Document title	**CLINICAL STUDY REPORT**
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**
Test drug code	**Pixantrone**
Indication	**Aggressive B-cell Non-Hodgkin Lymphoma**
Development phase	**Phase III**
Protocol code	**PIX306**
Study initiation date	**20 April 2011**
Data cut-off date	**31 May 2018**
Main coordinator	[redacted]
Sponsor	**CTI BioPharma Corp.** **3101 Western Avenue, Suite 800** **Seattle, WA 98121 - US**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**16 November 2018**
Version of the report	**Final version**
	CONFIDENTIAL

2. SYNOPSIS

Name of Sponsor: CTI BioPharma Corp.		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Pixuvri® **Name of Active Ingredient:** Pixantrone		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: 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

Protocol No.: PIX306.
EudraCT No.: 2012-001790-86.
IND No.: 62,678.

The description of the study protocol given hereafter includes the modifications made by the 9 substantial amendments to the protocol.

Main Investigator

[redacted]

Study countries:
Eighteen countries included 312 patients: in North America: 102 patients in United States, and 2 patients in Canada; in Europe: 13 patients in France, 2 patients in Denmark, 31 patients in Italy, 1 patient in Austria, 2 patients in Slovakia, 10 patients in United Kingdom, 6 patients in Germany, 24 patients in Bulgaria, 11 patients in Hungary, 28 patients in Czech Republic, 13 patients in Spain, 31 patients in Poland, 7 patients in Belgium, 4 patients in Romania, 6 patients in Russia, 19 patients in Ukraine.

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 20 April 2011 (first visit first patient) Cut-off date for core analysis: 31 May 2018 (this report) End of study: 14 September 2018 (last visit last patient)	III

Objectives:

Primary objective

The primary objective of this study was 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 lymphoma grade 3 (FL Grade 3) who had relapsed after at least 1 prior chemotherapy regimen and who were 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 FL Grade 3 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 non-Hodgkin lymphoma (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.

Objectives (Cont'd):
Patients ineligible for SCT included 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.
- Were unsuitable for SCT due to other medical conditions or age.
- Did not wish to undergo SCT.
- Had financial issues precluding SCT.
- Were considered by the investigator as unsuitable for SCT for any other reason.

Secondary Objectives
To compare the two treatment arms with regards to the following secondary endpoints:

- Overall survival (OS).
- Overall response rate (ORR).
- Complete response (CR) rate.
- Safety.

Exploratory Objectives

- To assess the duration of overall response between treatments.
- To assess the duration of complete response between treatments.
- To determine the proportion of randomized patients who received a SCT after study treatment.

Pharmacokinetics (PK) Sub-Study Objective

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

Methodology:
This was a phase III, multicenter, randomized (1:1 ratio), active-controlled study blinded for the sponsor, evaluating the efficacy of pixantrone + R *versus* gemcitabine + R in patients with the described indications.
Randomization was stratified on the number of prior therapies for DLBCL or FL Grade 3 (0-2 *versus* ≥ 3), International Prognostic Index (IPI) score (0-2 *versus* ≥ 3), and length of time from initiation of first-line therapy for DLBCL or FL Grade 3 until first relapse (< 1 year ≥ 1 year).

This study was performed in accordance with Good Clinical Practice standards. Patient safety was monitored by an Independent Data Monitoring Committee (IDMC).

Number of patients:
Planned: Approximately 320 patients were planned to be randomized in a 1:1 ratio to one of the two treatment arms.

Randomized: 312 patients. The study was closed for enrolment in August 2017 when 312 patients had been randomized. This number of randomized patients was considered as sufficient to achieve the 195 PFS events as assessed by the Independent Radiology Committee (IRC) that were required to detect a 35% improvement in primary outcome.

Diagnosis and main criteria for inclusion:
Patients with a diagnosis of DLBCL (*de novo* DLBCL or DLBCL transformed from indolent lymphoma), or FL Grade 3 on the basis of a tissue biopsy who had relapsed after at least 1 prior rituximab containing chemotherapy regimen and who were currently ineligible for high-dose (myeloablative) chemotherapy and SCT.
Patients with *de novo* DLBCL or FL Grade 3 should not have had a primary refractory disease, which was defined in the protocol as documented progression within 12 weeks of the last cycle of the first-line multi-agent regimen.
Patients with DLBCL transformed from indolent lymphoma should have had a complete or partial response to a therapy for NHL lasting at least 12 weeks.
Patients were to have at least one bi-dimensionally measurable site of disease that had not been previously irradiated: nodal disease ≥ 1.5 cm in short axis or extranodal disease > 1.0 cm in short axis. Lesion was to be positron emission tomography (PET) positive if PET scan was obtained.

