will be shipped to the investigator.

The investigator will ensure that all changes in the research activity and all unanticipated problems involving risks to human subjects are reported promptly to the IRB/EC, and that no changes are made to

the protocol without prior sponsor and IRB/EC approval, except when necessary to eliminate apparent immediate hazards to human subjects.

The investigator must promptly notify the IRB/EC of any SAEs occurring at that site according to IRB/EC policies. Copies of all study-related correspondence between the investigator and the IRB/EC must be forwarded to CTI by the investigator. The investigator is responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of patient risk involved in the study, but not less than once per year and at the completion or termination of the study.

The FDA considers any direct recruiting advertisements to be part of the informed consent and subject selection process and therefore governed by regulations 21 CFR 50.20,50.25, 56.11(a)(3), and 21 CFR 312.7(23). These regulations require that all advertisements for potential research subjects are reviewed and approved by an IRB or Independent Ethics Committee (IEC) before publication. In addition, any recruitment material developed by a site must be reviewed by CTI prior to use. Patient education material that does not mention specific studies or research is generally not subject to these requirements.

6.3 Patient Privacy

CTI and the investigator affirm and uphold the principle of the patient's right to privacy. CTI and the investigator shall comply with applicable privacy laws. To verify compliance with this protocol, CTI or its designee must be able to review the original medical records of patients. Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the investigator will obtain such permission in writing from the patient before the patient is entered into the study.

7 Study Administration

7.1 Good Clinical Practice and Regulatory Requirements

Investigators must agree to conduct this study in accordance with the ICH principles of Good Clinical Practice (ICH-E6), CFR parts 50, 56, 312, and 314, and with the Declaration of Helsinki (1989). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

Where applicable this study must also be conducted in accordance with "directive 2001/20/EC of the European Parliament and of the Council of April 4, 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use."

7.2 Quality Assurance Procedures

CTI's Quality Assurance (QA) department or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by CTI's QA department as part of the written record.

7.3 Changes to the Protocol

Significant changes to the protocol must be approved by the sponsor and the appropriate IRB/EC prior to implementation, except where immediate implementation is necessary to eliminate an imminent hazard to the patient. All protocol amendments must be signed and dated by both the sponsor and the investigator.

7.4 Site Training and Monitoring Procedures

Before initiation of the study, CTI or designated representatives will review and discuss the following items with the investigator and clinic staff: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE reporting, GCP guidelines, eCRF completion guidelines, monitoring requirements, and the ability of the site to satisfactorily complete the protocol. A study manual with instructions for study compliance and eCRF completion will also be provided. Investigator meetings to train investigators and study coordinators will be held, and eCRF training will be reviewed at that time as well.

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and enrolled patients' progress through the study at each site. The investigator will permit CTI's representatives to monitor the study as frequently as CTI deems necessary to determine that protocol adherence and data recording are prompt and satisfactory. CRAs will remotely view eCRF data and contact the site between monitoring visits. They will be available to answer questions about any aspect of the conduct of the study.

During monitoring visits, the CTI representative will usually review regulatory documentation, eCRFs, source documents, and study drug preparation, storage, and accountability. The eCRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared with the source documents. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm information contained in the eCRFs is complete, timely and accurate. This will include information about medical history, secondary diagnoses, and concomitant medications. Source documents must be available during the scheduled monitoring visits at the beginning of the visit. All source data and study records must also be available for inspection by representatives of the FDA or other regulatory agencies.

7.5 Record Retention

Investigative sites must retain study records, including source data, copies of eCRFs, and all study correspondence, according to local requirements but for a minimum of 2 years after the last market approval is received for this product, or for 2 years after all clinical and product development of this product has been discontinued. In addition, the investigator will keep a master log of all patients participating in the study with sufficient information to allow retrieval of a study patient's medical record. The investigator must notify CTI or its designee before destroying or moving any records relating to this study.

7.6 Financing and Insurance

Financing and insurance issues are addressed in detail in the Clinical Study Agreement.

7.6.1 Financial Disclosure

Each investigator (including the principal investigator and any sub investigator) directly involved in the treatment or evaluation of research subjects must disclose certain financial arrangements.

In this context *investigator* is defined as all individuals listed on FDA Form 1572—or, for non-IND studies performed outside the United States, listed in the signature list—who are directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.

