28 March 2019
EMA/250839/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pixuvri

International non-proprietary name: pixantrone

Procedure No. EMEA/H/C/002055/R/0046

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion**[2]
☐	Start of procedure:	03 Dec 2018	03 Dec 2018	☐
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	03 Jan 2019	07 Jan 2019	☐
☐	CHMP and PRAC members comments	07 Jan 2019	11 Jan 2019	☐
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	10 Jan 2019	17 Jan 2019	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	17 Jan 2019	17 Jan 2019	☐
☐	Request for supplementary information	31 Jan 2019		☒
☐	MAH responses to (RfSI) received on	05 Mar 2019	06 Mar 2019	☐
☐	CHMP and PRAC Rapporteurs' joint assessment report	13 Mar 2019	15 Mar 2019	☐
☐	PRAC endorsed relevant sections of the assessment report	14 Mar 2019	15 Mar 2019	☐
☐	CHMP and PRAC members comments	18 Mar 2019	21 Mar 2019	☐
☐	Updated CHMP and PRAC Rapporteurs joint assessment report	21 Mar 2019	22 Mar 2019	☒
☒	Opinion	28 Mar 2019	5 Apr 2019	☒

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for PRAC plenary discussion: interim results/outcome of the SOB that is a non-interventional PASS study challenging the benefit/risk balance of the product; new imposed non-interventional PASS resulting from the annual renewal (annex II condition); divergent positions between the Committees (CHMP and PRAC Rapp and CHMP and PRAC members) on specific aspects with significant impact on the B/R and any other situation at the discretion of the PRAC rapporteur.

Criteria for CHMP plenary discussion: interim results/outcome of the SOB challenging the benefit/risk balance of the product; fulfilment of all SOBs; new imposed PASS/PAES resulting from the annual renewal (annex II condition); divergent positions between the Committees (CHMP and PRAC Rapp and CHMP and PRAC members) on specific aspects with significant impact on the B/R and any other situation at the discretion of the CHMP rapporteur.

[3] Sections related to data on non-interventional PASS imposed as an SOB, Risk Management Plan (safety concerns, Pharmacovigilance plans, Risk minimisation Measures), sections on issues originating from parallel/recent PSUR or signal assessment, additional monitoring, pharmacovigilance inspections and

preliminary conclusions on the benefit/risk balance.

Declarations

☒ The assessor confirms that proprietary information on, or reference to, third parties or products are not included in this assessment, unless there are previous contracts and/or agreements with the third parties.

☒ (Non-Clinical/Clinical/Pharmacovigilance) The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

Table of contents

1. Background information on the annual renewal

The European Commission issued on 10 May 2012, a conditional marketing authorisation (MA) for Pixuvri This implied that, pursuant to Article 14(7) of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14 (7) of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH CTI Life Sciences Limited, submitted to the Agency on 30 November 2018 an application for renewal of the conditional MA for Pixuvri. The expiry date of the MA is 14 May 2019.

The period covered by this annual renewal is 1 September 2017 to 31 August 2018.

The application contained a justification in support of the possible granting of a marketing authorisation no longer subject to specific obligations.

2. Overall conclusions and benefit-risk balance

2.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal data on the SOBs have been submitted that overall are compliant in terms of adherence to deadlines.

Updated list of specific obligations (SOBs)

None remaining.

2.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have been reported from the trial conducted as part of the SOBs. These data are considered comprehensive in the sense of the CMA regulation, as well as supportive of the positive benefit-risk of Pixuvri in the approved indication.

Treatment of patients with relapsed DLBCL is challenging. If treatment with the currently most effective regimen in the first line (R-CHOP) fails to provide cure, the probability of achieving long-term disease suppression or cure with second or further lines of treatment is low. A potentially curative second line treatment is salvage chemotherapy followed by autologous stem cell transplantation (ASCT). However, significant associated toxicities preclude proceeding for a substantial fraction of patients, with comorbidities or advanced age, to this procedure.

Recently, two CAR-T cell immunotherapies (Yescarta and Kymriah) were authorised in the EU for patients with relapsed or refractory DLBCL after two or more lines of systemic therapy which are intended for patients with sufficient disease control to await the manufacturing times and who are able to tolerate the conditioning regimen. The use of these products is associated with life-threatening and in some cases even fatal toxicities, excluding the patient population for whom ASCT is not an option.

Pixuvri was approved in 2012 as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL) with palliative intent approach as a third or fourth line treatment.

With the results from study PIX306 the benefit of pixantrone in patients who had received prior treatment with rituximab would be corroborated and the requirement to convert a conditional MA into a full MA (that is, without specific obligations) fulfilled.

The MAH has now provided results from study PIX 306: "A Randomized Multicentre 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", and applies for the full marketing authorization of pixantrone for the approved indication.

Study PIX306 background

A conditional approval for pixantrone was granted in 2012 because additional efficacy data was needed to confirm the benefit of pixantrone in patients who had received prior treatment with rituximab. In Study PIX 301, pivotal for the conditional approval, only 54% (38 patients) in the pixantrone treatment group had received rituximab therapy prior to study entry. In Europe, rituximab in combination with CHOP chemotherapy has been a standard first line treatment in DLBCL after the EU approval of this DLBCL indication for rituximab in March 2002.

At that time, efficacy was based on the abovementioned single pivotal trial showing higher response rates at the end of treatment and also at the end of the follow up, with statistically significant improvement of PFS but not OS (both PFS and OS were secondary efficacy endpoints).

PIX306 was already underway in 2012 at the time of conditional approval. Despite the different patient population compared to PIX 301 (1-3 prior regimens vs. 2 or more prior regimens of chemotherapy, and combination therapy with rituximab vs. pixantrone single agent), this phase III study was considered appropriate to provide comprehensive data on the efficacy of pixantrone in patients that had received prior rituximab treatment, because all patients had to have received rituximab (as part of R-CHOP) before study entry.

Study plan

Study PIX306 was designed, prior to the CMA, to show superiority of pixantrone + rituximab over gemcitabine + rituximab in patients previously treated with at least 1 prior rituximab containing chemotherapy regimen and ineligible for high-dose chemotherapy and ASCT.

Similar to PIX301, up to 6 cycles of 28 days of treatment were planned to be administered. The inclusion and exclusion criteria of the study PIX306 seemed representative of a population of subjects with relapsed DLBCL. There were several differences in the inclusion and exclusion criteria when comparing studies 306 and 301, as highlighted below.

The most significant difference is number of prior therapies allowed: **1-3** prior regimens for DLBCL in study PIX306 vs. relapse after **2 or more** prior regimens of chemotherapy in study PIX301. Other important difference was the requirement that all patients in study PIX306 should have received a rituximab-containing multi-agent regimen, while in study PIX 301 patients must have received rituximab in prior regimens in those countries where it was the standard of care and available at the patient's institution.

Importantly, patients with prior treatment with a cumulative dose of doxorubicin or equivalent exceeding 450 mg/m² were excluded from both studies. There was a minor difference in the LVEF-criteria by

echocardiogram: in study 306 patients with LVEF < 45% were excluded, in study 301 the LVEF had to be ≥ 50%. The dose of pixantrone (in combination with rituximab) was identical compared to the dose administered in the pivotal study PIX301. The dose of rituximab was identical compared to dose used the in combination with CHOP chemotherapy in first line treatment. Basically all patients receive rituximab in first line and in case of relapse many patients develop disease that is refractory to rituximab. Combining pixantrone chemotherapy with the anti-CD20 agent rituximab was expected to produce synergistic effects. However, the role of rituximab in salvage treatment (like here in combination with either pixantrone or gemcitabine) in second or further line treatment is not clear.

The choice of the comparator, gemcitabine, was acceptable at the time study PIX306 was initiated. At that time there were no approved second-line treatments in relapsed DLBCL and gemcitabine had been shown to have at least some effect in the treatment of patients with relapsed DLBCL.

PFS is an acceptable primary efficacy endpoint in this setting, with OS as a key secondary endpoint. PFS has been previously approved as a measure of the clinical efficacy of therapy in comparable oncological and haematological settings.

The timetable and monitoring of the treatment efficacy with the disease assessments by CT, PET (at the end of study visit) and bone marrow biopsy (at the end of study visit, unless negative at baseline) are acceptable and follow the current guidelines for evaluating treatment response in DLBCL.

Final sample size calculations, planning to show superiority of the pixantrone + rituximab treatment-arm, were acceptable for both PFS and OS. Selected randomization procedure with the proposed stratifications was appropriate. The sponsor was blinded during the study until the core database lock which is appropriate in this type of study.

Based on subject selection, the study results (PIX306) can be generalised to the European DLBCL patients. This is important, because in the pivotal study PIX301, only 38/140 patients were recruited in “Western Europe”. This could possibly explain the lower than expected use of rituximab (already approved 3/2002 in EU) in the first line treatment of patients recruited into the study PIX301.

Conduct of the study

A total of 312 patients were randomized in this study: 155 patients in the pixantrone + rituximab group and 157 in the gemcitabine + rituximab group

Overall only 42.6% of patients completed the planned treatment (6 cycles of 28 days each) in study PIX306, with consent withdrawal being the reason for higher number of discontinuation in the gemcitabine + rituximab group (10.2% vs. 3.7%). In total 61.1% in the gemcitabine + rituximab group vs. 53.5% in the pixantrone + rituximab discontinued treatment, mostly due to progressive disease.

Overall, the total number of protocol deviations was high. The MAH was asked to summarise the number of patients in each category of major protocol deviations (including dosing errors) per treatment arm. As a response to the questions regarding the protocol violations, the MAH has submitted a summary table of subjects with major protocol deviations from the ITT population. The majority of major deviations were related to study drug administration and protocol non-adherence. The numbers of these major deviations are equally distributed between the two treatment arms. Importantly, none of the protocol deviations led to patient withdrawal from the study.

There were no discernible differences between the populations in the two treatment arms in the study PIX306 concerning demographic and baseline characteristics as well as baseline disease characteristics. The overall

population with median age of 73 years represents typical DLBCL patients. The baseline performance status (ECOG) was also comparable between the two treatment groups.

The main difference between studies PIX301 and PIX306 was the number of previous chemotherapy regimens. Most of patients have had only 1 previous therapy is study PIX306 (54.8%) while all patients had had at least 2, and 55% of the patients 3 to 5 prior regimens in study PIX301.

The listing of previous therapies and especially the use of previous cardiotoxic treatments was comprehensively presented (in Tables 5.12-5.14) from study PIX 301. Importantly, similar detailed presentation of prior NHL therapies in patients with DLBCL from study PIX306 and especially category of prior chemotherapies was initially missing. Almost all patients have received previous treatment with anthracyclines; 148 (95.5%) in the pixantrone + R-arm and 143 (91.1%) in the gemcitabine + R-arm. In addition, regarding all other previous treatments, the use of different prior DLBCL therapies are equally balanced between the two treatment arms.

Surprisingly high numbers of patients were excluded from the histology-confirmed ITT (HITT) population. This highlights the importance of reliable pathological diagnosis of an aggressive disease like DLBCL. There is a slight imbalance between the treatment groups regarding this HITT population; 128 patients in the pixantrone + rituximab group vs. 140 patients in the gemcitabine + rituximab group.

28 patients (almost 10% of the total patient population) were excluded from the PP population for major protocol violations. The most important reasons for these exclusions were related to baseline tumour assessment/ tumour response assessment after randomization. All patients were adequately excluded from the PP population following the exclusion rules of the SAP.

Efficacy

The primary endpoint IRC-assessed PFS was not met; median PFS was 7.3 months in the pixantrone + rituximab group versus 6.3 months in the gemcitabine + rituximab group, p=0.2782 and HR 0.85 (0.64 - 1.14). In addition, all sensitivity analyses were in line with the primary analysis with no significant statistical differences between the two treatment groups. The results from the subgroup analysis of PFS per IRC assessment produced mixed results with hazard ratios favouring variably the pixantrone + R arm or the comparator arm. However, there were no clear differences in any subgroup analysis.

The median of PFS in patients with ≥ 2 prior lines of therapy (like in the population in the pivotal study PIX301) was 3.9 months in the pixantrone + rituximab group versus 4.4 months in the gemcitabine + rituximab group.

Result from the first interim analysis showed a median OS of 13.3 months in the pixantrone + rituximab group versus 19.6 months in the gemcitabine + rituximab group. This difference was not statistically significant with HR of 1.13 (95% CI: 0.66-1.26), unstratified log-rank test p= 0.43). The final OS analysis was done using the final cut-off date of September, 14 2018. Six (6) additional OS events (3 in each arm) were included in this final OS analysis; 183 deaths had occurred with a median OS of 13.5 months in the pixantrone + rituximab group group versus 19.6 months in the gemcitabine + R group. The adjusted hazard ratio was 1.13 (95%CI [0.84 - 1.53]).

The results from the subgroup analysis of OS were consistent across most of the subgroups and with the results of the overall population analysis

The median of OS in patients with ≥2 prior lines of therapy (like in the population in the pivotal study PIX301) was 10.1 months in the pixantrone + rituximab group versus 10.5 months in the gemcitabine + rituximab group.

While the OS HR point estimate was on the wrong side of unity (HR 1.13), the confidence intervals are very wide. While information on post progression therapies is not available, there were no new safety concerns identified which would support a true detrimental effect on OS.

The ORR and CR rate (key secondary endpoints) were both significantly higher in the pixantrone + rituximab group compared to the gemcitabine + rituximab group (61.9% vs. 43.9%, p=0.0007, and 35.5% vs. 21.7%, p=0.0047).

In the pivotal study PIX301 for the initial marketing authorisation, the CR/CFu-rate was the primary efficacy endpoint, with CR/CFu-rate of 20% for single-agent pixantrone. In the corresponding subgroup of patients with ≥2 lines of prior therapy in the current study PIX306, the CR-rate was 22.6% in the pixantrone + rituximab group compared to 7.8% in the gemcitabine + rituximab group.

There were no significant differences in the duration of overall response or duration of complete response between the two treatment groups.

Safety

The pivotal study PIX301 for the CMA involved 68 subjects receiving pixantrone monotherapy. In Study PIX306 pixantrone was combined with rituximab for 153 patients, which slightly complicates the comparison of the adverse event profiles of pixantrone between the two studies.

In both studies, the pixantrone doses were reduced due to mainly tolerability issues. In PIX306 54.2% of patients received less than 70% of the protocol dose. Only 50.3% of the patients received 6 out of 6 study cycles as per protocol. For gemcitabine combined with rituximab, the dose reductions were even more frequently needed: 73.2% received less than 70% of the protocol dose and 43.6% of the patients went through 6 out of 6 study cycles.

The observed dose reductions of pixantrone in the clinical studies, and clinical use and the consequences to efficacy/safety of pixantrone, are being evaluated in the recently initiated legally binding procedure (LEG, see Section 6.5 of this AR).

There were some notable differences in the TEAE profiles between the treatments. Neutropenia was more common in pixantrone +rituximab group, and anaemia, thrombocytopenia, and leukopenia in gemcitabine + rituximab groups. These differences were also reflected to the number of transfusions the patients needed (any transfusion 8.5% vs 30.2%, platelets 0% vs 6.0%, RBCs 8.5% vs 28.9%, respectively) and to the use of growth factors (filgrastim was given to 66.0% and pegfilgrastim to 11.8% of pixantrone + rituximab patients, and to 47.7% and 4.7% of the gemcitabine + rituximab patients respectively).