Investigational therapy:
Pixantrone 50 mg/m^2 intravenously (IV) on Days 1, 8, and 15; up to six 28-day cycles.
Rituximab (R) was administered prior to Pixantrone at the dose 375 mg/m^2 IV on Day 1 of each cycle.

Control therapy:
Gemcitabine 1000 mg/m² IV on Days 1, 8, and 15; up to six 28-day cycles.
Rituximab (R) was administered prior to Gemcitabine at the dose 375 mg/m² IV on Day 1 of each cycle.

Study periods:
Screening period: up to 28 days before randomization. No specific antilymphoma treatment or any other experimental treatment was allowed.
Treatment period: was to be initiated as soon as possible after randomization and within 14 days.
Maximal treatment duration up to six 28-day cycles.
Follow-up periods:
- *Follow-up:* after treatment completion or drug withdrawal (End of Treatment) for reasons other than progressive disease (PD), patients entered a 6-month early follow-up period, followed by an 18-month intermediate follow-up to evaluate the disease response.
- *Survival follow-up:* after completing intermediate follow-up or in case of PD or if receiving a subsequent systemic anticancer therapy, or withdrawing consent until death or study end. At the time of this data cut-off, all patients in Early or Intermediate Follow up at that time, entered the survival follow-up period.

Criteria for evaluation:

Efficacy measurements:
Response was evaluated according to the modified International Working Group (IWG) 2007 Revised Response Criteria.
Disease assessment included neck, chest, abdomen, and pelvis via CT scan with IV contrast, if possible, or else MRI of the neck, abdomen and pelvis with non-contrast chest CT scan. At each evaluation time point, every target and non-target lesions were to be evaluated. The imaging method used at baseline was to be used throughout the study. All scans obtained during the course of the study were reviewed by an Independent Radiology Committee (IRC) that was blinded to treatment assignment. An end-of-treatment (EOT) PET scan was required, unless geographically unavailable, or if the patient had PD per Modified IWG criteria, or if the patient had started subsequent systemic anticancer therapy (except rituximab maintenance therapy). A bone marrow biopsy (with core) was also required at EOT to confirm a CR, unless a bone marrow biopsy was obtained at baseline and was negative.
Survival status was recorded at each scheduled visit during treatment and follow-up periods until the end of the study.

Safety measurements:
Adverse events (AEs), serious adverse events (SAEs), with a focus on cardiac events (including left ventricular ejection fraction and serum troponin T), hematologic and blood chemistry parameters, vital signs, performance status (PS), and any abnormal findings observed during physical examination.

Pharmacokinetic measurements:
Plasma parameters of pixantrone: samples were collected after rituximab administration, and at 7 nominal time-points relative to the initiation of pixantrone infusion (*i.e.* prior to start of pixantrone infusion, then 1h, 1.5h, 2h, 4h, 6h and 24-48h after start of pixantrone infusion).

Statistical methods:

Analysis Sets:
Intent-To-Treat (ITT) population: all randomized patients regardless of whether subjects received any study treatment, or received a different treatment from the treatment they were randomized to.

Histologically confirmed population (HITT): all randomized patients with DLBCL (*de novo* DLBCL or DLBCL transformed from indolent lymphoma) or FL Grade 3 confirmed by the central pathology review committee.

Per Protocol (PP) population: all randomized patients who received any study treatment, underwent at least one post baseline disease assessment or died before the first post baseline scheduled disease assessment, and had no major protocol violations.

Safety population: all randomized patients who received at least one administration of study drug.

Statistical methods (Cont'd):

Efficacy analysis:
For the efficacy analysis, pixantrone + R was compared with gemcitabine + R for all primary and secondary endpoints, which are presented below. The multiplicity arising from the testing of multiple endpoints was addressed using a closed testing procedure that required establishing significance in the primary endpoint prior to assessing the significance of secondary endpoints (OS, ORR and CR rate) to ensure the overall type I error at 0.05.