The following arrangements and interests involving investigators and their spouse and dependent children may be disclosed to the FDA:

Any compensation affected by the outcome of clinical studies.

Any ownership interest, stock options, or other financial interest, the value of which cannot be readily determined through reference to public prices (generally, interests in a non-publicly traded corporation), or any equity interest in a publically traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.

Payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, exclusive of the costs of conducting the clinical study or other clinical studies, (eg, a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the investigator is carrying out the study and for 1 year following the completion of the study.
A financial disclosure statement must be provided to the sponsor for each investigator at a study site before the study can commence. Financial disclosure statements must also be provided at the time the study is closed and at the 1-year anniversary of study closure.

7.7 Publication Policy

The publication policy is covered in the clinical study agreements. The investigator agrees to submit all manuscripts, abstracts, or other publications to CTI at least 1 month prior to submission for publication. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

8 Appendices

8.1 International Prognostic Index (IPI) Score Calculation

For the purposes of this study, baseline information is used to calculate the IPI.

IPI Points[a]	Characteristic
1	Age > 60 years
1	[ECOG] Performance Status 2, 3, or 4
1	NHL Stage III or IV
1	Elevated LDH
1	More than 1 extranodal site
Maximum Possible Score: 5	
Abbreviations: ECOG = Eastern Cooperative Oncology Group LDH = lactate dehydrogenase NHL = non-Hodgkin lymphoma. [a]The International Non-Hodgkin's Lymphoma Prognostic Factors Project[30].	

8.2 ECOG Performance Status Grades and Definitions

ECOG PS Grade[a]	Definition
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Abbreviations:
ECOG = Eastern Cooperative Oncology Group PS = performance status.
[a]Oken MM, et al.[31].

8.3 Ann Arbor Staging System

Ann Arbor Stage[a]	Definition
I	Involvement of a single lymph node or a single extranodal organ or site
II	Involvement of ≥2 lymph node regions on the same side of the diaphragm, or localized involvement of an extranodal site or organ (IIE) and ≥1 lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm, which may be also accompanied by local involvement of an extranodal organ or site (stage IIIE) spleen (Stage IIIS) or both (stage IIISE)
IV	Diffuse or disseminated involvement of one or more distant extranodal organs with or without associated lymph node involvement

[a]Carbone PP, et al.[32].

8.4 New York Heart Association Functional Classification

The New York Heart Association (NYHA) functional classification is often used to characterize limitation from left ventricular failure. Since 1973 the NYHA has not officially sanctioned the functional classification. However, it continues to be used widely and has a strong association with mortality that is independent of left ventricular ejection fraction (LVEF).

NYHA Class[a]	Definition
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea.
II	Slight limitation of physical activity. Comfortable rest, but ordinary physical activity results in fatigue or dyspnea.
III	Marked limitation of physical activity. Comfortable rest, but less than ordinary activity causes fatigue or dyspnea.
IV	Unable to carry on any physical activity without symptoms. Symptoms are present even at rest. If any physical activity is undertaken, symptoms are increased.

[a]The Criteria Committee of the New York Heart Association[33].

8.5 Anthracycline/Anthracenedione Equivalent Doses

Agent	Dose Equivalent to 450 mg/m^2 Doxorubicin (mg/m^2)
Doxorubicin	450
Lipo doxorubicin	450
Daunorubicin	490
Lipo daunorubicin	818
Epirubicin	736
Idarubicin	112.5
Mitoxantrone	160

To calculate the doxorubicin-equivalent dose, use the following expanded formula for the appropriate drugs:

Doxorubicin equivalent dose = A + 0.9184*B + 0.5501*C + 0.6114*D + 4*E + 2.8125*Y, where:

- A is the combined doxorubicin and liposomal doxorubicin dose in mg/m^2
- B is the daunorubicin dose in mg/m^2
- C is the liposomal daunorubicin dose in mg/m^2
- D is the epirubicin dose in mg/m^2
- E is the idarubicin dose in mg/m^2
- Y is the mitoxantrone dose in mg/m^2

8.6 Evaluation of Target and Non-target Lesions

The following calculations and assessments should be performed for scanned lesions at radiologic assessment time points as specified in the protocol and for unscheduled CT/MRI assessments.