Stomatitis, oral candidiasis, dysgeusia, and anorexia were more common in patients receiving pixantrone + rituximab. Skin discolouration affected 9.2% of pixantrone + rituximab patients and 0.7% of gemcitabine + rituximab patients.

The overall incidence of TEAEs in study PIX306 patients receiving pixantrone + rituximab was comparable to that of study PIX301 patients receiving pixantrone monotherapy, 91.5% vs. 97.1%. For grade 3 to 4 TEAEs the figures were 85.0% and 76.5% implying to a worse tolerability of the combination therapy. *E.g.*, neutropenia 63.4% vs. 41.2%, anaemia 17.0% vs. 5.9%, or lymphopenia, 5.9% vs. 2.9%, in PIX306 vs. PIX301, respectively. However, these trends were reversed when looking at the SAEs.

The percentage of on-treatment deaths was lower in PIX306 patients receiving pixantrone + rituximab compared to PIX301 patients receiving pixantrone monotherapy.

The incidences of serious treatment emergent adverse events did not differ significantly between the treatment groups in study PIX306, including cardiotoxicity.

There were no significant differences in the blood chemistry abnormalities between the treatment groups in PIX306. No hepatorenal toxicity was reported.

Close follow-up of haematology parameters (4 cases of myelodysplasia were reported from pixantrone patients) and LVEF seems necessary during pixantrone + rituximab therapy.

The rate of discontinuations due to TEAEs was lower in study PIX306 patients receiving pixantrone + rituximab compared to study PIX301 patients receiving only pixantrone (42.6% vs. 21.6%), which also implies to not worse tolerability of the combination treatment compared to monotherapy.

No new safety concerns for pixantrone were identified.

Other relevant studies

Study AZA302

The population recruited into study AZA302 consisted of relapsed follicular lymphoma patients. The prognosis and estimated treatment efficacy in second line is much higher compared to patients with relapsed, more aggressive lymphoma, DLBCL.

In this study, pixantrone + rituximab performed better than rituximab alone, but it is difficult to draw conclusions from this very small study (38 patients) with different patient population than in studies PIX301 and PIX306.

Favourable effects

Current indication: "*Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.*"

PIX301 (pivotal study in assessment for initial marketing authorisation)

Primary efficacy variable

- PFS: Pixantrone (n=70) 5.3 months vs. Investigator's choice (n=70) 2.6 months ,HR 0.60 (95% CI 0.42 -0.86), p=0.005
- Secondary efficacy variables
- CR/CRu rate end of treatment: Pixantrone (n=70) 14 (20.0%) vs. Investigator's choice (n=70) 4 (5.7%), p=0.021
- CR/Cru rate end of study: Pixantrone (n=70) 17 (24.3%) vs. Investigator's choice (n=70) 5 (7.1%), p=0.009
- ORR end of treatment: Pixantrone (n=70) 26 (37.1%) vs. Investigator's choice (n=70) 10 (14.3%), p=0.003
- ORR end of study: Pixantrone (n=70) 28 (40.0%) vs. Investigator's choice (n=70) 10 (14.3%), p=0.003

- OS: Pixantrone (n=70) 10.2 months vs. Investigator's choice (n=70) 7.6 months , HR 0.79 (95% CI 0.53 - 1.18) , p=0.251

PIX306 (study to support efficacy of pixantrone in rituximab-pretreated patients)

Primary efficacy variable

- PFS: Pixantrone + rituximab (n=155) 7.3 months vs. gemcitabine + rituximab (n=157) 6.3 months , p=0.2782, HR 0.85 (95% CI 0.64 - 1.14).

Secondary efficacy variables

- OS: Pixantrone + rituximab (n=155) 13.3 months vs. gemcitabine + rituximab (n=157) 19.6 months , p=0.4326, HR 1.13 (95% CI 0.83 - 1.53).
- Updated OS: Pixantrone + rituximab (n=155) 13.5 months vs. gemcitabine + rituximab (n=157) 19.6 months, p=0.4053, HR 1.13 (95% CI 0.84 - 1.53).
- ORR: Pixantrone + rituximab (n=155) 96 (61.9)% vs. gemcitabine + rituximab (n=157) 69 (43.9%), p=0.0007
- CR rate: Pixantrone + rituximab (n=155) 55 (35.5%) vs. gemcitabine + rituximab (n=157) 34 (21.7%), p=0.0047

Uncertainties and limitations about favourable effects

PIX301 (as assessed at the time of the initial marketing authorisation)

The advantage of pixantrone over comparator detected in the ITT population is lower in the group of patients pre-treated with rituximab and diminishes further with increasing number of prior regimens. Pixantrone showed to be more active than the comparator in the group of patients pretreated with up to 3 regimens, including rituximab. However, the benefit in this subset needs to be further confirmed in view of the low number of patients.

PIX306

The primary efficacy endpoint in PIX306 PFS did not show statistically significant superiority of pixantrone + rituximab over pixantrone + gemcitabine, nor did OS.

Unfavourable effects

PIX301 (as assessed at the time of the initial marketing authorisation)

- AEs: Any adverse event, Pixantrone 97.1% / Comparator 91.0%
- Grade 3/4 AE:s, respectively
    - Neutropenia 41.2% / 19.4%
    - Leukopenia 23.5% / 7.5%
    - Anaemia 5.9% / 13.4%
    - Lymphopenia 2.9% / 0%
    - Pneumonia 5.9%/4.5%
    -

- SAEs: Any serious adverse event, Pixantrone 51.5% / Comparator 44.8%
    - Neutropenia 13.2% / 9.0%
    - Thrombocytopenia 1.5% / 9.0%
    - Anaemia 2.9% / 7.5%
    - Febrile leukopenia 5.9% / 3.0%
    - Pneumonia 7.4% / 6.0%
- Deaths (not due progression of disease): Pixantrone 5/68 / Comparator 2/67
- Cardiovascular adverse reactions:
    - AE decreased ejection fraction 19.1% / 10.4%
    - SAE cardiac failure 2.9% / 1.5%
    - SAE congestive cardiac failure 2.9% / 0.0%

PIX306

- TEAEs: Any adverse event, Pixantrone + rituximab 91.5% / Gemcitabine + rituximab 98.0%%
- Grade 3/4 AE:s, respectively
    - Neutropenia 63.4% / 55.7%
    - Leukopenia 7.8% / 10.1%
    - Anaemia 17.0% / 37.6%
    - Lymphopenia 5.9% / 2.0%
    - Infections and infestations 15.7% / 20.1%
- SAEs: Any serious adverse event, Pixantrone + rituximab 38.6% / Gemcitabine + rituximab 38.3%
    - Thrombocytopenia 1.3% / 2.0%
    - Anaemia 3.3% / 5.4%
    - Febrile neutropenia 3.3% / 0.7%
    - Infections and infestations 11.8% / 15.4%
    - Pneumonia 5.2% / 2.7%
    - Myelodysplastic syndrome 2.6% / 0.0%
- Deaths (not due progression of disease): Pixantrone + rituximab 3.3% / Gemcitabine + rituximab 6.0%
- Cardiovascular adverse reactions, respectively:
    - AE decreased ejection fraction 3.9% / 0.7%
    - SAE cardiac failure 2.0% / 3.3%
    - SAE congestive cardiac failure 0.0% / 1.3%

For the most part, pixantrone vs. comparator and pixantrone-rituximab vs. gemcitabine + rituximab had similar ADR-potential.

Uncertainties and limitations about unfavourable effects

Consistent dose reductions in both clinical studies and in clinical use pose a question about optimal dose, efficacy and safety - a LEG-procedure has been initiated by PRAC. The assessment is currently under way.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

The original positive opinion of pixantrone was based on the pivotal study PIX301 where an improvement was seen in CR/Cru, supported by the result of secondary endpoint, PFS. Two CAR-T cell immunotherapies were recently authorized in EU, targeting patients with relapsed or refractory DLBCL after two or more lines of systemic therapy, indication being partly comparable to pixantrone. However, these products are not an option for all patients due to tolerability and availability issues.

In study PIX306, all patients were previously treated with rituximab. While the superiority of pixantrone + rituximab over comparator was not met, both PFS and OS results in patients with ≥ 2 prior treatment lines are roughly similar to that of the active comparator.

There were no new toxicity concerns regarding pixantrone.

Balance of benefits and risks

The request to the MAH was to provide comprehensive data relevant to the approved indication, with particular respect to activity in patients pretreated with rituximab, which was specifically identified as non-comprehensive. The MAH has provided the requested data. The study included a broader patient population than covered by the authorisation (1-3 prior regimens vs. 2 or more prior regimens of chemotherapy) and a more intensive therapy (combination therapy of pixantrone + rituximab vs. pixantrone monotherapy).

If the results from the same patient population (patients with ≥2 prior treatment lines) are compared indirectly, activity is roughly similar. Results are compatible with a conclusion that pixantrone is efficacious also in patients who had received prior rituximab; taking into account that prior rituximab was part of an intensive, standard regimen (R-CHOP). From the data provided, it is not possible to conclude, whether rituximab has an additive value in combination with pixantrone in the second or further line treatment in relapsed DLBCL, in patients who have experienced disease progression despite prior treatment with rituximab.

The benefit-risk balance in the originally approved indication remains positive and is corroborated by the data from the study PIX306, a specific obligation to the initial conditional marketing authorisation. The MAH is considered to have provided comprehensive data through the designated specific obligation on which the CMA was contingent. B/R remains positive in the approved indication. The conversion of the CMA to FMA is therefore recommended.

Scientific grounds for recommending the granting of a marketing authorisation not subject to specific obligations

The result of study PIX306 support that pixantrone is efficacious in patients with multiply relapsed or refractory DLBCL after rituximab treatment. This conclusion meets the specific obligation of the conditional marketing

authorisation. The data submitted at the time of the marketing authorisation were not comprehensive with regards to patients previously treated with rituximab, which is part of standard of care in first line treatment of DLBCL.

The result of study PIX306 corroborate the benefit of pixantrone in the authorised indication, including patients previously treated with rituximab, as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL).

Therefore, there are no further obligations in respect of using pixantrone in the authorised indication and the marketing authorisation not subject to specific obligations can be granted.

3. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the benefit-risk balance for Pixuvri in its approved indication (please refer to the Summary of Product Characteristics) continues to be favourable and all specific obligations have been fulfilled, and therefore the granting of a marketing authorisation no longer subject to specific obligations is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

In view of new data submitted as part of the renewal application, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Please refer to the Attachment which includes comments to the proposed changes to the Product Information.

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4. EPAR changes

The table in the “Steps after” module of the EPAR will be updated as follows:

Scope

Renewal of conditional marketing authorisation

Summary

The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated. Furthermore, the CHMP considered that, as all Specific Obligations have been fulfilled, there are no remaining grounds for the marketing authorisations to remain conditional and therefore recommends the granting of the MA no longer subject to Specific Obligations for Pixuvri.

Annex: Rapporteurs' assessment comments on the renewal

PRAC input

In this annual renewal,	**Yes**	**No**
- RMP submitted (If yes is ticked, discussion should be included in the Risk management plan section of the Annex)	☒	☐
- Outstanding SOB is a non-interventional PASS study (If yes is ticked, the relevant discussion should be included in the sub-section Outstanding Specific Obligations – status report for period covered of the Annex)	☐	☒
- There are issues originating from a parallel/recent PSUR or signal assessment to be flagged to the CHMP rapporteur (If yes is ticked, the relevant discussion should be included in the Clinical safety section of the Annex)	☒	☐
- PhV inspections have been conducted/are ongoing with an impact on the MA under annual Re-Assessment (If yes is ticked, the relevant discussion should be included in the Pharmacovigilance inspections section of the Annex)	☒	☐

5. Specific Obligations

5.1. Specific Obligations adopted with the initial marketing authorisation

Table 1: Full list of SOBs as adopted with the initial marketing authorisation

Number	Description	Status
SOB 001 (category 2)	To conduct a randomised controlled Phase 3 study (PIX306) of pixantrone- rituximab vs gemcitabine-rituximab in patients with aggressive B-cell NHL, who failed front line CHOP-R who are not eligible for autologous stem cell transplant (ASCT) (2nd line) or failed ASCT (3rd or 4th line). A clinical study report should be submitted.	31/12/2018

Since the granting of the conditional MA, the MAH has submitted the following SOBs:

- SOB 001: A randomised controlled Phase 3 study (PIX306) of pixantrone- rituximab vs gemcitabine-rituximab in patients with aggressive B-cell NHL, who failed front line CHOP-R who are not eligible for autologous stem cell transplant (ASCT) (2nd line) or failed ASCT (3rd or 4th line). A clinical study report has been submitted.

5.2. Outstanding Specific Obligations – status report for period covered

SOB 01 Clinical Study PIX 306

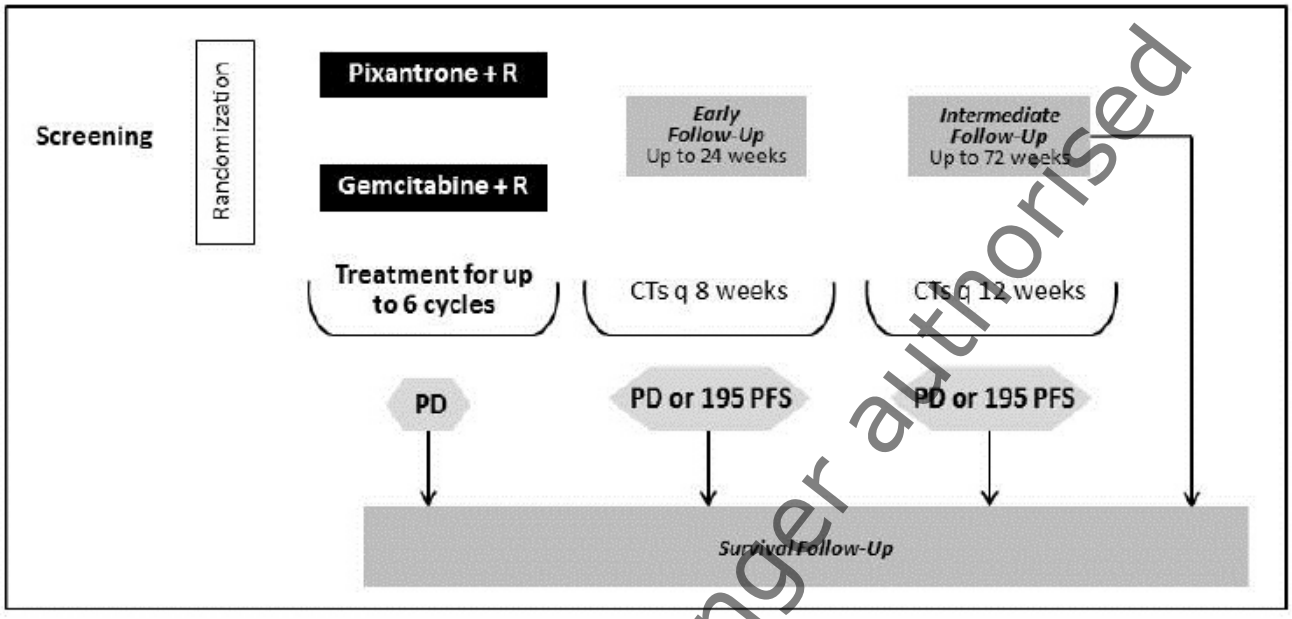
This was an international, phase III, multicentre, randomized (1:1 ratio), active-controlled study, blinded for the sponsor, evaluating the efficacy of pixantrone + rituximab versus gemcitabine + rituximab. The randomization was stratified by the number of prior therapies for DLBCL or FL grade 3 (0-2 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 versus ≥ 1 year).