The tests hierarchy, which reflected the importance of the clinical endpoints in the study, was planned as follows:

- First, the primary hypothesis test for PFS was to be performed at the 2-sided 0.05 α-level.
- If the associated p-value was significant, the secondary hypothesis of OS would be tested using an overall 0.05 α-level considering a sequential procedure.
- If the hypothesis test of OS was achieved, then the secondary hypotheses of ORR, followed by CR, would be tested at the 2-sided 0.05 α-level.

No interim analysis was planned for PFS, the primary objective of the study.

The analysis of the secondary objective of OS in this report was an interim since the survival assessment was still on-going at the time of this data cut-off. This analysis was performed by the IDMC so that the Sponsor remained blinded to the randomization.

This prespecified core data cut-off was performed after 195 PFS events per IRC. It was estimated that by this time, approximately 165 deaths would have occurred. The final analysis for OS was planned to be conducted when 220 deaths were recorded. It was decided by the Sponsor however to terminate the study before this target was reached.

Primary endpoint:
The primary endpoint was PFS: the time from the date of randomization to the date of PD or death due to any cause (whichever was first reported). The primary analysis was PFS per IRC in the ITT population compared between the two treatment groups using a stratified log-rank test and a Cox regression model adjusted on the randomization stratification factors (IPI score, prior lines of therapy for DLBCL and FL Grade 3, and time from initiation of therapy for DLBCL or FL Grade 3 until first relapse). Hazard ratios and corresponding 95% CI as estimated from the Cox regression model were also presented. Summary statistics, including median PFS and the corresponding 95% CI based on Kaplan-Meier estimates, were presented by treatment group. The Kaplan-Meier curve was also plotted.

To assess the robustness of the primary PFS results, exploratory sensitivity analyses using different rules for censoring/defining PD event, varying the stratification factor variables, or using different sets of patients were performed.

Secondary endpoints:
OS, defined as the time from the date of randomization to the date of death due to any cause. The comparison of the treatment effect on OS was performed using same methods as described for PFS.

Overall Response Rate (ORR), defined as the proportion of patients who achieved a CR or PR without additional anticancer therapy. For the primary analysis, based on disease response per IRC assessment, between-arm comparison of the ORRs was performed using the exact Cochran-Mantel-Haenszel (CMH) test, controlling for stratification factors.

Complete Response (CR) Rate, defined as the proportion of patients who achieved a CR without additional therapy, was analyzed in the same manner as for ORR.

Exploratory endpoints:
Duration of Overall Response (DOR), Duration of Complete Response (DCR), proportion of patients receiving SCT after study treatment.

Safety analysis:
Descriptive statistics were provided.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 312 patients were randomized in the study. The distribution of patients according to treatment group was well-balanced: 155 patients in the pixantrone + R group and 157 in the gemcitabine + R group (see Table below).

Disposition of patients

Status	Pixantrone + R n (%)	Gemcitabine + R n (%)	All n (%)
All randomized	**155**	**157**	**312**
Patients who discontinued treatment due to	**83 (53.5)**	**96 (61.1)**	**179 (57.4)**
progressive disease	47 (30.3)	50 (31.8)	97 (31.1)
adverse event	21 (13.5)	15 (9.6)	36 (11.5)
consent withdrawal	6 (3.9)	16 (10.2)	22 (7.1)
death	5 (3.2)	10 (6.4)	15 (4.8)
other	4 (2.6)	5 (3.2)	9 (2.9)
Patients who completed the treatment	**72 (46.5)**	**61 (38.9)**	**133 (42.6)**
Patients who withdrew from the study due to	**103 (66.5)**	**94 (59.9)**	**197 (63.1)**
death	94 (60.6)	84 (53.5)	178 (57.1)
consent withdrawal	6 (3.9)	8 (5.1)	14 (4.5)
lost to follow-up	1 (0.6)	2 (1.3)	3 (1.0)
other	2 (1.3)	-	2 (0.6)
ITT Population	**155**	**157**	**312**
Histologically Confirmed Population (HITT)	128 (82.6)	140 (89.2)	268 (85.9)
Per Protocol Population (PP)	145 (93.5)	139 (88.5)	284 (91.0)
Safety Population	153 (98.7)	149 (94.9)	302 (96.8)
Pharmacokinetic population	14 (9.0)	-	14 (4.5)

% : Expressed as percentage of the randomized patients

MAIN BASELINE CHARACTERISTICS

In the ITT population (N = 312), patients had a median age of 73.0 years (range: 26 – 91), with 78.8% aged 65 years or older, and more than half of the patients were female (56.4%).