8.6.1 Baseline Target Lesion Evaluation

1. For each target lesion, identify and measure the longest diameter. From this point forward, this will be referred to as the target lesion's long diameter (LDi). The LDi will be assessed in all subsequent target lesion evaluations.
2. For each target lesion, identify and measure the longest diameter ***that is perpendicular*** to the LDi. From this point forward, this will be referred to as the target lesion's short diameter (SDi).The SDi will be assessed in all subsequent target lesion evaluations.
3. For each target lesion, multiply the LDi × SDi to calculate the PPD. The PPD will be assessed in all subsequent target lesion evaluations.
4. Add the PPDs of the entire group of target lesions to arrive at the Sum of Products of the Perpendicular Diameters (SPD).The SPD will be assessed in all subsequent target lesion evaluations.

8.6.2 All Subsequent Target Lesion Evaluations

Do all of the calculations (steps 1-4) in Section 8.6.1. After each step, answer the following questions and make the indicated calculations.

For the LDi and SDi: has the length increased, decreased, or has it remained the same?

- If increased in length, calculate the percentage of increase from the shortest prior length measured at baseline or at any other prior evaluation (nadir).

For each target lesion: calculate the PPD (LDi × SDi)

- If increased in size, calculate the percentage of increase from the smallest prior PPD measured at baseline or at any other prior evaluation (nadir).

Calculate the SPD (sum of PPDs of all target lesions)

- If increased in size, calculate the percentage of increase from the smallest prior SPD measured at baseline, or at any other prior evaluation (nadir).
- If decreased in size, calculate the percentage of decrease from baseline.
- No change, note.

8.6.3 Baseline and Post-Baseline Non-target Lesion Evaluations

Identify the non-target lesions and note their locations. At each post-baseline assessment, visually assess change in size and categorize each lesion as one of the following:

- Absent
- Decreased
- Stable
- Increased

9 Investigator Responsibilities, Required Documentation, and Signature

CTI BioPharma Corp. will select the investigator(s) on the basis of their expertise in the field of clinical studies in hematologic oncology and in the care and treatment of patients with cancer. Investigators will also be selected on the appropriateness of the facility to conduct a research study of this nature, and the patient population treated at the institution. The investigator will:

- Obtain Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval of the protocol or amendments to the protocol and Informed Consent Form before initiation of the study, and obtain annual Institutional Review Board or Independent Ethics Committee (IEC) renewal, as required.
- Be responsible for ensuring that current FDA and/or ICH-E6 regulations are followed.
- Select all patients in accordance with the selection criteria outlined in Section 3.
- Treat and follow patients as described in this research protocol; complete all case report forms in a timely manner, review CRFs for accuracy and completeness, and provide the original clinical source documents with a clinical summary to the sponsor's clinical research monitor.
- Report all adverse events to CTI BioPharma Corp. or designee as required by the protocol.
- Ensure that investigational drug is kept in a secured, limited access area and stored under proper conditions. Ensure that all investigational drug receipt and dispensing is recorded and all drug can be accounted for at all times.
- If participating in the study, will submit to CTI before initiation of the study:
  - FDA Form 1572 and, if applicable, other Ministry of Health-required forms
  - Copies of the medical licenses of principal investigator and subinvestigators
  - Address and a description of all clinical laboratory facilities to be used
  - Laboratory certification and expiration dates
  - Normal ranges and effective date for all required laboratory tests
  - IRB/IEC Approval Letter referencing the protocol (and amendments, if applicable)
  - IRB/IEC Membership List: A list of the IEB/EC members, their respective titles or occupations, and their institutional affiliations
  - A sample copy of the IRB/IEC-approved Informed Consent
  - Curricula vitae for the principal investigator and all subinvestigators
  - Financial disclosure for the principal investigator and all subinvestigators
  - Protocol signature page signed by the investigator

Investigator Statement and Signature:

I attest that I have read this protocol, understand and agree to the provisions of the protocol, and accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature Date