Adult patients with DLBCL (either *de novo* or 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 ASCT.

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. The study plan is presented in Figure 5.1.

Additionally, PIX306 included a PK substudy to compare pixantrone concentrations in PIX306 patients who received rituximab to concentration predictions from an earlier developed population PK model of individuals who did not received routine rituximab therapy.

Figure 1 Study plan (Study PIX306)



Abbreviations:
CT = computed tomography; q 8 and q 12 = every 8 and 12 weeks, respectively; R = rituximab.
PD = progressive disease per Modified IWG criteria or initiation of subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy

The underlying research hypothesis for this study was that the combination of pixantrone + rituximab would have a higher efficiency than treatment with gemcitabine + rituximab in patients with DLBCL (or FL grade 3) who were not eligible for high-dose myeloablative chemotherapy and SCT. Indeed, no therapy has demonstrated a survival prolongation in this patient population, and thus there is no standard of care.

The EMA granted a conditional approval for pixantrone with the specific obligation to conduct this phase III study (PIX306) to confirm the efficacy of pixantrone in patients previously treated with rituximab. Since PIX306 was originally designed as a request by the FDA for pixantrone new application with OS as primary endpoint and was already underway at the time of conditional approval, it was modified by amendment.

The analysis plan was thus subject to various changes following authorities' requests and enrolment issues. In the original protocol, the primary study endpoint was PFS, but this was changed before the start of recruitment (Amendment No. 2) to combined primary of PFS and OS (with a resulting modification of the size of the patient population). Amendment 4 changed the primary endpoint to OS only (as requested by the US Food and Drug Administration [FDA]) with PFS as a secondary endpoint. In agreement with the EMA, Amendment 8 changed the primary endpoint back to PFS (due to enrolment difficulties). The target population size was increased by Amendment 9 in order to reach the required 195 PFS events as assessed by the IRC. Following the analysis of the primary endpoint of this study, it was decided by the Sponsor not to continue the study until the target 220 events for the OS analysis, analysis, but terminate it within six months of the data cut-off date (the actual date was 14 September 2018). For rest of the amendments, refer to section "Conduct of the study" below.

A GCP-inspection of CTI Biopharma clinical trial PIX306 was conducted by the MHRA in December 2018 and the inspection report is expected by the end of January 2019.

comment

A conditional approval for pixantrone was granted in 2012 because additional efficacy data was needed to confirm the benefit of pixantrone in patients that had received prior treatment with rituximab. In the pivotal

study PIX301, only 54.3% (38 patients) in the pixantrone treatment group received rituximab therapy prior to study entry.

In addition, efficacy was supported by a small single pivotal trial showing statistical significance in PFS but not in OS (both PFS and OS were secondary efficacy endpoints).

In Europe, rituximab in combination with CHOP chemotherapy has been a standard first line treatment in DLBCL after the EC approval of this DLBCL indication for rituximab in March 2002.

Clinical study PIX 306 was already underway in 2012 at the time of conditional approval and despite the different patient population compared to PIX301 (1-3 prior regimens vs. 2 or more prior regimens of chemotherapy, and combination therapy with rituximab vs. pixantrone single agent), this phase III study was considered appropriate to support the efficacy of pixantrone in patients that had received prior rituximab treatment.

Study PIX 306 was originally planned to show superiority of pixantrone + rituximab versus gemcitabine + rituximab in patients previously treated with at least 1 prior rituximab containing chemotherapy regimen and ineligible for high-dose chemotherapy and ASCT.

Methods

Study periods

Screening period: up to 28 days before randomization. No specific anti-lymphoma treatment or any other experimental treatments were allowed.

Treatment period: up to 6 cycles of 28 days, during which disease response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) every 8 weeks. Treatment was to be initiated as soon as possible and within 14 days after randomization. The treatment period continued until the end-of-treatment (EOT) visit, which was foreseen 4 to 7 weeks (inclusive) after the last dose of study drug administration (or scheduled administration), or before subsequent systemic anticancer therapy was given, whichever occurred first.

Follow-up periods (without study treatment):

- Early Follow-up: after treatment discontinuation for reason other than progressive disease or completion, patients were to enter the 24-week Early Follow-up Period, during which they were followed every 8 weeks for safety and progression.
- Intermediate Follow-up: after completing the 24-week Early Follow-up period, patients were to enter an additional 72-week Follow-up period, during which they were followed every 12 weeks for safety and progression.
- Survival Follow-up: patients entered the Survival Follow-up period when one of the following occurred:
    - Completed Intermediate Follow-up.
    - Developed progressive disease per Modified IWG criteria.
    - Received a subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy.
    - Withdrew consent for study procedures.

- If 195 PFS events were confirmed by IRC during the course of the study while the patient had completed the study treatment and EOT evaluations.
- If 195 PFS events were confirmed by IRC during the course of the study while the patient was in Early or Intermediate Follow-up period.

During the Survival Follow-up period, each patient was followed for survival status every 12 ± 2 weeks until death, consent withdrawal or study termination by the Sponsor.

comment

The design of this study was similar compared to the study PIX 301; up to 6 cycles of 28 days of treatment were planned to be administrated.

Bioanalytical method for quantitation of pixantrone in plasma

Plasma concentrations of pixantrone were determined with a validated (ATL-15-1486) LC-MS/MS method (BAM513). Pixantrone dimaleate was used as a reference standard and pixantrone-D8 diformate as an internal standard. Samples were processed by protein precipitation. Lithium Heparin was used as anticoagulant. Initially, the sample storage condition was -80°C with the option that samples could also be stored at -20°C, if necessary. Later the optional storage condition at -20°C was removed. Long term stability results of samples at -20°C or -80°C have not been presented, and it is stated that the overall sample storage period of 576 days is not covered by stability data.

Chromatographic separation was achieved on a liquid chromatography system equipped with a C18 reversed phase column. Detection was achieved by tandem mass spectrometry with a triple quadrupole mass spectrometer working in the electrospray ionisation positive mode.

Eight calibration standards with a concentration ranging from 5 ng/ml to 1000 ng/ml were used. The back calculated concentrations of the calibration standards are presented. QC samples at thee concentration levels 15.0 ng/ml (QC low), 250 ng/ml (QC med) and 800 ng/ml (QC high) were included.

A total of 98 human plasma samples were collected and each sample was stored as 2 aliquots, corresponding to 196 aliquots. Originally, 78 analyses were done on 70 aliquots using the first analytical method and surprisingly low pixantrone concentrations were obtained. Investigation was started to identify the cause for the low concentrations. After investigations, it was identified that the reference material used to prepare calibration standard and QC samples was not pixantrone as administered to clinical subject. A new method validation was performed (ATL-17-1841) with the adequate reference material. All the 98 samples were then analysed with this new method.

comment

There were fourteen patients in this PK sub-study. For each patient, 7 samples were collected and each sample was stored as 2 aliquots. The total number of samples was 98 corresponding to 196 aliquots. Originally, 78 analyses were done on 70 aliquots using the first method. Due to surprisingly low concentrations of pixantrone measured in these samples, an investigation was started. After investigation, it was identified that the there was a problem with the reference material. A new updated method was developed and validated and all the 98 samples were analysed with this second method.

Validation reports ATL-15-1486 and ATL-17-1841 have been provided corresponding to the original and updated bioanalytical method, respectively.

Stability data to support sample storage period of 576 days is not available yet but MAH commits to submit the amendment 1 to the validation report ATL-17-1841, containing the requested stability data as soon as it is available (July 2019).

Study Participants

The inclusion and exclusion criteria in studies PIX306 and PIX301 are described below:

Table 2 The inclusion and exclusion criteria in studies PIX306 and PIX301

PIX306	PIX301
Inclusion criteria: 1. Signed IRB or IEC-approved Informed Consent Form (ICF). 2. Age ≥ 18 years old. 3. Diagnosis of DLBCL (de novo DLBCL, or DLBCL transformed from indolent lymphoma) or FL grade 3 on the basis of a tissue biopsy. 4. Pathology and immunohistochemistry reports documenting the current histological diagnosis according to WHO classification were 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 FL grade 3 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 (e.g., R-ICE, R-ESHAP or R-DHAP), along with the subsequent high-dose myeloablative therapy (e.g., BEAM) and SCT, was counted as a single regimen. Maintenance therapy with rituximab or similar agents,*	Inclusion criteria: 1. Histologically confirmed aggressive [de novo or transformed] NHL according to REAL/WHO classification. The histological specimen used to determine eligibility was to be the most recently obtained specimen. If the histology sample was more than 2 years old, the case was to be discussed with the medical monitor before enrolling the patient. Clear documentation of transformation from indolent lymphoma was needed, if applicable. Lymph node biopsy slides or tissue blocks suitable for review were to be available. Lymphoma types permitted were: a. follicular lymphoma – grade III b. transformed indolent lymphoma (areas of follicularity allowed) c. diffuse large B-cell lymphoma d. mediastinal large B-cell lymphoma e. primary effusion lymphoma (includes previously called immunoblastic lymphoma) f. peripheral T-cell lymphoma not otherwise characterized (encompasses diffuse mixed cell lymphoma) anaplastic large cell lymphoma and T/null cell, primary systemic type 2. Patients must have received rituximab in prior regimens in those countries where it was the standard of care and available at the patient's institution and when neoplastic cells

single-agent corticosteroids, and local radiation therapy were not counted as treatment regimens.

6. Received a rituximab-containing multi-agent regimen (e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP-R]; 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 included 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. Were unsuitable for SCT due to other medical conditions or age.
    e. Did not wish to undergo SCT.
    f. Had financial issues precluding SCT.
    g. Were 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 had not been previously irradiated: nodal disease ≥ 1.5 cm in short axis or extranodal disease > 1.0 cm in short axis. Lesion had to be positron emission tomography (PET) positive if PET scan was obtained.
11. Slides confirming diagnosis of FL grade 3 or DLBCL available for independent histology expressed CD20.
3. At least one objectively measurable lesion as demonstrated by CT, spiral CT, or MRI that could be followed for response as a target lesion. Patients with skin lesions, palpable lymph nodes, spleen or bone marrow as the only site of disease were NOT eligible.
4. Relapse (with evidence of disease progression) after 2 or more prior regimens of chemotherapy, including: first-line treatment with a standard anthracycline-containing regimen such as CHOP or equivalent, at least 1 additional combination chemotherapy regimen. High dose chemotherapy or chemoradiotherapy with autologous stem cell support counted as 1 prior regimen. Allogenic transplant counted as 1 prior regimen. In patients with a previous allotransplant, there was not to be any serious or active graft-versus-host disease requiring immunosuppressive therapy.
5. Patients must have been sensitive to the last anthracycline/anthracenedione containing regimen. Sensitive was defined as a response (confirmed or unconfirmed PR or CR) to an anthracycline/anthracenedione with relapse after a response duration ≥ 6 months.
6. Age ≥ 18 years.
7. ECOG performance status of 2.
8. Life expectancy ≥ 3 months according to investigator's opinion.
9. Hb ≥ 8g/dL, neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 50 x109/L; if there was bone marrow involvement, neutrophils > 0.5 x 10^9/L, platelets >10 x 109/L and the ability to provide platelet transfusion were acceptable.
10. Serum bilirubin 1.5 x the institution's upper limit normal (ULN) and creatinine 1.5 ULN and alkaline phosphatase 2.0 x the institution's ULN and AST or ALT 2.0 x the institution's ULN. If hepatic involvement by lymphoma was present, AST or ALT could be 5.0 x the

review.

12. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2.
13. Life expectancy ≥ 12 weeks in investigator's judgment.
14. LVEF ≥ 45% by echocardiogram and normal serum troponin T.
15. Haemoglobin ≥ 8 g/dL (could 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 ≥ 1.5 × 10^9/L; a value ≥ 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 could 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 was 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) were to 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

institution's ULN.

11. Patients previously treated with one of the comparative agents had to be sensitive to that agent, if it was to be used in this trial. Sensitive was defined as previous response to that agent with relapse after a response duration ≥ 6 months.
12. Patients must have recovered from all acute toxicities from prior therapy (except alopecia and grade 1 peripheral neuropathy).
13. LVEF ≥ 50% determined by MUGA scan.
14. Ability to comply with the visit schedule and assessments required by the protocol.
15. Signed approved informed consent, with understanding of study procedures.

Exclusion criteria:

1. Prior treatment with a cumulative dose of doxorubicin or equivalent exceeding 450 mg/m² according to the calculation index X/450 + Y/160 > 1 where X was the doxorubicin dose in mg/m² and Y the mitoxantrone dose in mg/m².
2. Histological diagnosis of Burkitt lymphoma, lymphoblastic lymphoma, or mantle cell lymphoma.
3. Active CNS lymphoma involvement based on clinical evaluation (if the patient required a diagnostic lumbar puncture due to high risk criteria, ie., sinus involvement, high LDH, high IPI, or bone marrow involvement, it was to be acceptable to administer intrathecal chemotherapy, which could include methotrexate, cytarabine, and corticosteroids, according to institutional standards).
4. HIV-related lymphoma.
5. Any chemotherapy, radiotherapy, or other anticancer treatment (including corticosteroids ≥ 10 mg/day of prednisone or equivalent) within the 2 weeks before randomization. For radioimmunoconjugate

study treatment and for 12 months after last dose of study drug. The contraceptive methods that were considered highly effective were intrauterine devices and hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release).

Exclusion criteria:

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 FL 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.
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 central nervous system (CNS) involvement by lymphoma:
    a. Any history or evidence of current leptomeningeal involvement by lymphoma was prohibited.
    b. Patients with prior localized CNS involvement who had been without recurrence for ≥ 12 months and currently had a negative head MRI could be eligible; following approval therapy, there was to be 8 weeks since last dose or platelet recovery to ≥ 50×10^9/L prior to randomization.
6. Major thoracic and/or abdominal surgery within the 2 weeks before randomization from which the patient had not fully recovered. Patients who had minor surgery could be enrolled after a ≥ 1 week recovery period.
7. Clinically significant cardiovascular abnormalities (equal to NYHA grade III- IV), myocardial infarction within the prior 6 months, severe arrhythmia, uncontrolled hypertension, or uncontrolled angina.
8. Serious (NCI CTCAE grade 3-4) intercurrent infection at randomization or deep-seated or systemic mycotic infections.
9. History of, or clinical symptoms suggesting, HIV infection. Patients with a previous history of hepatitis B or hepatitis C infection without clinical symptoms and whose hepatic parameters complied with inclusion criterion number 10 (serum bilirubin, creatinine, alkaline phosphatase, ALT and AST levels) and patients with seropositivity presumed to be due to prior vaccination against hepatitis B were not to be excluded.
10. History of another malignancy except curatively treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated stage I or II cancer from which the patient was currently in remission, or any other cancer from which the patient had been disease-free for 5 years.
11. Any condition which, in the judgment of the investigator, would place the subject at undue risk, interfere with the results of the study, or make the subject otherwise unsuitable.
12. Participation in any other investigational drug study within 2 weeks before randomization. Patients must have recovered from all side effects of other investigational therapy.
13. Known hypersensitivity to the excipients or

by the Responsible Medical Officer.