Patients were diagnosed at a median of 22.8 months prior to study entry (*i.e.* 1.9 years, with a maximum of 15 years). The most frequent histological subtype assessed by the investigator was DLBCL (77.6%), followed by DLBCL transformed from indolent (13.8%) and FL Grade 3 (8.7%). According to the Central Pathology Review Committee (CPRC), 78.5% of patients had DLBCL, 4.8% had DLBCL with follicular components and 2.6% had FL Grade 3. Alternative diagnoses were "non-diagnostic for lymphoma" (6.5% *versus* 3.2%; pixantrone + R *versus* gemcitabine + R, respectively), "other lymphoma" (5.2% *versus* 2.5%), "not assessed" (3.9% *versus* 3.2%) and "assessment was missing" (1.9% in both groups).

Most patients (61.9%) had received 1 prior line of systemic therapy for NHL, 21.8% had received 2 prior lines and 11.5% had received 3 prior lines. Most patients (53.2%) had an IPI score ≥ 3.

Time from initiation of first-line therapy for DLBCL or FL Grade 3 until first relapse was less than 1 year for 37.2% of patients.

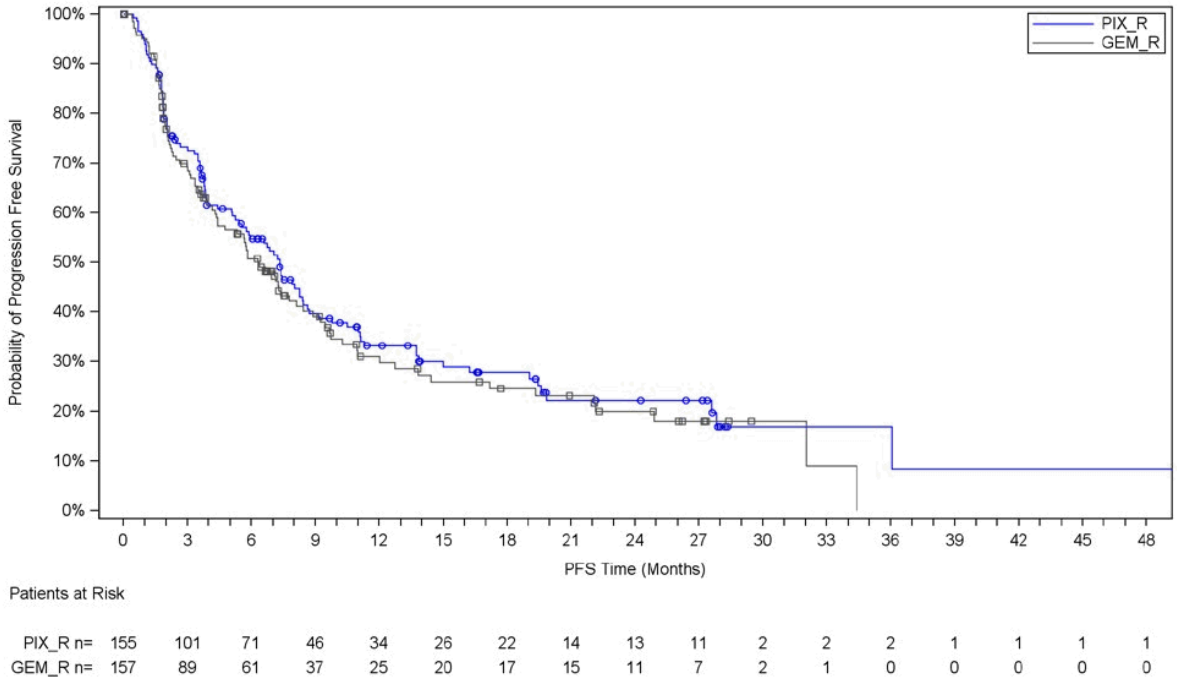
Treatment groups were well-balanced while considering the main baseline characteristics. Baseline characteristics were in line with the target population as defined in the study protocol and representative of this population.