Investigator Name, Printed

10 Document History

Protocol Version	Effective Date	
Original	December 7, 2010	
Amendment 1	December 9, 2010	
Amendment 2	March 10, 2011	
Amendment 3	August 3, 2011	
Amendment 4	January 5, 2012	
Amendment 5	April 9, 2012 (NA)[d]	June 18, 2012 (NNA)[d]
Amendment 6[a]	August 31, 2012 (NA)[d]	October 17, 2012 (NNA)[d]
Amendment 7[b]	None (NA)[d]	September 16, 2013 (NNA)[d]
Amendment 8[c]	July 25, 2014	
Amendment 8a PK [e]	November 10, 2015	
Amendment 9	July 10, 2017	

[a] The North America and Non-North America versions of Amendment 6 were identical, except for minor formatting differences.
[b] Only Non-North America Amendment 6 was updated to Amendment 7; see details in Note to File in the CTMF dated 25 June 2014.
[c] Amendment 8 protocol unifies the previous NA and NNA versions. Changes include those from Amend 6 NA and Amend 7 NNA.
[d] NA = North America, NNA = Non-North America
[e] Applicable only to sites performing pharmacokinetics evaluations

11 References

1. Surveillance Epidemiology and End Results Web site. Cancer Statistics. SEER Stat Fact Sheets: Non-Hodgkin Lymphoma. http://seer.cancer.gov/statfacts/html/nhl.html. Accessed on 21 July 2014.
2. Horner MJ, Ries LAG, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2006, National Cancer Institute web site, Bethesda, MD: http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009. Accessed on 01 July 2014.
3. Fisher RI1, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CA Jr, Miller TP. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993 Apr 8;328(14):1002-6.
4. Prichard M, Harris T, Williams ME, Densmore JJ. Treatment strategies for relapsed and refractory aggressive non-Hodgkin's lymphoma. Expert Opin Pharmacother 2009 Apr;10(6):983-95.
5. Gisselbrecht C, Glass B, Mounier N, et al. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study. J Clin Oncol 2009;27(suppl abstr 8509):152.
6. Center for International Blood & Marrow Transplant Research (CIBMTR) web site, accessed on 01 July 2014: http://www.cibmtr.org/pages/index.aspx.
7. Mordente A1, Meucci E, Silvestrini A, Martorana GE, Giardina B. New developments in anthracycline-induced cardiotoxicity. Curr Med Chem. 2009;16(13):1656-72.
8. Doxorubicin Prescribing Information. Pfizer Labs, A Division of Pfizer Inc. Sep 2011.
9. Sissi C, Moro S, Richter S, Gatto B, Menta E, Spinelli S, Krapcho AP, Zunino F, Palumbo M. DNA-interactive anticancer aza-anthrapyrazoles: biophysical and biochemical studies relevant to the mechanism of action. Mol Pharmacol 2001 Jan;59(1):96-103.
10. Evison BJ, Bilardi RA, Chiu FC, Pezzoni G, Phillips DR, Cutts SM. CpG methylation potentiates pixantrone and doxorubicin-induced DNA damage and is a marker of drug sensitivity. Nucleic Acids Res 2009 Oct;37(19):6355-70.
11. Cavalletti E1, Crippa L, Mainardi P, Oggioni N, Cavagnoli R, Bellini O, Sala F. Pixantrone (BBR 2778) has reduced cardiotoxic potential in mice pretreated with doxorubicin: comparative studies against doxorubicin and mitoxantrone. Invest New Drugs 2007 Jun;25(3):187-95.
12. Marcus R, Hagenbeek A. The therapeutic use of rituximab in non-Hodgkin's lymphoma. Eur J Haematol Suppl 2007 Jan;(67):5-14.
13. Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, Ma D, Johnson P, Lister A, Feuring-Buske M, Radford JA, Capdeville R, Diehl V, Reyes F. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998 Sep 15;92(6):1927-32.
14. Tobinai K, Igarashi T, Itoh K, Kobayashi Y, Taniwaki M, Ogura M, Kinoshita T, Hotta T, Aikawa K, Tsushita K, Hiraoka A, Matsuno Y, Nakamura S, Mori S, Ohashi Y; IDEC-C2B8 Japan Study Group. Japanese multicenter phase II and pharmacokinetic study of rituximab in relapsed or refractory patients with aggressive B-cell lymphoma. Ann Oncol 2004 May;15(5):821-30.
15. Decaudin D, Marszak FB, Couturier J, Mathiot C, Martin A, Némati F, Lantz O, Santo Jd, Arnaud P, Bordier V, Vincent-Salomon A, Poupon MF. High efficacy of combined rituximab and gemcitabine on Epstein-Barr virus-associated human B-cell lymphoma obtained after Hodgkin's xenograft in immunodeficient mice. Anticancer Drugs. 2006 Jul;17(6):685-95.
16. Chau I, Watkins D, Cunningham D. Gemcitabine and its combinations in the treatment of malignant lymphoma. Clin Lymphoma. 2002 Sep;3(2):97-104.
17. Bernell P, Ohm L. Promising activity of gemcitabine in refractory high-grade non-Hodgkin's lymphoma. Br J Haematol. 1998 Apr;101(1):203-4.
18. Savage DG1, Rule SA, Tighe M, Garrett TJ, Oster MW, Lee RT, Ruiz J, Heitjan D, Keohan ML, Flamm M, Johnson SA. Gemcitabine for relapsed or resistant lymphoma. Ann Oncol 2000 May;11(5):595-7.