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.
13. Other malignancy within the last 5 years. Exceptions were:
    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 could be eligible; to 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 were 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.

Removal of patients from treatment or assessment:

the study drug that the patient would receive.

14. Pregnant women or nursing mothers.
15. Potentially fertile men and women not willing to use adequate contraception during the study and for 6 months after the last day of study drug administration.
16. Any circumstance at the time of study entry that would have precluded completion of the study or the required follow-up.

Protocol therapy was to be discontinued in event of the following:

- Completion of treatment
- Progressive disease/relapsed disease
- The development of toxicity which, in the investigator's judgment, precluded further therapy
- Cardiac toxicity as described in Section 9.4.1
- Patient refusal to continue
- Patient lost to follow-up or noncompliance
- Intercurrent illness precluding further therapy, in the investigator's opinion
- Pregnancy

Patients who discontinued pixantrone/gemcitabine or rituximab for toxicity could remain in the study on monotherapy with the other study treatment for up to six cycles. Treatment (*i.e.*, pixantrone + rituximab or gemcitabine + rituximab) could be discontinued by the investigator for any of the following reasons: • PD per Modified IWG criteria. • Any clinical AE, laboratory abnormality, abnormal test result or intercurrent illness which, in the opinion of the investigator, indicated that continued treatment with study therapy was not in the best interest of the patient. • PD due to symptomatic deterioration (patients unable to continue study treatment due to progressing lymphoma that did 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.	

comment

The inclusion and exclusion criteria of the study PIX306 seemed representative of a population of subjects with relapsed DLBCL. There were several differences in the inclusion and exclusion criteria when comparing studies 306 and 301, as highlighted below.

The most significant difference is number of prior therapies allowed: ***1-****3 prior regimens for DLBCL in study PIX306 vs. relapse after* ***2 or more*** *prior regimens of chemotherapy in study PIX301. Other important difference was the requirement that all patients in study PIX306 should have received a rituximab-containing multi-agent regimen, while in study PIX 301 patients must have received rituximab in prior regimens in those countries where it was the standard of care and available at the patient's institution.*

Importantly, patients with prior treatment with a cumulative dose of doxorubicin or equivalent exceeding 450 mg/m² were excluded from both studies. There was a minor difference in the LVEF-criteria by echocardiogram: in study 306 patients with LVEF < 45% were excluded, in study 301 LVEF had to be ≥ 50%.

Treatments

Investigational treatments

The investigational treatment in this trial is pixantrone in combination with rituximab. The regimen was given in up to six 28-day cycles, consisting of pixantrone 50 mg/m^2 (in its base form) IV on Days 1, 8, and 15 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle. Refer to Table 5.2.

The investigational treatment in this trial is gemcitabine in combination with rituximab. The regimen was given in up to six 28-day cycles, consisting of gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle.

Table 3: Treatment administration (Study PIX306)

		Screening/ Baseline	Cycle 1			Cycles 2-6			EOT
		Day -28 to Randomization	D1	D8	D15	D1	D8	D15	
			W1	W2	W3				
PIX + R	Rituximab 375 mg/m^2 IV		X			X			
	Pixantrone 50 mg/m^2 IV		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	

The choice of pixantrone dose (50 mg/m^2 on Days 1, 8, and 15 in 28-day cycles) was based on preclinical testing and clinical evaluation in phase 1 to 3 studies. The phase 1 and 2 studies (in which pixantrone doses were expressed in terms of the salt, pixantrone dimaleate) administered dose-dense monotherapy to heavily pre-treated patients with lymphoid neoplasia or solid tumours. These studies defined a pixantrone dimaleate dose range of ≥ 56 mg/m^2 (with which no grade 3 toxicity was observed) and ≤ 112.5 mg/m^2 (with which 50% of patients had grade 3 or 4 neutropenia). Although some responses were noted at lower dose levels, in patients with relapsed or refractory lymphoma, 84 mg/m² pixantrone dimaleate (dose intensity 60.5 mg/m^2/week) was the lowest dose at which durable CRs were seen. This dose choice (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 III study PIX-301.

Combining pixantrone chemotherapy with the anti-CD20 agent rituximab was expected to produce synergistic effects with minimal overlapping toxicity and minimal drug interactions. This combination was compared to rituximab alone in a small randomized trial of 38 patients with relapsed follicular NHL (study AZA302). The combination was well tolerated and associated with a significantly higher response rate (75% versus 33% on monotherapy, p = 0.038) and time to progression than rituximab alone (395 days versus 245 days, HR = 0.14, p < 0.001). Long term responses (> 1 year) were only observed in patients treated with pixantrone.

The choice of comparator was based on the NCCN guidelines published at that time, for patients with relapsed or refractory DLBCL who are not candidates for SCT, recommending entry to a clinical study, or single-agent, doublet, or multiagent regimens, some containing gemcitabine and/or rituximab. The ESMO guidelines also propose a gemcitabine-based regimen including rituximab as salvage treatment, or clinical trials with novel

drugs, in patients non-eligible for transplant. Small studies have shown promising results in patients with relapsed or refractory DLBCL (Wenger *et al.*, 2005; Corazzeli *et al.*, 2009). The combination of gemcitabine and rituximab therefore appeared to be a reasonable therapeutic option in patients with relapsed NHL if ineligible for SCT.

comment

The dose of pixantrone (in combination with rituximab) was identical compared to the dose administered in the pivotal study PIX301 and to the dose recommended in the marketing authorisation.

The dose of rituximab was identical compared to dose used the in combination with CHOP chemotherapy in first line treatment. Basically all patients receive rituximab in first line and in case of relapse many patients develop disease that is refractory to rituximab. Combining pixantrone chemotherapy with the anti-CD20 agent rituximab was expected to produce synergistic effects. However, the role of rituximab in salvage treatment (like here in combination with either pixantrone or gemcitabine) in second or further line treatment is not clear.

The choice of the comparator, gemcitabine, seems to be acceptable at the time study PIX306 was initiated. At that time there were no approved second-line treatments in relapsed DLBCL and gemcitabine was shown to have at least some effect in the treatment of patients with relapsed DLBCL.

There is still an unmet medical need for effective second-line therapies for relapsed DLBCL because even today there are no approved or universally used second-line regimens especially in patients with comorbidities or advanced age.

Concomitant treatments

Patients could receive all concomitant therapy deemed necessary to provide adequate support (only study-prescribed investigational agents), including antiemetics, medications to prevent or treat rituximab hypersensitivity and medications to prevent tumor lysis syndrome (allopurinol or rasburicase). Patients could not receive any other systemic anticancer therapy or radiotherapy while receiving treatment in this study. Low dose corticosteroids were allowed for the treatment of non-cancer-related illness at the discretion of the investigator.

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

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

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

Patients receiving pixantrone were encouraged to avoid excessive exposure to sunlight and use effective sun blocker agents. Topical sun blocking agents were not reported as concomitant medications.

In vitro -studies with the most common human cytochrome P450 (CYP) 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 metabolized 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 were carefully monitored in the weeks immediately following initiation of pixantrone concurrent therapy. Warfarin is partially metabolized 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 normalized ratio (INR), were monitored in the days immediately following the initiation of pixantrone concurrent therapy. Amitriptyline, haloperidol, clozapine, ondansetron and propranolol are metabolized 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 were 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, and the anti-HIV agents, ritonavir, saquinavir, or nelfinavir. In addition, caution was taken when pixantrone was 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.

comment

Follow-up of patients receiving concomitant treatments with interaction potential with the study drugs has been appropriate.

Objectives

The primary objective is to evaluate the efficacy of pixantrone + rituximab compared with gemcitabine + rituximab in patients with a diagnosis of de novo DLBCL, DLBCL transformed from indolent lymphoma, or follicular grade 3 lymphoma who have relapsed after at least 1 prior chemotherapy regimen and who are not currently eligible for high-dose (myeloablative)chemotherapy and SCT.

The objective of the PK substudy was to compare the PK of pixantrone in patients who receive rituximab therapy *versus* patients who do not receive routine rituximab therapy.

Primary objective

The primary objective of this study was to evaluate the efficacy (as measured by progression-free survival [PFS]) of pixantrone + rituximab (pixantrone + rituximab) compared with gemcitabine + rituximab (gemcitabine + rituximab) 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 NHL (any type).

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

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

Pharmacokinetics sub-study objective

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

Outcomes/endpoints

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. The imaging method used for each participant at baseline was used throughout the study. Disease assessment was carried out at baseline and every 8 weeks ± 1 week from Day 1 of Cycle 1 (see Table 5.3) 1) during the treatment and early follow-up periods and then every 12 weeks ± 2 weeks during intermediate follow-up period.

PET was not required, even at baseline, except at the end of study visit (EOT, 4 to 7 weeks following the last study drug dose administration) unless geographically unavailable or the patient had PD per Modified IWG criteria, or the patient had received subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy. PET scans obtained alone or in combination with CT scan (PET/CT) were acquired from the skull base to the upper thighs following standard imaging protocols. 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.

At each evaluation time point, every target and non-target lesion were evaluated. Once a patient was assessed by the investigator as having PD as defined by the modified IWG 2007 Revised Response Criteria no further CT or PET scans or disease response assessments were required by the study.

Table 4: Disease assessment schedule (study PIX306)

Screening and Treatment period										
	Screening/Baseline Day -28 to Randomization			W8 (± 1 week)		W16 (± 1 week)		W24 (± 1 week)		EOT[7]
CT scan[1]	X			X		X		X		
PET scan[2]										X
Bone marrow biopsy with core[3]										X
Follow-up periods										
	Early follow-up[6] (± 1 week)			Intermediate follow-up (± 2 weeks)					Survival follow-up (± 2 weeks)	
	FU W8	FU W16	FU W24	FU W36	FU W48	FU W60	FU W72	FU W84	FU W96	Every 12 W Until Death or Study Termination	EOS
Adverse events[4]	X										
LVEF[5]			X								
Troponin T[5]			X								
CT scan[1]	X	X	X	X	X	X	X	X	X		
LDH	X	X	X	X	X	X	X	X	X		
Documentation of all subsequent systemic anticancer therapy	X	X	X	X	X	X	X	X	X		
Survival	X	X	X	X	X	X	X	X	X	X	X

[1] CT with IV contrast of the neck, chest, abdomen, and pelvis. Patients intolerant to IV contrast were to have MRI and non-contrast CT and the reason for not using contrast specified in source documents. The imaging method used at baseline was used throughout the study. All time points for CT/MRI were calculated from Day 1 Cycle 1. In case an assessment was done off schedule, the next assessment was calibrated as closely as possible back to the original schedule starting at Day 1 Cycle 1.

[2] PET scan could be obtained alone or in combination with CT scan. PET scan was not required at baseline, but any PET images obtained at baseline or during the study were submitted for central review. PET scan was required at EOT visit, unless geographically unavailable or patient had PD per Modified IWG criteria, or patient had started subsequent systemic anticancer therapy, except for rituximab given as maintenance therapy.

[3] A bone marrow biopsy (with core) was 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 were submitted for local review.

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

[5] LVEF was assessed at Follow-up Week 24; troponin T samples were obtained at Follow-up Week 24.

[6] The Early FU Week 8 visit occurred 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.

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

Table 5: Modified IWG 2007 revised response criteria for malignant lymphoma

Response[1]	Evaluation	Criteria
Complete response (CR) All criteria are required [2]	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 is involved by lymphoma before treatment, the infiltrate must have cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
	LDH	Normal
Partial response (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
Stable disease (SD)	Criteria for PD, PR or CR are NOT met.	
Progressive or relapsed disease (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

[1] Assessment of response was compared with baseline; assessment of PD was compared with nadir (i.e. lowest value, whether at baseline or any other study time point).

[2] PET and bone marrow were required evaluations at EOT only and were required to assess CR status. If not obtained at EOT, bone marrow and PET could be subsequently obtained to assess CR status at that time. CR assessments during FU (after EOT) required the bone marrow and PET results obtained at or after EOT in order to assess CR status.

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) (PPD = SDi x LDi); 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.

The study committees were involved in the confirmation of diagnosis (CPRC), the assessment of radiological images (IRC) and in the evaluation of treatment toxicity and appropriateness of treatment doses (IDMC). The interim OS analysis for this report was performed by the IDMC.

The primary endpoint is progression-free survival (PFS), and secondary endpoints include overall surviva (OS), overall response rate (ORR), complete response rate (CR), and safety.

PFS as assessed by the IRC. PFS was defined as the time from the date of randomization to the date of PD or death due to any cause (whichever occurred first).

The outcome of the PK substudy is the time-concentration data of pixantrone, measured before the start of pixantrone infusion and approximately at 1h, 1.5h, 2h, 4h, 6h, and 24 to 48h after the start of pixantrone infusion.

comment

The optimal primary efficacy endpoint in this kind of study population would have been OS.

In the original protocol, the primary study endpoint was PFS, but this was changed before the start of recruitment (Amendment No. 2) to combined primary of PFS and OS (with a resulting modification of the size of the patient population). Amendment 4 changed the primary endpoint to OS only (as requested by the FDA) with PFS as a secondary endpoint. Amendment 8 changed the primary endpoint back to PFS (due to enrolment difficulties).

Regardless of the above mentioned slightly confusing changes to the primary efficacy endpoint, PFS is an acceptable primary efficacy endpoint with OS as a key secondary endpoint. PFS has been previously approved as a measure of the clinical efficacy of therapy in comparable oncological and haematological settings.

The timetable and monitoring of the treatment efficacy with the disease assessments by CT, PET (at the end of study visit) and bone marrow biopsy (at the end of study visit, unless negative at baseline) are acceptable and follow the current guidelines for evaluating treatment response in DLBCL.

One hundred ninety-five (195) PFS events confirmed by an independent review are required for the analysis of the primary endpoint to detect at least a 35% improvement (i.e., HR = 0.65) in PFS with 85% power and a 2-sided alpha of 0.05. Based on results from the study by Pettengell *et al.*, it was assumed that the median PFS for the control group is 2.8 months. It was estimated that approximately 320 patients were needed to reach the required 195 PFS events within approximately 80 months after randomization of the first patient. However, further to an increase of the enrolment rate in the last 2 months, the recruitment was stopped in August 2017 with 312 randomized patients.

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 results from the study by Pettengell *et al.*, it was assumed that the median OS for the control group is 7 months.

For the PK substudy, the objective was to enrol approximately 20 patients.

comment

Final sample size calculations, planning to show superiority in the pixantrone + rituximab treatment-arm, were acceptable for both PFS and OS.

Randomisation

Approximately 320 patients are planned to be randomized in a 1:1 ratio to one of the two treatment arms stratified by number of prior therapies (0 to 2 vs. ≥ 3), IPI score (0 to 2, ≥ 3), and length of time from initiation of first-line therapy until first relapse (< 1 year vs ≥ 1 year).

comment

Selected randomization procedure with the proposed stratifications was appropriate.

Blinding (masking)

Treatment assignment was known by investigators, site personnel and patients, but the sponsor (with the exception of certain CTI personnel responsible for pharmacovigilance activities, regulatory submissions and GCP Compliance) remained blinded during the study until the core database lock.