EFFICACY RESULTS

- *Primary efficacy endpoint*

At the data cut-off, the median PFS in the pixantrone + R group was 7.3 months (95% CI [5.2, 8.4]) compared to 6.3 months (95% CI [4.4, 8.1]) in the gemcitabine + R group. The adjusted hazard ratio was 0.85 (95% CI [0.64, 1.14]) indicating that there was no statistically significant superiority of pixantrone + R over gemcitabine + R (p = 0.2782 on stratified log-rank test). All sensitivity analyses were consistent with the primary PFS analysis. The Kaplan-Meier curve of PFS is shown below.

Kaplan-Meier curve of the PFS per IRC assessment in the ITT population



- *Secondary efficacy endpoints*

According to the hierarchical testing design of the study and given that the primary endpoint PFS did not reach its significance, the hypotheses of the secondary endpoints (OS, ORR and CR) were not formally tested.

At the time of the data cut-off, the first interim analysis of OS showed a median OS of 13.3 months (95% CI [10.1, 19.8]) in the pixantrone + R group *versus* 19.6 months (95% CI [12.4, 31.9]) in the gemcitabine + R group (HR = 1.13, 95% CI [0.83, 1.53]).

The ORR was numerically higher in the pixantrone + R group (61.9% of patients) than in the gemcitabine + R group (43.9% of patients), with a between-group difference of 18.0% (95% CI [6.9, 28.6]). Similarly, a numerically higher CR rate was observed in the pixantrone + R group (35.5% of patients) compared to gemcitabine + R (21.7% of patients), with a between-group difference of 13.8% (95% CI [3.8, 23.5]).

Subgroup analyses based on baseline demographic and disease characteristics (number of prior lines of therapy, IPI score, time from start of 1st line therapy to 1st relapse, age, gender, region, Ann Arbor Stage, ECOG PS and number of extranodal sites) were globally in line with the results observed in the overall population.

EXTENT OF EXPOSURE

In the Safety Population (N = 302), the overall median duration of treatment exposure was 17.0 weeks in the pixantrone + R group and 15.6 weeks in the gemcitabine + R group. Slightly more patients received all 6 cycles of study treatment in the pixantrone + R group (50.3%) than in the gemcitabine + R group (43.6%), with a median number of cycles of 6.0 *versus* 5.0, respectively.

The median percentage of protocol nominal dose was numerically greater in the pixantrone + R group (66.7%) than in the gemcitabine + R group (51.3%).

SAFETY RESULTS

The plasma concentrations pixantrone in the PK population were within the expected variability and the median value was in agreement with the simulated median profile.

- **Treatment-emergent adverse events**

Overall summary of TEAEs in the Safety Population

Patients having reported at least one:		**Pixantrone + R (N = 153)**	**Gemcitabine + R (N = 149)**
Any Treatment-Emergent Adverse Event (TEAE)	n (%)	153 (100)	146 (98.0)
TEAE of Grade 3/4	n (%)	130 (85.0)	132 (88.6)
TEAE Related to Study Drug (pixantrone or gemcitabine)	n (%)	140 (91.5)	140 (94.0)
TEAE Related to Study Drug of Grade 3/4	n (%)	118 (77.1)	123 (82.6)
TEAE Related to Rituximab	n (%)	104 (68.0)	92 (61.7)
Serious TEAE (SAE)	n (%)	59 (38.6)	57 (38.3)
Serious TEAE Related to Study Drug	n (%)	30 (19.6)	22 (14.8)
TEAE Leading to Study Drug Discontinuation	n (%)	33 (21.6)	36 (24.2)
TEAE Leading to Death	n (%)	14 (9.2)	8 (5.4)

During the study, 100% of patients in the pixantrone + R group and 98.0% in the gemcitabine + R group reported at least one TEAE. The most frequently reported PTs in the pixantrone + R group were neutropenia, fatigue, anemia, nausea and constipation.
Neutropenia, nausea and constipation were reported more frequently in the pixantrone + R group than in the gemcitabine + R group (neutropenia: 69.3% *versus* 59.1%; nausea: 24.8% *versus* 16.1%; constipation: 23.5% *versus* 13.4%, respectively). Anemia was reported with a lower frequency in the pixantrone + R group (27.5% *versus* 50.3%).
In addition myelodysplastic syndrome (MDS) was reported in 4 patients (2.6%) in the pixantrone + R group *versus* none in the gemcitabine + R group.