19. Fosså A, Santoro A, Hiddemann W, Truemper L, Niederle N, Buksmaui S, Bonadonna G, Seeber S, Nowrousian MR. Gemcitabine as a single agent in the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol 1999 Dec;17(12):3786-92.

20. Wenger C1, Stern M, Herrmann R, Rochlitz Ch, Pless M. Rituximab plus gemcitabine: a therapeutic option for elderly or frail patients with aggressive non Hodgkin's lymphoma? Leuk Lymphoma. 2005 Jan;46(1):71-5.

21. Rothe A, Schulz H, Elter T, Engert A, Reiser M. Rituximab monotherapy is effective in patients with poor risk refractory aggressive non-Hodgkin's lymphoma. Haematologica. 2004 Jul;89(7):875-6.

22. Palacios A, Navarrete M, Gallur L. Retreatment with Rituximab plus chemotherapy in patients with aggressive lymphoma treated previously with CHOP or CHOP-like combinations plus rituximab. Blood (ASH Annual Meeting Abstracts) 2006;108:Abstr 4707.

23. National Comprehensive Cancer Network Clinical Practice Guidelines (NCCN Guidelines): http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed on 30 June 2014.

24. Morschhauser F1, Illidge T, Huglo D, Martinelli G, Paganelli G, Zinzani PL, Rule S, Liberati AM, Milpied N, Hess G, Stein H, Kalmus J, Marcus R. Efficacy and safety of yttrium-90 ibritumomab tiuxetan in patients with relapsed or refractory diffuse large B-cell lymphoma not appropriate for autologous stem-cell transplantation. Blood 2007 Jul 1;110(1):54-8.

25. Corazzelli G, Capobianco G, Arcamone M, Ballerini PF, Iannitto E, Russo F, Frigeri F, Becchimanzi C, Marcacci G, De Chiara A, Pinto A. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol. 2009 Oct;64(5):907-16.

26. Genentech, Inc., 2010. Rituxan Prescribing Information.

27. Eli Lilly and Company, 2010. Gemzar Prescribing Information.

28. Cheson B, Pfistner B, Juweid M, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;26(5):579-85.

29. Pettengell R1, Coiffier B, Narayanan G, de Mendoza FH, Digumarti R, Gomez H, Zinzani PL, Schiller G, Rizzieri D, Boland G, Cernohous P, Wang L, Kuepfer C, Gorbatchevsky I, Singer JW. Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. Lancet Oncol. 2012 Jul;13(7):696-706.

30. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993 Sep 30;329(14):987-94.

31. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982 Dec;5(6):649-55.

32. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res. 1971 Nov;31(11):1860-1.

33. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th Ed., Boston, Mass: Little, Brown & Co; 1994:253-6.

12 Addendum: Pharmacokinetics Sub-Study

Previously, the pharmacokinetics (PK) of pixantrone was assessed in patients with malignancy when pixantrone was given alone or in combination with multiple chemotherapeutic agents (see Investigator's Brochure), but not in combination with rituximab. This sub-study is designed to provide additional information regarding the PK of pixantrone when administered as a single agent in combination with rituximab.

Approximately 20 sites have been selected to participate in this sub-study, and were identified based on their qualifications, experience in collecting samples for PK analysis, and willingness to participate in the sub-study. The goal is to enroll approximately 20 patients into the PK sub-study.