At the time of the core database lock, the sponsor was unblinded to all data except the OS datasets. Indeed, the OS interim results were produced by the IDMC and the sponsor had only access to those unblinded OS interim results (no patient data). At that time, all patients had completed their treatment. However, the deaths contributing to the PFS events in the core locked database were part of the unblinded data. The sponsor remains blinded to OS datasets until the final OS analysis.

This study was conducted using sponsor's blinding procedures. The official clinical database stayed blinded for the primary endpoint analysis until data review had been completed, protocol violations identified, data declared clean, and a detailed Statistical Analysis Plan (SAP) was written and approved.

Members of the IRC, who were to determine the disease response for all randomized patients, remained blinded to site identifiers, patient treatment arm and investigator's target lesions.

comment

The sponsor was blinded during the study until the core database lock which is appropriate in this type of study.

Statistical methods

The statistical plans were changed frequently; the changes were documents as protocol amendments. It is assumed that the sponsor remained blinded throughout the process. The primary endpoint was initially PFS, was changed PFS and OS as co-primary, OS as primary, and finally back to initial plan with PFS as primary.

Through all the changes the primary aim was to demonstrate superiority of pixantrone + rituximab over gemcitabine + rituximab in terms of efficacy measured with tumour response and/or overall survival.

Analysis populations

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

This set is the primary population used for all efficacy analyses.

In addition histologically confirmed, per-protocol and safety populations were defined.

Primary endpoint

The primary efficacy endpoint for the study was PFS, defined as the time from the date of randomization to the date of PD or death of any cause), whichever occurred first, for patients in the ITT population. The primary analysis of PFS was based on disease progression as determined by the IRC. Censoring rules are presented below.

Table 6: Event and censoring rules for PFS primary analysis (Study PIX306)

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

For the primary efficacy analysis, PFS between the two treatment arms was compared in the ITT population using a stratified log-rank test, on the randomization stratification factors as reported in the eCRF. Summary statistics, including median PFS time and the corresponding 95% confidence interval based on KM estimates, were presented by treatment group. The KM curves by treatment group were plotted.

A Cox regression model with a term for treatment arm, adjusted for the randomization stratification factors (actual strata), was used to quantify the treatment difference in PFS. HRs and corresponding 95% CIs as estimated from the Cox regression model are also presented.

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

Secondary endpoints

Overall Survival (OS)

OS was defined as the time from the date of randomization to the date of death due to any cause. If a patient was alive or the survival status was unknown by the data cut-off date for analysis, survival was censored at the date that patient was last known to be alive. This primary OS analysis was performed in the ITT population using stratified log-rank test and adjusted Cox-regression model, stratified by the actual strata values as documented in the eCRF.

Overall response rate (ORR)

The ORR was defined as the proportion of patients who achieved a CR or PR without additional anticancer therapy. Patients who discontinued before any response was observed, or received additional anticancer therapy before a response was observed were considered non-responders.

The primary analysis of ORR was based on the IRC response assessments in the ITT population. Comparison of the ORRs between the 2 treatment arms was performed using the exact Cochran-Mantel-Haenszel test, controlling for the stratification factors used for randomization with actual strata values as documented in the eCRF (if a mis-stratification occurred).

Complete Response (CR) Rate

CR rate was defined as the proportion of patients who achieved a CR without additional therapy. Patients who discontinued before any response has been observed or received additional anticancer therapy before a response has been observed were considered non-responders. CR was analysed in the same manner as for ORR.

Multiplicity

For the efficacy analysis, treatment arms were compared all primary and secondary endpoints. The multiplicity arising from the testing of multiple endpoints was addressed using a closed hierarchical testing procedure that required establishing significance in the primary endpoint prior to assessing the significance of secondary endpoints to ensure the overall type I error at 0.05.

The order of secondary endpoints in the hierarchical testing was: OS, ORR, CR.

The multiplicity of OS analyses was to be addressed using group sequential methods.

Study analyses

The study analyses are planned as follows:

- 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. Projections suggest that 195 PFS events will be observed by February 2018.
- The first interim analysis (IA) of OS will be performed after approximately 165 OS events (75%) have occurred and confirmation of 195 PFS events and it is projected to be observed by January 2018.
- The second IA of OS will be performed when 190 OS events (86%) have occurred and it is projected to be observed by January 2019.
- The final analysis will be performed at the end of the study, when the 220 OS events have occurred and it is projected to be observed by January 2022.

PK analyses were performed using data from all randomized patients who received any dose of study treatment and provided at least one appropriate sample for plasma PK analysis. The PK analysis consisted of creating a Visual Predictive Check (VPC) for the new patients, based on a previously developed population PK model. No new PK modelling was conducted; the goal was to compare the predictions from the existing population PK model to the new data (external validation).

comment

The statistical analyses followed the standards in this type of trial for definition of analysis population, endpoints, censoring rules, multiplicity, and analysis methods including sensitivity analysis. The main issue with the analysis plans was the frequent change of the primary endpoint in a trial where MAH's blinding cannot be ensured; however the primary endpoint has been PFS or OS or both, which both are well-accepted endpoints in this indication, and the MAH have ensured that the blinding was retained. Furthermore as the trial outcome was negative, this is not an issue with regards to the type I error rate.

The MAH decided to conduct a visual inspection of whether the PK of pixantrone is different in patients receiving rituximab, versus the patient population that was studied earlier. This approach is rational. Nevertheless, the MAH was asked to present additional evidence to show that there are no trends in the PK of pixantrone in rituximab-treated patients, when compared to the rest of the patient population. Two RSI's were requested. First, the MAH was asked to demonstrate via descriptive statistics and t-test that the CWRES residuals of the PK samples of the current study are not significantly different from zero. The aim of this request was to verify that the overall pixantrone concentrations are not significantly different in the currently studied patient population, when compared to the patient population studied earlier. Second, the MAH was requested to incorporate the newly generated data into the existing population pharmacokinetic dataset, and to test rituximab co-treatment separately as a covariate of pixantrone clearance and volume of distribution. The aim of this request was to specifically verify that pixantrone clearance and volume of distribution are not significantly different in the currently studied patient population, when compared to the patient population studied earlier.

The MAH was able to convincingly demonstrate that the PK of pixantrone in patients receiving rituximab is not significantly different from the PK of pixantrone in patients not receiving rituximab, in these data. For details, please see Section 10.2 Q7-Q8.

Results

Participant flow

A total of 312 patients were randomized in this study: 155 patients in the pixantrone + rituximab group and 157 in the gemcitabine + rituximab group. The disposition of patients and their follow-up is presented below

Table 7 Randomised patients by country and by group (Study PIX306)

Region and Country	Pixantrone + R N = 155 n (%)	Gemcitabine + R N = 157 n (%)	Total N = 312 n (%)
North America	**51 (32.9)**	**53 (33.8)**	**104 (33.3)**
United States	51 (100)	51 (96.2)	102 (98.1)
Canada	-	2 (3.8)	2 (1.9)
Europe	**104 (67.1)**	**104 (66.2)**	**208 (66.7)**
Italy	17 (16.3)	14 (13.5)	31 (14.9)
Poland	14 (13.5)	17 (16.3)	31 (14.9)
Czech Republic	12 (11.5)	16 (15.4)	28 (13.5)
Bulgaria	11 (10.6)	13 (12.5)	24 (11.5)
Ukraine	7 (6.7)	12 (11.5)	19 (9.1)
France	7 (6.7)	6 (5.8)	13 (6.3)
Spain	8 (7.7)	5 (4.8)	13 (6.3)
Hungary	8 (7.7)	3 (2.9)	11 (5.3)
United Kingdom	4 (3.8)	6 (5.8)	10 (4.8)
Belgium	6 (5.8)	1 (1.0)	7 (3.4)
Germany	3 (2.9)	3 (2.9)	6 (2.9)
Russian Federation	3 (2.9)	3 (2.9)	6 (2.9)
Romania	2 (1.9)	2 (1.9)	4 (1.9)
Denmark	2 (1.9)	-	2 (1.0)
Slovakia	-	2 (1.9)	2 (1.0)
Austria	-	1 (1.0)	1 (0.5)

The percentage in each country is based on the number of randomized patients within each region and treatment arm.

Table 8 Disposition of randomised patients by group (Study PIX306)

Status		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)	All (N = 312)
All randomized	**n**	**155**	**157**	**312**
Patients who discontinued treatment due to	**n (%)**	**83 (53.5)**	**96 (61.1)**	**179 (57.4)**
progressive disease	n (%)	47 (30.3)	50 (31.8)	97 (31.1)
adverse event	n (%)	21 (13.5)	15 (9.6)	36 (11.5)
consent withdrawal	n (%)	6 (3.9)	16 (10.2)	22 (7.1)
death	n (%)	5 (3.2)	10 (6.4)	15 (4.8)
other	n (%)	4 (2.6)	5 (3.2)	9 (2.9)
Patients who completed the treatment	**n (%)**	**72 (46.5)**	**61 (38.9)**	**133 (42.6)**
Patients who withdrew from the study due to	**n (%)**	**103 (66.5)**	**94 (59.9)**	**197 (63.1)**
death	n (%)	94 (60.6)	84 (53.5)	178 (57.1)
consent withdrawal	n (%)	6 (3.9)	8 (5.1)	14 (4.5)
lost to follow-up	n (%)	1 (0.6)	2 (1.3)	3 (1.0)
other	n (%)	2 (1.3)	-	2 (0.6)

%: Expressed as percentage of the randomized patients

A total of 133 patients (42.6%) completed the treatment: 72 patients (46.5%) in the pixantrone + rituximab group and 61 patients (38.9%) in the gemcitabine + rituximab group.

Patients were withdrawn from treatment mostly because of progressive disease: 47 patients (30.3%) in the pixantrone + rituximab group versus 50 patients (31.8%) in the gemcitabine + rituximab group, or AE (13.5% versus 9.6%, respectively). There was a slight imbalance in the proportion of patients who withdrew consent for treatment (3.9% versus 10.2%); no information is available on follow-on therapies.

As of the data cut-off date (31 May 2018), a total of 197 patients (63.1%) were withdrawn from the study (103 [66.5%] patients in the pixantrone + rituximab arm and 94 [59.9%] patients in the gemcitabine + rituximab arm). Main reasons for withdrawal from the study were death (178 patients overall, 57.1%) and consent withdrawal (14 patients overall, 4.5%).

Table 9: Disposition of randomised patients by group (Study PIX301)

	Pixantrone	Comparator
ITT Population	70 (100%)	70 (100%)
HITT Population	54 (77.1%)	50 (71.4%)
Safety Population	68 (97.1%)	67(95.7%)
STUDY COMPLETION		
Completion of Protocol Treatment (6 Cycles)	20 (28.6%)	16 (22.9%)
DISCONTINUED TREATMENT	50 (71.4%)	54 (77.1%)
Reasons for Treatment Discontinuation		
Progressive/Relapsed Disease	28 (40.0%)	39 (55.7%)
Adverse Events	15 (21.4%)	9 (12.9%)
Withdrawal of Consent	2 (2.9%)	5 (7.1%)
Lost to Follow-Up or Noncompliant	2 (2.9%)	0
Other	3 (4.3%)	1 (1.4%)
FOLLOW-UP PERIOD		
Entered Follow-Up	52 (74.3%)	43 (61.4%)
Completed 18 Months of Follow-up	15 (28.8%)	11 (25.6%)
Died During Follow-up	30 (57.7%)	26 (60.5%)
Patient Withdrew Consent	3 (5.8%)	5 (11.6%)
Other/Not Verified	4 (7.7%)	1 (2.3%)

Patients continuing to Followup were defined as patients who completed at least one follow-up visit.

comment

Based on subject selection, the study results (PIX306) can be generalised to the European DLBCL patients. This is important, because in the pivotal study PIX301, only 38/140 patients were recruited in "Western Europe". This could possibly explain the lower than expected use of rituximab (already approved 3/2002 in EU) in the first line treatment of patients recruited into the study PIX301.

Overall only 42.6% of patients completed the planned treatment in study PIX306, with consent withdrawal being the reason for higher number of discontinuation in the gemcitabine + rituximab group (10.2 vs. 3.7). In total 61.1% in the gemcitabine + rituximab group vs. 53.5% in the pixantrone + rituximab discontinued treatment.

The number of patients withdrawn from treatment because of progressive disease, the main reason, was comparable: 47 patients (30.3%) in the pixantrone + rituximab group versus 50 patients (31.8%) in the gemcitabine + rituximab group.

Conduct of the study

Amendments:

Nine protocol amendments were issued for this study. The significant changes consisted of:

Amendment No. 1, dated 9 December 2010 concerned the clarification of PFS definition and the modification of censoring rules. For patients "who received any new lymphoma-directed therapy (other than rituximab as maintenance) before progression of disease", the date of censoring was defined as the date of the "last radiologic assessment prior to the start of the new therapy", instead of the "date of first administration of additional treatment".

Amendment No. 2, dated 10 March 2011, concerned mainly:

- The change in the study primary objective: OS, initially a secondary objective, was added to PFS as a combined primary objective. Statistical methods including sample size determination were updated taking into account this modification.
- The increase in the number of patients to be randomized (from 300 to 350).
- The replacement of the stratification factor "prior SCT" by "length of time from initiation of first-line therapy for aggressive NHL until first relapse".
- The addition of safety criteria (study-related AEs and some cardiac events and assessments) during the Follow-up periods.
- As regards to the reporting of AEs, it was also specified that cardiac AEs ≥ grade 3 were to be collected until the end of the study and followed until resolution or no further improvement was expected.
- Specifications on clinical examination were added.
- The modification of inclusion criteria (bone core biopsy was to be obtained within 8 weeks prior to randomization, addition of the necessity to confirm the response to CHOP-R by a second radiographic assessment; removal of the 24-week delay between day 1 of last cycle of CHOP-R or equivalent treatment and subsequent relapse, and update of the laboratory requirements for platelets and absolute neutrophil count).
- The addition of primary refractory aggressive NHL as an exclusion criterion.
- An update of pixantrone and gemcitabine dose adjustments and delays for hematologic toxicity.

Amendment No. 3, dated 3 August 2011, included:

- An update of Safety information in the background section.
- The clarification of the use of the terms "NHL" and "DLBCL".
- The modification of inclusion criteria: bone marrow biopsy criteria were clarified, prior CHOP-R was allowed for any type of NHL, patients with transformed follicular lymphoma who may not have received CHOP-R as first-line therapy for aggressive NHL could also be included in the study, definition of

measurable disease was adjusted to be consistent with other Sections in the protocol, and it was specified that DLBCL diagnosis was to be confirmed by pathologic review.

- The modification of exclusion criteria: definitions of measurable disease and primary refractory disease were updated and clarified, CNS involvement was further detailed, and enrolment of patients who had had certain low-risk cancers commonly found in this population was finally allowed.
- Disease Assessment Criteria were extensively clarified.
- PET scan requirements were modified.
- The prior requirement for central evaluation of echocardiograms was removed, since implementing the central read processes negatively impacted timely site initiation and accrual of patients. There was no clear need for a retrospective central read, but there was considerable negative impact; therefore, central read was deleted. Local echo evaluations were used for safety and treatment decisions.
- Procedures for dose adjustments and delays were detailed.