TEAEs of **grades 3 or 4** were reported by 85.0% of patients in the pixantrone + R group *versus* 88.6% in the gemcitabine + R group. The most frequent were: neutropenia, observed at numerically higher rate in the pixantrone + R group (63.4% *versus* 55.7%), and anemia and thrombocytopenia, observed at numerically lower rates in the pixantrone + R group (17.0% *versus* 37.6% and 11.1% *versus* 36.9%, respectively).

Transfusions were less frequent in the pixantrone + R group: red blood cell transfusions were reported at 8.5% *versus* 28.9%; platelet transfusions at zero *versus* 6.0%, respectively.

TEAEs related to study drug were reported in 91.5% of patients in the pixantrone + R group and 94.0% in the gemcitabine + R group. The most frequently reported events were (pixantrone + R *versus* gemcitabine + R): neutropenia (68.6% *versus* 59.1%), anemia (22.9% *versus* 43.6%) and thrombocytopenia (15.0% *versus* 63.8%).

Serious TEAEs were reported at similar rates in the 2 groups: 38.6% of patients in the pixantrone + R group *versus* 38.3% in the gemcitabine + R group. The most frequently reported treatment-emergent SAEs were pneumonia (5.2% *versus* 2.7%, respectively), anemia (3.3% *versus* 5.4%) febrile neutropenia (3.3% *versus* 0.7%), and pyrexia (2.6% *versus* 5.4%).

Overall, the incidence of **TEAEs leading to study drug discontinuation** was similar in both treatment groups (21.6% in the pixantrone + R group and 24.2% in the gemcitabine + R group). The most frequent were neutropenia (5.2% *versus* 1.3% respectively), ejection fraction decreased (3.3% *versus* none), and thrombocytopenia (2.6% *versus* 2.7%).

SAFETY RESULTS (Cont'd)

All-cause deaths (occurring within 30 days of the last dose of study drug) totalled 12 in the pixantrone + R group (7.8%) and 16 in the gemcitabine + R group (10.7%).

- Seven (7) patients in each group died due to disease progression.
- Three (3) patients in the pixantrone + R group and 7 in the gemcitabine + R group died due to adverse event.
- Two patients in each group died due to "other reason" (*i.e.* viral pneumonia and asthenia; and acute renal failure and sepsis, respectively).

TEAEs leading to death were more frequent in the pixantrone + R group (14 patients, 9.2%) than in the gemcitabine +R group (8 patients, 5.4%). TEAEs leading to death that were reported in at least 2 patients in the pixantrone group were MDS and pneumonia (each in 2 patients *versus* none in the gemcitabine + R group). Regarding cardiac events, atrial fibrillation and supraventricular tachycardia leading to death were reported in 1 patient each in the pixantrone + R group (*versus* none in the gemcitabine + R group). In contrast, cardiac failure or acute cardiac failure was the cause of death 5 patients in the gemcitabine + R group (*versus* none in the pixantrone + R group).

Cardiac TEAEs of the standardized MedDRA queries system-group and having a CTCAE grade 3/4 were reported in 18.3% (28 patients) in the pixantrone + R group *versus* 8.1% (12 patients) in the gemcitabine + R group. More frequent Grade 3/4 events were syncope in 5 patients *versus* 2 patients, atrial fibrillation in 4 patients *versus* 3 patients, and ejection fraction decreased in 4 patients *versus* 1 patient, respectively.

All reported events of LVEF decrease were considered as non-serious by the investigator and no concern was raised regarding the LVEF evaluation. An emergent troponin T elevation at EOT was reported in 26.2% in the pixantrone + R group *versus* 5.1% in the gemcitabine + R group.

According to the subgroup analyses, there was no suggestion that toxicities were higher in patients having received 2 or more prior therapies.

CONCLUSIONS

The PIX306 study was an international, multicenter, Phase III, randomized study comparing pixantrone + rituximab (R) with gemcitabine + R in patients with a diagnosis of *de novo* DLBCL, DLBCL transformed from indolent lymphoma, or FL grade 3 who have relapsed after at least 1 prior rituximab-containing chemotherapy regimen and who were not currently eligible for high-dose (myeloablative) chemotherapy and stem cell transplant. The primary endpoint was PFS assessed by the IRC in the ITT population at the time of data cut-off.

A total of 312 patients were enrolled in the study and randomized between the 2 treatment arms (155 to pixantrone + R and 157 to gemcitabine + R).