12.1 Background

As shown in studies to date, clinical PK of pixantrone is linear over a wide dose range. Pixantrone has a large volume of distribution (eg, $V_{ss,}$ approx. 15–20 L/kg), a high systemic clearance (CL, approx. 1 L/h/kg), and a relatively long terminal elimination half-life ($t_{½,z}$, approx. 20 hours). Biliary excretion appears to be the major route of systemic clearance for pixantrone. Modest amounts of phase I metabolites were produced by side-chain cyclization and N-dealkylation. Two monoacetylated metabolites have also been observed. Renal excretion is a minor route of drug elimination (<10%).

A comprehensive population PK analysis was also conducted, using PK data from six phase 1 studies (139 patients) following single or multiple dose administrations. Covariates that were tested included age, sex, body weight, calculated creatinine clearance (CL_{CR}), concomitant antiemetic medication, total bilirubin, race, and body surface area (BSA). Across the full dose range in the clinical program, clearance was nearly proportional to BSA, suggesting that dosing according to BSA appropriately normalizes exposures (see Investigator's Brochure).

The recommended monotherapy dose of pixantrone is 50 mg/m^2 pixantrone base form (equivalent to 85 mg/m^2 pixantrone dimaleate), given on Days 1, 8, and 15 of up to six 28-day cycles. In the present study (PIX306), patients are randomized to the combination of gemcitabine plus rituximab, or pixantrone plus rituximab for up to 6 cycles, with rituximab co-administered on Day 1 of each 28-day cycle.

12.2 Objective of Pharmacokinetics Sub-Study

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

The PK sub-study of this trial (PIX306) is being conducted to characterize the pharmacokinetics of pixantrone in patients also receiving rituximab. These data will complement the pharmacokinetic results collected to date for pixantrone, provide a reference set of pharmacokinetic parameters in patients treated with the combination of pixantrone and rituximab and support the assumption that pixantrone PK is not influenced by rituximab co-administration. Rituximab is co-administered with pixantrone on Day 1 of each 28-day cycle; therefore, plasma samples for PK analysis (7 samples) will be collected relative to the Day 1 dose of pixantrone in one of the six treatment cycles for each participating patient.

12.3 Pharmacokinetics Sub-Study Population

PK Sub-Study Inclusion Criteria

- Patient must have been randomized to the PIX306 pixantrone + rituximab arm at a participating clinical site. Patients newly randomized or already randomized in the pixantrone group can be included.
- Patients must be willing to participate in the PK sub-study and cooperate with the PK sampling schedule, as described in the written consent for participation in the sub-study.

Patient enrollment in the PK sub study will commence upon approval of this PIX306 amendment and will continue until the sub-study accrual goal of approximately 20 patients is reached or the PIX306 study accrual ceases, whichever comes first (see Section 12.6 for discussion of sample size).

Patients already randomized at the time this amendment is initiated can also participate in the PK sub-study, provided that one or more 28-day cycles remain to be completed, and after providing informed consent.

12.4 Pharmacokinetics Sub-Study Assessment

Seven blood samples (up to 10 mL/sample) for PK assessment will be collected into lithium heparinized polypropylene tubes per the table in Section 12.4.1 on Day 1 in one of the six treatment cycles. When possible, complete the PK sampling during cycle 1 or 2.

Patients must have successfully received their dose of rituximab prior to pixantrone infusion for post-infusion PK samples to be obtained.

12.4.1 PK Sampling Schedule

Collect PK samples only when rituximab has been administered on Day 1 prior to pixantrone, per Section 3.4. The sampling schedule for the study is provided below; plasma samples are to be collected at the indicated nominal time points *relative to the initiation of the pixantrone infusion*. Refer to Table--14 for the collection regimen.

Table--14 Sample Collection Times for Pharmacokinetic Evaluation

Sample Number	Nominal Sample Time	Collection Window
1	Prior to start of pixantrone infusion	Within 1 hour of initiation of infusion
2	1 hour after start of pixantrone infusion	Within 10 minutes *after* the end of infusion
3	1.5 hours after start of pixantrone infusion	±10 minutes
4	2 hours after start of pixantrone infusion	±10 minutes
5	4 hours after start of pixantrone infusion	±30 minutes
6	6 hours after start of pixantrone infusion	±1 hour
7	24–48 hours after start of pixantrone infusion	

12.4.2 Adverse Events During PK Sampling

Adverse events associated with blood sampling for this PIX306 PK evaluation will be collected and reported consistent with Section 3.10.1 of the protocol.