Amendment No. 4, dated 5 January 2012, aimed to:

- Change the primary endpoint of the study to "overall survival" only, following FDA recommendations. PFS was therefore a secondary objective. All the protocol (primary and secondary endpoints, statistical analyses, etc) was modified accordingly.
- An interim analysis of OS, to be done when 150 deaths (50%) had occurred, was planned. The final OS analysis was to be performed when 300 deaths had occurred.
- Stratification factors were adjusted.
- Criteria for eligible patients were modified and clarified to ensure safety and enrolment of the target population.

Amendment No. 5, dated 9 April 2012 for North America (NA), concerned:

- For the primary objective, eligibility of patients was further detailed: patients were to "have no progression for at least 12 weeks after last dose of a treatment regimen" instead of "were to have had a response to prior therapy".
- 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.

Amendment No. 5 NNA, dated 18 June 2012 for Non-North America (NNA), included:

- 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).

Amendment No. 6 NNA, dated 17 October 2012 for NNA, concerned mainly:

- 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.

Amendment No. 7 NNA, dated 16 September 2013, was applicable in NNA, and aimed to:

Change in EOT window: The EOT visit was to occur at 4 to 7 weeks after last study drug dose, inclusive, or before non-protocol NHL therapy was given, whichever occurred first instead of "the EOT visit occurs at 5 weeks ± 1 week after the last study drug administration or before non-protocol NHL therapy is given".

Gemcitabine dose modifications for hematologic toxicity were completed.

Gemcitabine and pixantrone dose modifications for non-hematologic toxicity were completed.

Amendment No. 8, dated 25 July 2014 for NA and NNA, unified the previous NA and NAA versions. Changes included those from Amendment No. 6 NA and Amendment No. 7 NNA. Major changes (Amendment No. 8 NA) were:

- The primary endpoint (previously OS) was replaced by PFS, as it reflects the effect of therapy on tumour 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. OS was a secondary endpoint, as a standard endpoint used to measure clinical benefit. All the protocol (primary and secondary endpoints, statistical analyses […]) was modified accordingly.
- The number of subjects to be randomized was decreased from 350 to 260 patients. It was specified that enrolment was to be continued until 195 PFS events occurred, or approximately 260 patients were enrolled, whichever occurred first. Enrolment period was planned approximately 60 months from study initiation.
- It was specified that no interim analysis of PFS was planned.
- Exploratory objectives (assessment of duration of overall response between treatments, assessment of duration of CR between treatments, proportion of patients who received a SCT after study treatment) were added.
- Rituximab given as maintenance therapy was not allowed prior to the EOT visit per protocol window.
- A PK study was added.

Amendment No. 9, dated 10 July 2017, aimed to:

- Update the total number of patients to be enrolled, after simulation performed by the sponsor, from 260 to 320 patients, to reach the 195 PFS events (per IRC) within a reasonable timeline to meet the study report due date.
- Increase enrolment period from 60 to 80 months, to accommodate the increase in the number of planned patients' enrolment.
- Add one additional interim analysis for secondary efficacy endpoint OS, i.e. when 190 OS events (86% of the required number of OS events) have occurred, due to much slower occurrence of OS events than expected. Indeed, based on the updated projection, the time to achieve 220 OS events is year 2022, more than 3 years from the first interim analysis. Adding the 2nd OS interim analysis would provide a chance to stop the trial earlier if the treatment demonstrated superior survival benefit.
- The hierarchy order for testing the secondary efficacy endpoints was updated. In view of the importance of OS in these patients and in order to better match the study objectives, there was reorganization of the

order of endpoints testing, to put OS ahead of overall response and CR, in the hypothesis testing hierarchy of secondary endpoints.

- Clarify treatment blinding.
- Add a sub-group analysis. As the current indication is in 3rd and 4th line, a subgroup analysis defined by 0-1 line versus more than 2 lines was added to confirm the efficacy and safety of pixantrone in the current indication and to evaluate them in 2nd line.

comment

The primary efficacy endpoint was changed several times in the above described amendments.

Briefly, in the original protocol, the primary study endpoint was PFS, but this was changed before the start of recruitment (Amendment No. 2) to combined primary of PFS and OS (with a resulting modification of the size of the patient population). Amendment 4 changed the primary endpoint to OS only (as requested by the FDA) with PFS as a secondary endpoint. In agreement with the EMA, Amendment 8 changed the primary endpoint back to PFS (due to enrolment difficulties). This change of primary efficacy endpoint could be agreed on.

The other above listed amendments are all well justifiable.

Protocol deviations:

Overall, 115 patients (36.9%) had at least one protocol deviation: 56 patients (36.1%) in the pixantrone + rituximab group and 59 patients (37.6%) in the gemcitabine + rituximab group. The most frequent deviations in both groups were related to study drug administration (20.0% of patients in the pixantrone + rituximab group versus 24.8% in the gemcitabine + rituximab group) and protocol non-adherence (11.0% versus 13.4%, respectively).

The deviations were thoroughly documented and reported. The major deviations included:

- Single cases of less than 28 days from previous NHL treatment prior to study dose.
- Single errors in doses based on incorrect BSA calculations or otherwise not following the protocol.
- Single errors in dose modifications to be performed according to blood counts
- Some cases of missing CT-scans or out of time window CT-scans.
- Some missing bone marrow biopsies at EOS visit (also after CR).

Assessor's comment

Overall, the total number of protocol deviations was high. As a response to the questions regarding the protocol violations, the MAH has submitted a summary table of subjects with major protocol deviations from the ITT population. The majority of major deviations were related to study drug administration and protocol non-adherence. The numbers of these major deviations are equally distributed between the two treatment arms.

Importantly, none of the protocol deviations led to patient withdrawal from the study.

For intentional dose reductions refer to section "Safety - Safety exposure", below.

Baseline data

At baseline, the median age was 73.0 years ranging from 26 to 91 years. Most patients were 65 years old or older (78.8% overall). Just over half of the patients were women (56.4%) and the large majority (96.8%) were white. Two thirds of patients (66.7%) were enrolled in Europe and one third (33.3%) in North America.

Table 10: Main baseline characteristics in the ITT population (Study PIX306)

		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)	p-value*	All (N = 312)
Age (years)				*0.535*	
	n	155	157		312
	Mean ± SD	70.3 ± 10.69	71.0 ± 11.31		70.6 ± 10.99
	Median	73.0	73.0		73.0
	Q1, Q3	65.0, 77.0	67.0, 79.0		66.0, 78.0
	Min, Max	30, 91	26, 90		26, 91
18-64	n (%)	36 (23.2)	30 (19.1)	*0.659*	66 (21.2)
65-84	n (%)	113 (72.9)	120 (76.4)		233 (74.7)
≥ 85	n (%)	6 (3.9)	7 (4.5)		13 (4.2)
Gender				*0.819*	
Female	n (%)	86 (55.5)	90 (57.3)		176 (56.4)
Male	n (%)	69 (44.5)	67 (42.7)		136 (43.6)
Region					
North America	n (%)	51 (32.9)	53 (33.8)		104 (33.3)
Europe	n (%)	104 (67.1)	104 (66.2)		208 (66.7)
Race				*0.165*	
White	n (%)	147 (94.8)	155 (98.7)		302 (96.8)
Black or African American	n (%)	4 (2.6)	1 (0.6)		5 (1.6)
Asian	n (%)	1 (0.6)	1 (0.6)		2 (0.6)
Other	n (%)	2 (1.3)	-		2 (0.6)
Unknown	n (%)	1 (0.6)	-		1 (0.3)
BMI (kg/m^2)				*0.849*	
	n	151	148		299
	Mean ± SD	27.5 ± 5.99	27.4 ± 5.65		27.5 ± 5.81
	Q1, Q3	23.7, 30.7	23.8, 30.3		23.7, 30.6
	Min ; Max	15, 62	16, 48		15, 62

Baseline = D-28 to randomization.
** p-values comparing the treatment groups are based on Fisher exact test for categorical variables and t-test for continuous variables.*

The most common histological subtype assessed by local investigators was DLBCL (77.6% of patients), 13.8% of patients had DLBCL transformed from indolent, and 8.7% had FL Grade 3 lymphoma. According to CPRC, 78.5% of patients had DLBCL, 4.8% had DLBCL with follicular components and 2.6% had FL Grade 3. Other patients were not diagnosed for lymphoma (4.8%), had other lymphoma (3.8%), were not assessed (3.5%) or assessment was missing (1.9%). The initial diagnosis was made at a median of 1.9 years (*i.e.*, 22.8 months; ranging from 0 to 15 years) prior to study entry.

Most patients had received 1 prior therapy (61.9%) for DLBCL or FL Grade 3 lymphoma; 21.8% had received 2 prior therapies and 11.5% received 3 prior therapies. Most patients (53.2%) had a baseline IPI score ≥ 3. Time from initiation of first-line therapy for DLBCL or FL grade 3 until first relapse was a median of 1.4 years (i.e. 16.8 months). Main reason for non-eligibility for HDC and SCT was “patient is not adequately fit” (39.4%).

Table 11: Baseline disease characteristics - ITT population (Study PIX306)

		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)	All (N = 312)
Histology assessed by local investigator				
DLBCL	n (%)	122 (78.7)	120 (76.4)	242 (77.6)
DLBCL transformed from indolent	n (%)	22 (14.2)	21 (13.4)	43 (13.8)
FL Grade 3	n (%)	11 (7.1)	16 (10.2)	27 (8.7)
	p-value[1]			*0.644*
Histology assessed by CPRC				
DLBCL	n (%)	120 (77.4)	125 (79.6)	245 (78.5)
DLBCL with follicular components	n (%)	5 (3.2)	10 (6.4)	15 (4.8)
FL Grade 3	n (%)	3 (1.9)	5 (3.2)	8 (2.6)
Non-diagnostic for lymphoma	n (%)	10 (6.5)	5 (3.2)	15 (4.8)
Other lymphoma (none of the above)	n (%)	8 (5.2)	4 (2.5)	12 (3.8)
Not Assessed	n (%)	6 (3.9)	5 (3.2)	11 (3.5)
Missing	n (%)	3 (1.9)	3 (1.9)	6 (1.9)
	p-value[1]			*0.388*
Time since initial diagnosis of DLBCL or FL grade 3 (years)				
	n	155	157	312
	Mean ± SD	2.8 ± 2.8	2.9 ± 2.6	2.9 ± 2.7
	Median	1.8	2.0	1.9
	Q1, Q3	1.1, 3.4	1.1, 3.7	1.1, 3.6
	Min, Max	0, 15	0, 14	0, 15
	p-value[1]			*0.782*
Current Ann Arbor Stage of NHL				
I	n (%)	11 (7.1)	9 (5.7)	20 (6.4)
II	n (%)	32 (20.6)	30 (19.1)	62 (19.9)
III	n (%)	38 (24.5)	37 (23.6)	75 (24.0)
IV	n (%)	74 (47.7)	81 (51.6)	155 (49.7)
	p-value[2]			*0.902*
Number of extranodal sites at screening				
0	n (%)	57 (36.8)	60 (38.2)	117 (37.5)
1	n (%)	49 (31.6)	38 (24.2)	87 (27.9)
> 1	n (%)	49 (31.6)	59 (37.6)	108 (34.6)
	p-value[2]			*0.309*
Number of prior lines of therapy for DLBCL or FL Grade 3*				
0	n (%)	9 (5.8)	6 (3.8)	15 (4.8)
1	n (%)	93 (60.0)	100 (63.7)	193 (61.9)
2	n (%)	35 (22.6)	33 (21.0)	68 (21.8)
3	n (%)	18 (11.6)	18 (11.5)	36 (11.5)
	p-value[2]			*0.823*
0-1	n (%)	102 (65.8)	106 (67.5)	208 (66.7)
≥ 2	n (%)	53 (34.2)	51 (32.5)	104 (33.3)
	p-value[2]			*0.810*

Baseline = day-28 to randomization; CPRC: Central Pathology Review Committee *(Continued)*

[1] *p-value: compare the two treatment groups based on t-test*

[2] *p-value: compare the two treatment groups based on Fisher's exact test*

** As documented in the eCRF*

Baseline disease characteristics - ITT population (Study PIX306) continued

		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)	All (N = 312)
Used for IWRS stratification factor:				
0-2	n (%)	137 (88.4)	139 (88.5)	276 (88.5)
≥ 3	n (%)	18 (11.6)	18 (11.5)	36 (11.5)
	p-value[2]			*1.000*
IPI score*				
0	n (%)	2 (1.3)	-	2 (0.6)
1	n (%)	24 (15.5)	17 (10.8)	41 (13.1)
2	n (%)	47 (30.3)	56 (35.7)	103 (33.0)
≥ 3	n (%)	82 (52.9)	84 (53.5)	166 (53.2)
	p-value[2]			*0.285*
Used for IWRS stratification factor:				
0-2	n (%)	73 (47.1)	73 (46.5)	146 (46.8)
≥ 3	n (%)	82 (52.9)	84 (53.5)	166 (53.2)
	p-value[2]			*1.000*
Time from initiation of first-line therapy for DLBCL or FL grade 3 until first relapse* (years)	n	144	151	295
	Mean ± SD	2.2 ± 2.20	2.3 ± 2.17	2.3 ± 2.18
	Median	1.4	1.4	1.4
	Min, Max	0, 11	0, 11	0, 11
	p-value[1]			*0.778*
Used for IWRS stratification factor:				
< 1 year	n (%)	58 (37.4)	58 (36.9)	116 (37.2)
≥ 1 year	n (%)	97 (62.6)	99 (63.1)	196 (62.8)
	p-value[2]			*1.000*
Prior Stem Cell Therapy				
Yes	n (%)	17 (11.0)	16 (10.2)	33 (10.6)
No	n (%)	138 (89.0)	141 (89.8)	279 (89.4)
	p-value[(2)]			*0.856*
Reason for ineligibility for HDC and SCT				
Patient is not adequately fit	n (%)	57 (36.8)	66 (42.0)	123 (39.4)
Patient refused	n (%)	22 (14.2)	18 (11.5)	40 (12.8)
Prior transplant	n (%)	16 (10.3)	12 (7.6)	28 (9.0)
Co-morbid conditions	n (%)	11 (7.1)	15 (9.6)	26 (8.3)
Failure to mobilize adequate number of cells	n (%)	2 (1.3)	-	2 (0.6)
Other	n (%)	47 (30.3)	46 (29.3)	93 (29.8)
	p-value[(2)]			*0.579*

Baseline = day-28 to randomization; HDC: High-Dose Chemotherapy; SCT: Stem Cell Transplant
[1] p-value: compare the two treatment groups based on t-test
[2] p-value: compare the two treatment groups based on Fisher's exact test
** As documented in the eCRF*
Note: patients with FL grade 3 or DLBCL transformed from indolent lymphoma could have 0 prior lines of treatment for these conditions

While every patient should have had at least 1 line of prior treatment, the patients with FL Grade 3 or DLBCL transformed from indolent lymphoma could have 0 prior lines of treatment for DLBCL or FL Grade 3 (which was a stratification criterion). For example, an FL Grade 3 patient could have had one prior line of treatment for FL Grade 2 and thus meet the inclusion criteria (while his number of prior lines for FL Grade 3 would be 0).