The median PFS in the pixantrone + R group was 7.3 months (95% CI [5.2, 8.4]) compared to 6.3 months (95% CI [4.4, 8.1]) in the gemcitabine + R group. The adjusted HR was 0.85 (95% CI [0.64, 1.14]), indicating that pixantrone showed no statistically significant superiority over gemcitabine, when individually combined with rituximab, on this primary endpoint (p = 0.2782). As the primary endpoint PFS did not reach its significance, the hypotheses of the secondary endpoints (OS, ORR and CR) were not formally tested. At the time of the data cut-off, the first interim analysis of OS showed a median OS of 13.3 months (95% CI [10.1, 19.8]) in the pixantrone + R group *versus* 19.6 months (95% CI [12.4, 31.9]) in the gemcitabine + R group (HR = 1.13, 95% CI [0.83, 1.53]). A numerically higher ORR (between-group difference of 18.0% (95% CI [6.9, 28.6]) and CR rate (between-group difference of 13.8% (95% CI [3.8, 23.5]) were observed with pixantrone + R, while response durations were comparable between the two arms.

CONCLUSIONS (Cont'd)

The safety profile of pixantrone + R was generally consistent with the known safety profile of the individual compounds. The most common severe toxicity was bone marrow suppression affecting the neutrophil lineage, which was generally uncomplicated and manageable. Of note, the percentages of patients with at least 1 cardiac (SMQ) TEAE were similar between the two groups; however, there was a higher percentage of patients with Grade 3/4 cardiac (SMQ) TEAE's in the pixantrone + R group (18.3% [28 patients] *versus* 8.1% [12 patients], respectively), but only 5 events were considered as serious and related to pixantrone. Although there were more LVEF decreased and increases in troponin T levels in the pixantrone group, most were of CTCAE grade 1 or 2 severity, none were considered as serious and they did not translate into clinically relevant cardiac events.

Date of the report: 16 November 2018

Version of the report: Final version

SUMMARY OF SUBSTANTIAL CHANGES IN THE PROTOCOL AMENDMENTS

Amendment number	Date	Key changes
Original	December 7, 2010	Not applicable
1	December 9, 2010	Definition of PFS was slightly modified and the censoring rules for PFS analysis were modified
2	March 10, 2011	Change of primary endpoint to combined primary of PFS and OS
3	August 3, 2011	Modification of inclusion criteria and exclusion criteria; a recommendation was added that rituximab be administered first
4	January 5, 2012	Change the primary endpoint to OS only (as requested by the US Food and Drug Administration [FDA] with PFS as a secondary endpoint
5 North America	April 9, 2012	For the primary objective, eligibility of patients was further detailed; in response to a recommendation from the EMA, pixantrone dose was expressed in its base form (instead of its salt form) in the whole document; it was specified that the study would be conducted in the United States, Canada, Eastern and Western Europe and South America; requirements for entering Survival Follow-up period were updated..
5 non North America	June 18, 2012	The rationale for rituximab-pixantrone combination was further detailed (NA + NNA); It was specified that the study would be conducted in NA, Western Europe and potentially Eastern Europe (NNA).
6 North America	August 31, 2012	
6 non North America	October 17, 2012	In response to EMA, the

		pixantrone dose was expressed in its base form (instead of its salt form) in the whole document; It was specified that the study would be conducted in NA, Eastern and Western Europe; Procedures for reporting AEs updated.
7 non North America	September 16, 2013	Change in EOT window; Gemcitabine dose modifications for hematologic toxicity were completed; Gemcitabine and pixantrone dose modifications for non-hematologic toxicity were Completed; The description of disease assessment was also modified (in case no EOT PET scan could be obtained, for bone marrow biopsy…).
8	July 25, 2014	unified the previous NA and NAA versions Change of primary endpoint back to PFS (due to enrolment difficulties)
9	July 10, 2017	Increase of target population size in order to reach the required 195 PFS events as assessed by the IRC

EARLY TERMINATION/DISCONTINUATION

In March 2018, the pre specified core data cut-off was performed after 195 PFS events per IRC (final PFS analysis). A survival follow-up was planned in the protocol until 220 deaths were recorded. However, since the primary endpoint of the study was not statistically significant, the Sponsor decided not to continue the study until the targeted 220 OS events, and instead terminate it within 6 months after the primary data cut-off date (Final OS analysis: 14 September 2018).