12.5 Sample Collection and Handling Procedures

Plasma samples for measurement of pixantrone are to be collected, processed and shipped according to the PK Plasma Sample Handling and Collection Manual (provided separately). Samples will be subsequently analyzed for pixantrone levels according to a validated bioanalytical assay method. All samples collected will be shipped to the PK laboratory, even if sampling is incomplete and/or rescheduled.

The treatment cycle, nominal sample times, date, and 24-hour actual collection times for each sample will be recorded on the case report form. The start and end times of the infusion will be separately recorded in the case report form.

Sample Rescheduling

Ideally, PK sampling should occur in the earliest possible treatment cycle. However, PK sampling should be rescheduled or repeated for a subsequent cycle if any of the below events occur:

- Rituximab was not administered prior to pixantrone
- Pixantrone infusion is not administered per protocol, including, but not limited to, such deviations as interrupted infusion, infiltrated infusion, and infusion that does not occur in the protocol-specified time frame (1 hour ±10 minutes).
- Significant and acute changes are noted in predose liver function tests or general medical condition on the day of dosing, as compared to their screening baseline. In case of study site questions about this criterion, the unblinded medical monitor should be consulted for answers and decision-making. (Unblinded medical monitor will notify the CTI PIX306 pharmacokineticist in a blinded fashion.)
- A clinical event occurs that interferes with proper collection of samples.

All samples collected will be shipped to the PK laboratory, even if sampling is incomplete and/or rescheduled.

12.6 PK Analysis

This amendment is being initiated after a significant number of patients have already been enrolled in the PIX 306 study, but before the efficacy and safety results have been analyzed. The goal is to enroll approximately 20 patients receiving pixantrone into the PK sub-study. This sample size is considered clinically reasonable to obtain estimates of PK parameters of pixantrone when co-administered with rituximab, to supplement currently available PK analyses.

The PK sample analysis will be performed by Atlanbio (St. Nazaire, France) using a validated analytical method. Additionally, using the bioanalytical data provided by Atlanbio and clinical covariate data from the study database, Quantitative Solutions (Certara, Princeton, NJ, USA) will be used to supplement the population analyses that were previously conducted (see Section 12.1) and examine the impact of coadministration of rituximab with pixantrone on PK parameters in the population model.

Descriptive statistics (n, mean, standard deviation (SD), median, minimum, maximum) of blood concentrations of pixantrone will be performed at each nominal time point.

A population modeling approach will be used to describe the PK of pixantrone. In a first stage, the individual concentration-time profiles of patients will be compared to existing data using the model previously developed. This will be done by simulations (Visual Predictive Checks). Then, in a second stage, the model will be used to generate individual secondary PK parameters (eg, exposure, half-life etc.) of patients with relapsed, aggressive B-cell NHL receiving pixantrone in association with rituximab. To do that, for each subject, due to the sparse sampling time design (ie, 7 blood samples), a compartmental analysis will be first performed on the individual concentration-time data, using the population PK model previously developed, to provide individual predicted PK profiles simulated with a rich sampling time design (step 1). Second (step 2), a non-compartmental analysis (NCA) will be performed on the predicted PK obtained by the Bayesian approach in step 1. The following parameters will be determined in plasma, as well as others, as deemed appropriate: Cinf (concentration at the end of the infusion), AUC0-24, t1/2, z, CL, Ke Vss and Vz. Descriptive statistics will be performed on the plasma concentrations and on the pharmacokinetic parameters of pixantrone.

12.7 Pharmacokinetics Sub-Study Ethical Considerations

This amendment and specific procedures for the PK sub-study will be included in a properly constituted supplemental informed consent to be reviewed and approved by the respective Institutional Review Board/Ethics Committee responsible for those sites agreeing to enroll patients into the PK sub-study. Informed consent for the sub-study will be obtained only from patients eligible for (randomized to pixantrone plus rituximab treatment arm) and willing to participate in the PK sub-study.