Table 12: Baseline ECOG PS (Study PIX306)

		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)	All (N = 312)
ECOG PS				
0	n (%)	45 (29.0)	40 (25.5)	85 (27.2)
1	n (%)	77 (49.7)	84 (53.5)	161 (51.6)
2	n (%)	33 (21.3)	32 (20.4)	65 (20.8)
Missing	n (%)	-	1 (0.6)	1 (0.3)
	*p-value**			*0.735*

Baseline = day-28 to randomization
** p-value: compare the two treatment groups based on Fisher's exact test*

comment

There were no discernible differences between the populations in the two treatment arms in the study PIX306 concerning demographic and baseline characteristics as well as baseline disease characteristics. The overall population with median age of 73 years represents typical DLBCL patients.

The baseline performance status (ECOG) was also comparable between the two treatment groups.

Overall, more than half of the patients (54.8%) received one prior systemic therapy, 24.7% received 2 prior systemic therapies and 17.6% received 3 prior systemic therapies. For the majority of patients (87.2%) the most recent systemic therapies for NHL prior to inclusion in the study pursued a curative intent. The best response to the most recent systemic therapy was CR or CRu in 55.4% of patients and PR in 30.1%.

Table 13 Prior NHL therapies - ITT population (Study PIX306)

		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)	All (N = 312)
Patients with prior systemic therapies*	n (%)	155 (100)	157 (100)	312 (100)
Number of prior systemic therapies	n	155	157	312
	Mean ± SD	1.7 ± 0.88	1.7 ± 0.89	1.7 ± 0.88
	Median	1.0	1.0	1.0
	Min, Max	1, 5	1, 5	1, 5
Number of prior systemic therapies				
1	n (%)	83 (53.5)	88 (56.1)	171 (54.8)
2	n (%)	39 (25.2)	38 (24.2)	77 (24.7)
3	n (%)	29 (18.7)	26 (16.6)	55 (17.6)
4	n (%)	4 (2.6)	5 (3.2)	9 (2.9)
Time since the start of the most recent systemic therapy (months)	n	155	157	312
	Mean ± SD	22.9 ± 24.66	23.1 ± 24.11	23.0 ± 24.35
	Median	13.3	14.7	13.9
	Min, Max	0, 132	1, 127	0, 132
Type of the most recent systemic therapies				
Curative	n (%)	131 (84.5)	141 (89.8)	272 (87.2)
Maintenance	n (%)	15 (9.7)	8 (5.1)	23 (7.4)
Palliative	n (%)	5 (3.2)	5 (3.2)	10 (3.2)
Other	n (%)	4 (2.6)	3 (1.9)	7 (2.2)
Best response to the most recent systemic therapy[1]				
CR/CRu	n (%)	83 (53.5)	90 (57.3)	173 (55.4)
PR	n (%)	49 (31.6)	45 (28.7)	94 (30.1)
SD	n (%)	10 (6.5)	11 (7.0)	21 (6.7)
PD	n (%)	11 (7.1)	9 (5.7)	20 (6.4)
Unknown	n (%)	2 (1.3)	2 (1.3)	4 (1.3)
Patients with prior radiation therapies	n (%)	33 (21.3)	34 (21.7)	67 (21.5)
Best response to the most recent radiation therapies[2]				
CR/CRu	n (%)	16 (48.5)	12 (35.3)	28 (41.8)
PR	n (%)	11 (33.3)	16 (47.1)	27 (40.3)
SD	n (%)	3 (9.1)	3 (8.8)	6 (9.0)
PD	n (%)	2 (6.1)	1 (2.9)	3 (4.5)
Unknown	n (%)	1 (3.0)	2 (5.9)	3 (4.5)
Patients with prior surgeries	n (%)	18 (11.6)	10 (6.4)	28 (9.0)

** Chemotherapies, steroids, immunotherapy, immunoconjugates, vaccines…*
[1] Denominator is the number of patients who received any systemic therapies for NHL.
[2] Denominator is the number of patients who received any radiotherapy for NHL.

Table 14 Prior NHL therapies - ITT population (Study PIX301)

	Pixantrone (N=70)	Comparator (N=70)
Chemotherapy Regimens		
Mean (SD)	2.9 (1.2)	3.1 (1.2)
Median (range)	3.0 (2.0-9.0)	3.0 (2.0 -9.0)
Number of Chemotherapy Regimens		
2	32 (45.7%)	24 (34.3%)
3-5	35 (50%)	42 (60%)
≥ 6	3 (4.3%)	4 (5.7%)
Category of Prior Chemotherapy		
Biologics (anti-CD20 mAB)	38 (54.3%)	39 (55.7%)
Anthracyclines/anthracenediones	70 (100.0%)	70 (100.0%)
Other Topoisomerase Inhibitors[1]	53 (75.7%)	55 (78.6%)
Platinum-based agents	36 (51.4%)	35 (50.0%)
Antimetabolites	42 (60.0%)	44 (62.9%)
Alkylating agents	70 (100.0%)	70 (100.0%)
SPs/MIs (spindle poison/mitotic inhibitors)	70 (100.0%)	69 (98.6%)
Corticosteroids	66 (94.3%)	65 (92.9%)
Other[2]	21 (30.0%)	30 (42.9%)
Disease Response Category		
Refractory	40 (57.1%)	40 (57.1%)
Relapsed	28 (40.0%)	30 (42.9%)
Missing	2 (2.9%)	0
Patients who had Radiotherapy, n (%)		
	34 (48.6%)	30 (42.9%)
Received SCT, n (%)		
	11 (15.7%)	10 (14.3%)
Anthracycline Dose Equivalent (mg/m^2)*		
Mean (SD)	284.8 (98.1)	321.9 (119.0)
Median (range)	292.9 (51-472)	315.5 (15-681)

[1] Other topoisomerase inhibitors were etoposide and teniposide.
[2] "Other" included targeted therapies, nonclassified anticancer therapies and supportive therapies.
Fisher exact test was used to compare proportions between groups and a two-sided student's t test was used to compare means between treatment groups. P values are for reference purposes only.
* P value ≤ 0.05.

Table 15 Summary of last NHL treatment and response - ITT population (Study PIX301)

Category of Last Chemotherapy	Pixantrone (N=70)	Comparator (N=70)
Biologics (anti-CD20 mAB)	18 (25.7%)	15 (21.4%)
Rituximab	18 (25.7%)	14 (20.0%)
Zevalin	4 (5.7%)	1 (1.4%)
Topoisomerase inhibitors		
Anthracyclines/anthracenediones*	8 (11.4%)	20 (28.6%)
Other Topoisomerase Inhibitors[1]	33 (47.1%)	31 (44.3%)
Platinum-based agents	21 (30.0%)	17 (24.3%)
Antimetabolites	31 (44.3%)	22 (31.4%)
Alkylating agents	38 (54.3%)	46 (65.7%)
SPs/MIs (spindle poison/mitotic inhibitors)	16 (22.9%)	24 (34.3%)
Corticosteroids	29 (41.4%)	31 (44.3%)
Other[2]	8 (11.4%)	12 (17.1%)
Time from Last Chemotherapy to Randomization (months)		
Mean (SD)	13.6 (15.7)	13.2 (23.5)
Median (range)	9.0 (1-86)	8.0 (1-190)
Response to Most Recent Chemotherapy		
CR /CRu	17 (24.3%)	18 (25.7%)
PR	19 (27.1%)	25 (35.7%)
SD	9 (12.9%)	6 (8.6%)
PD	22 (31.4%)	21 (30.0%)
Missing	3 (4.3%)	0

[1] Other topoisomerase inhibitors are etoposide and teniposide.
[2] Other includes targeted therapies, nonclassified anticancer therapies and supportive therapies.
Fisher exact test was used to compare proportions between groups and a two-sided student's t test was used to compare means between treatment groups. P values are for reference purposes only
* P value ≤ 0.05.

Table 16 Prior NHL therapies in patients with DLBCL (Study PIX301)

	Pixantrone (N=53)	Comparator (N=51)
Chemotherapy Regimens		
Mean (SD)	3.1 (1.37)	3.0 (1.27)
Median (range)	3.0 (2-9)	3.0 (2-8)
Number of Chemotherapy Regimens		
2	22 (41.5%)	21 (41.2%)
3-5	28 (52.8%)	27 (52.9%)
≥ 6	3 (5.7%)	3 (5.9%)
Category of Prior Chemotherapy		
Biologics (anti-CD20 mAB)	34 (62.4%)	30 (58.8%)
Anthracyclines/anthracenediones	53 (100.0%)	51 (100.0%)
Other Topoisomerase Inhibitors[1]	39 (73.6%)	41 (80.4%)
Platinum-based agents	26 (49.1%)	28 (54.9%)
Antimetabolites	32 (60.4%)	34 (66.7%)
Alkylating agents	53 (100.0%)	51 (100.0%)
SPs/MIs (spindle poison/mitotic inhibitors)	53 (100.0%)	50 (98.0%)
Corticosteroids	50 (94.3%)	47 (92.2%)
Other[2]	17 (32.1%)	20 (39.2%)
Disease Response Category		
Refractory	34 (64.2%)	28 (54.9%)
Relapsed	17 (32.1%)	23 (45.1%)
Missing	2 (3.8%)	0
Patients who had Radiotherapy, n (%)	27 (50.9%)	23 (45.1%)
Received Stem Cell Transplant n (%)	11 (20.8%)	7 (13.7%)
Anthracycline Dose Equivalent (mg/m^2)*		
Mean (SD)	276.9 (105.4)	327.5 (108.12)
Median (range)	291.0 (51-472)	318.2 (75-681)

[1]Other topoisomerase inhibitors are etoposide and teniposide.
[2] Other includes targeted therapies, nonclassified anticancer therapies and supportive therapies.
Fisher exact test was used to compare proportions between groups and a two-sided student's t test was used to compare means between treatment groups. P values are for reference purposes only.
* P value ≤ 0.05.

comment

The main difference between studies PIX301 and PIX306 was the number of previous chemotherapy regimens. Most of patients have had only 1 previous therapy is study PIX306 (54.8%) while all patients had had at least two and 55% of patients' 3-5 prior regimens in study PIX301.

The listing of previous therapies and especially the use of previous cardiotoxic treatments was comprehensively presented (in Tables 5.12-5.14) from study PIX 301. Importantly, similar detailed presentation of prior NHL therapies in patients with DLBCL from study PIX306 and especially category of prior chemotherapies was missing. The MAH has updated the information with the data regarding the missing information of the previous potentially cardiotoxic treatments (anthracyclines) and other DLBCL therapies. Almost all patients have received previous treatment with anthracyclines; 148 (95.5%) in the pixantrone + R-arm and 143 (91.1%) in the gemcitabine+R-arm. In addition, regarding all other previous treatments, the use of different prior DLBCL therapies are equally balanced between the two treatment arms.

Most patients presented with a cardiac history at baseline: 63.9% in the pixantrone + rituximab group and 66.2% in the gemcitabine + rituximab group. There was on-going baseline history of coronary artery disease (CAD) in 10.3% of patients in the pixantrone + rituximab group and 17.2% in the gemcitabine + rituximab group; all cases were currently stable. A history of myocardial infarction was reported by 2.6% of the pixantrone + rituximab group compared to 5.1% of the gemcitabine + rituximab; all were resolved. CHF was reported in 5.2% versus 5.7%, respectively. Among them, 2 (both in the pixantrone group) were resolved at baseline and 15 were on-going and currently stable (6 in the pixantrone + rituximab group and 9 in the gemcitabine + rituximab group).

Table 17 Summary of Cardiac Histories - ITT population (Study PIX306)

System Organ Class Preferred Term		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)	All (N = 312)
Patients with any cardiac history events	**n (%)**	**99 (63.9)**	**104 (66.2)**	**203 (65.1)**
Hypertension				
Resolved	n (%)	6 (3.9)	4 (2.5)	10 (3.2)
Ongoing & currently stable	n (%)	89 (57.4)	90 (57.3)	179 (57.4)
Coronary artery disease				
Resolved	n (%)	2 (1.3)	6 (3.8)	8 (2.6)
Ongoing & currently stable	n (%)	16 (10.3)	27 (17.2)	43 (13.8)
Myocardial infarction				
Resolved	n (%)	4 (2.6)	8 (5.1)	12 (3.8)
Congestive heart failure				
Resolved	n (%)	2 (1.3)	-	2 (0.6)
Ongoing & currently stable	n (%)	6 (3.9)	9 (5.7)	15 (4.8)
Valvular heart disease				
Resolved	n (%)	1 (0.6)	1 (0.6)	2 (0.6)
Ongoing & currently stable	n (%)	10 (6.5)	8 (5.1)	18 (5.8)
Cardiomyopathy				
Resolved	n (%)	-	2 (1.3)	2 (0.6)
Ongoing & currently stable	n (%)	3 (1.9)	2 (1.3)	5 (1.6)

comment

The provided history of cardiac co-morbidity is comparable between the two treatment groups.

Numbers analysed

The ITT population consisted of all 312 patients randomized, refer to Table 5.16. A total of 44 patients were excluded from the HITT after the histological diagnosis by the Central Pathology Review Committee (27 patients in the pixantrone + rituximab group and 17 patients in the gemcitabine + rituximab group). Thus, in these patients, de novo DLBCL, DLBCL transformed from indolent lymphoma, or FL grade 3 could not be confirmed.

A total of 28 patients were excluded from the PP for major protocol violations (10 patients in the pixantrone + rituximab group and 18 patients in the gemcitabine + rituximab group).

The Safety Population consisted of 302 patients (153 patients in the pixantrone + rituximab group and 149 patients in the gemcitabine + rituximab group) who were randomized and received at least one dose of the study drug. Ten patients were excluded (2 in the pixantrone + rituximab group and 8 in the gemcitabine + rituximab group) for not having taken any study drug.

Table 18 Analysis sets (Study PIX306)

Analysis sets		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)	All (N = 312)
ITT Population	**n**	**155**	**157**	**312**
Histologically Confirmed Population (HITT)	**n (%)**	128 (82.6)	140 (89.2)	268 (85.9)
Per Protocol Population (PP)	**n (%)**	145 (93.5)	139 (88.5)	284 (91.0)
Safety Population	**n (%)**	**153 (98.7)**	**149 (94.9)**	**302 (96.8)**
Pharmacokinetic population	**n (%)**	14 (9.0)	-	14 (4.5)
Subgroups of the ITT				
Stratification factors:				
IPI score = 0-2		73	73	146
IPI score = 3 or more		82	84	166
Number of prior lines = 0-2		137	139	276
Number of prior lines = 3 or more		18	18	36
Time (initiation to 1st relapse) < 1 year		58	58	116
Time (initiation to 1st relapse) 1 year or more		97	99	196
Other prespecified subgroups:				
Number of prior lines = 0-1		102	106	208
Number of prior lines = 2 or more		53	51	104
Gender = Male		69	67	136
Gender = Female		86	90	176
Age < 65 years		36	30	66
Age ≥ 65 years		119	127	246
Region = North America		51	53	104
Region = Europe		104	104	208
Ann Arbor Stage = I-III		81	76	157
Ann Arbor Stage = IV		74	81	155
ECOG performance status = 0-1		122	124	246
ECOG performance status ≥ 2		33	32	65
Number of extranodal sites = 0		57	60	117
Number of extranodal sites ≥ 1		98	97	195

%: % of randomized patients

comment

Surprisingly high number of patients were excluded from the HITT population. This highlights the importance of reliable pathological diagnosis of an aggressive disease like DLBCL. There is a slight imbalance between the treatment groups regarding this HITT population; 128 patients in the pixantrone + rituximab group vs. 140 patients in the gemcitabine + rituximab group.

28 patients (almost 10% of the total patient population) were excluded from the PP population for major protocol violations. The MAH has provided in detail information of the patient population excluded from the PP population. The most important reasons for these exclusions were related to baseline tumor assessment/ tumor response assessment after randomization. All patients were adequately excluded from the PP population following the exclusion rules of the SAP.

Outcomes and estimation

Primary efficacy criterion

Progression free survival

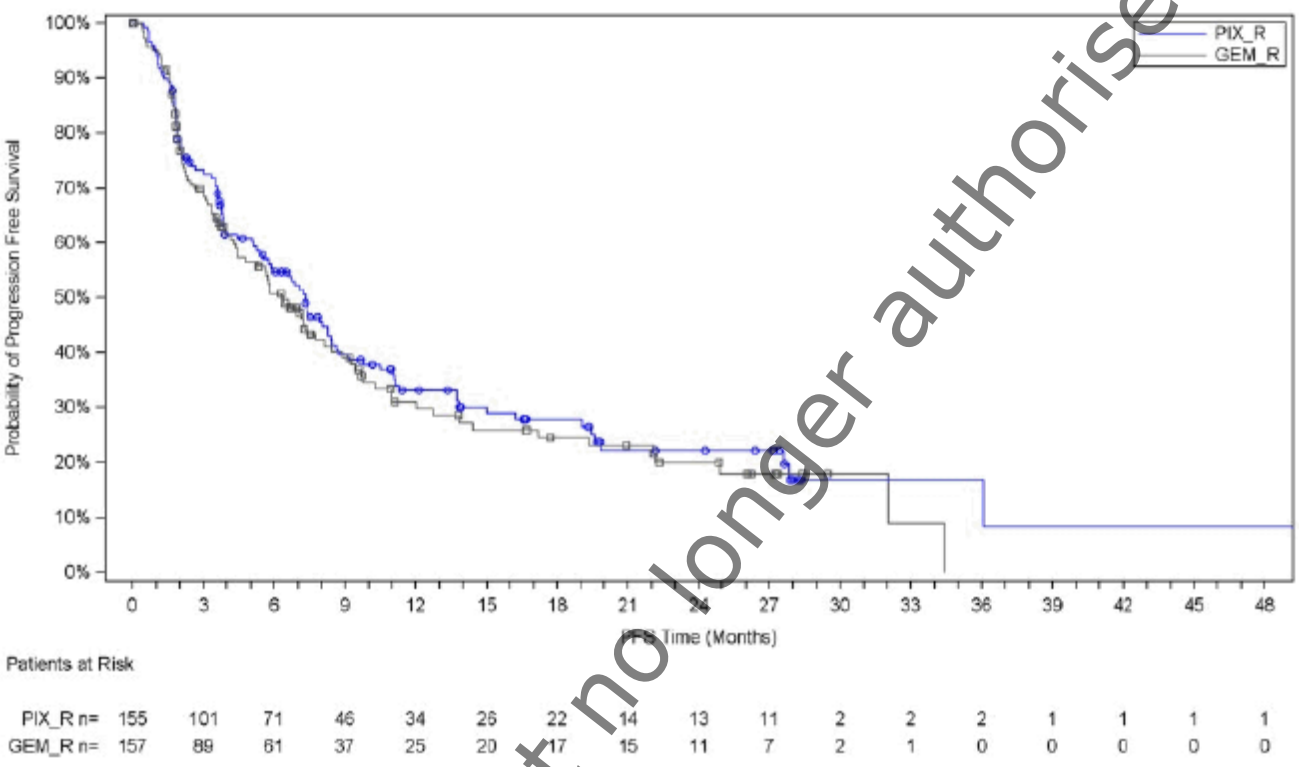
PFS per IRC assessment is presented in Table 5.17 and Figure 5.2 in the ITT Population. The median PFS was 7.3 months in the pixantrone + rituximab group versus 6.3 months in the gemcitabine + rituximab group. Compared with the gemcitabine + rituximab group, the adjusted HR (95% CI) of PFS in the pixantrone + rituximab group was 0.85 (95% CI [0.64, 1.14]). No statistically significant difference between the two treatment groups was demonstrated in terms of PFS (p = 0.2782 on log-rank test). All sensitivity analyses were consistent with the primary analysis – there was no significant statistical difference between the two groups.

Table 19 PFS per IRC assessment in the ITT population (Study PIX306)

Number (%) of patients with PFS events	**102 (65.8)**	**95 (60.5)**
Disease Progression	73 (47.1)	68 (43.3)
Death	29 (18.7)	27 (17.2)
Number (%) of patients censored	**53 (34.2)**	**62 (39.5)**
Study ongoing without PFS event	27 (17.4)	22 (14.0)
Study withdrawal (including lost to follow-up) without PFS event	2 (1.3)	-
Received another anti-tumor treatment	17 (11.0)	23 (14.6)
Do not have baseline tumor or post-baseline tumor response assessment	7 (4.5)	17 (10.8)
Median PFS (95% CI) (Month)[1]	**7.3 (5.2, 8.4)**	**6.3 (4.4, 8.1)**
PFS Rate (%) (95% CI) /Number of patients at risk[1]		
At 2 months	79 (71, 85) /113	77 (69, 83) /102
At 4 months	62 (53, 69) / 82	61 (53, 69) / 76
At 6 months	55 (46, 63) / 71	51 (42, 59) / 61
At 9 months	40 (31, 48) / 46	39 (30, 48) / 37
At 12 months	33 (25, 42) / 34	31 (23, 40) / 25
At 18 months	28 (20, 36) / 22	25 (17, 34) / 17
At 24 months	22 (15, 31) / 13	20 (12, 29) / 11
At 36 months	17 (9, 27) / 2	-
At 48 months	8 (1, 26) / 1	-
Stratified Log-rank Test p-value[2]	**0.2782**	
Adjusted Hazard Ratio (95% CI)[3]	**0.85 (0.64, 1.14)**	

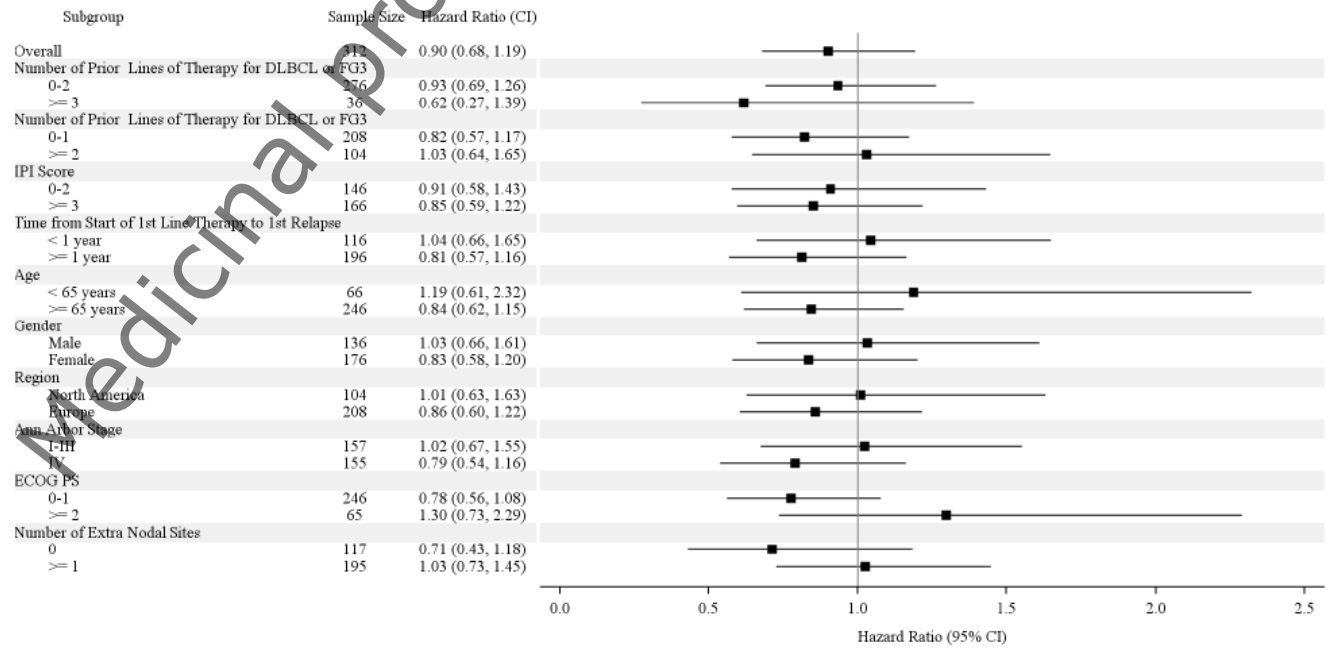
[1] Median PFS and PFS rate were estimated using Kaplan-Meier method;
[2] P-value is from stratified log-rank test, adjusted for randomization stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse);
[3] HR and 95% CIs were calculated using the Cox proportional hazards model, adjusted for randomization stratification factors.

Figure 2 Kaplan-Meier curve of the PFS per IRC assessment in the ITT population (Study PIX306)



Due to the limited sample sizes, subgroup analyses results should be interpreted cautiously.

Figure 3 Subgroup analysis of PFS per IRC assessment in the ITT population (Study PIX306)



Note: a Hazard Ratio < 1 favors the Pixantrone + R arm

Analysis in patients with ≥ 2 prior lines of therapy for DLBCL or FL Grade 3

Main demographic characteristics of this subgroup were consistent with the overall study population. Their median age was 69.0 years, 51.0% were female, 82.7% of patients had DLBCL, with an initial diagnosis was made at median of 2.6 years (*i.e.*, 22.8 months).

PFS per IRC assessment is presented in Table 5.18 in the subgroup of patients with ≥ 2 prior lines of therapy.

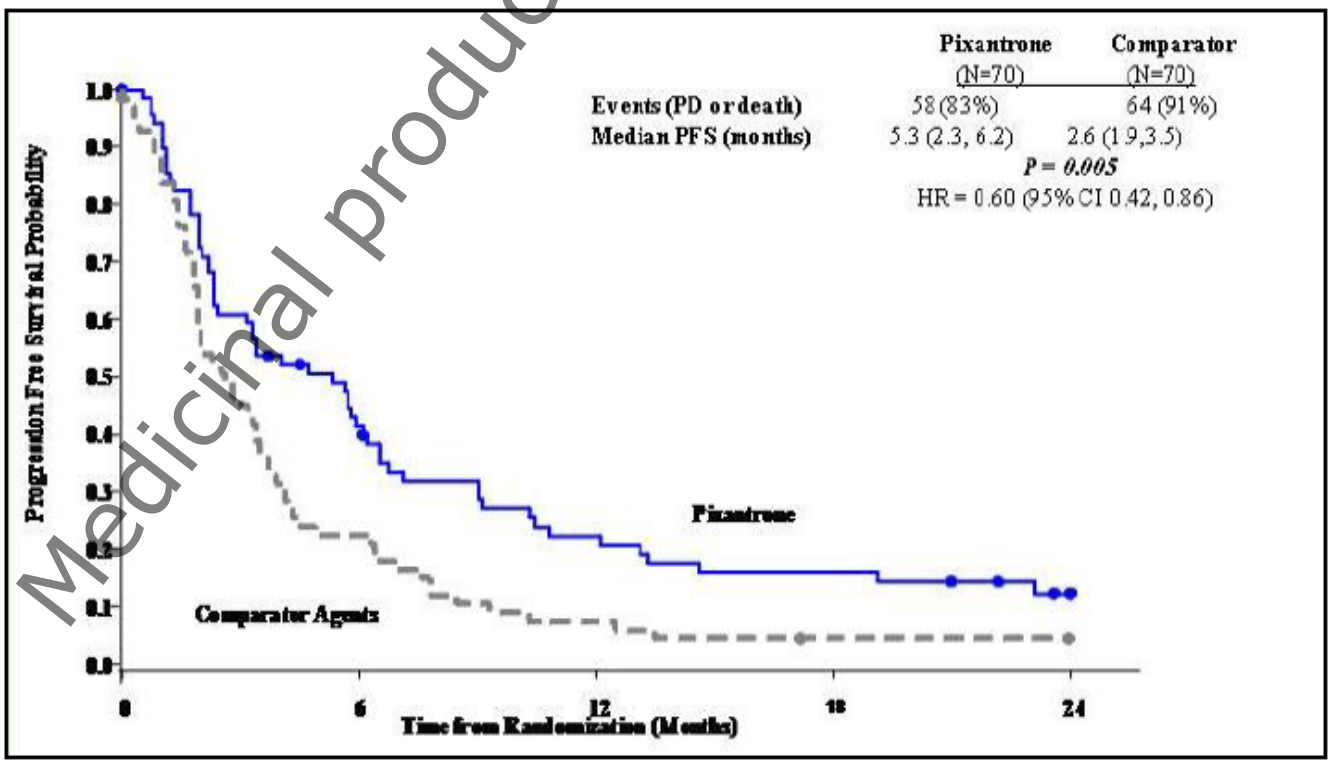
The median of PFS in patients with ≥ 2 prior lines of therapy was 3.9 months [2.5, 7.4] in the pixantrone + rituximab group versus 4.4 months [3.2, 7.8] in the gemcitabine + rituximab group, HR = 1.03 [0.64, 1.65].

Table 20 PFS per IRC assessment in patients with ≥ 2 prior lines of therapy ITT population (Study PIX306)

	Pixantrone + R (N = 53)	Gemcitabine + R (N = 51)
Median PFS (95% CI) (Month)	3.9 (2.5, 7.4)	4.4 (3.2, 7.8)
Hazard Ratio (95% CI)	1.03 (0.64, 1.65)	

For comparison, the PFS-findings from study PIX301 are presented in Figure 5.4. Pixantrone treatment was associated with a significant increase in PFS to 5.3 months for the pixantrone group compared with 2.6 months for the comparator group.

Figure 4: PFS by Kaplan-Meier estimation (Study PIX301)



comment

The primary endpoint IRC-assessed PFS was not fulfilled; median PFS was 7.3 months in the pixantrone + rituximab group versus 6.3 months in the gemcitabine + rituximab group, p=0.2782 and HR 0.85 (0.64, 1.14).

Thus the superiority claim of pixantrone + rituximab was not met and with this regard this study failed to show PFS benefit over the comparator arm.

In addition, all sensitivity analyses were in line with the primary analysis with no significant statistical differences between the two treatment groups. The results from the subgroup analysis of PFS per IRC assessment produced mixed results with hazard ratios favouring the pixantrone + R arm on the other hand and the comparator arm on the other. However, there were no clear differences in any subgroup analysis.

The median of PFS in patients with ≥2 prior lines of therapy (like in the population in the pivotal study PIX301) was 3.9 months in the pixantrone + rituximab group versus 4.4 months in the gemcitabine + rituximab group.

In comparison, in study PIX301 the median PFS in the pixantrone alone group was 5.0 months.

Secondary efficacy criteria

Overall survival

The following analysis of OS is the first interim analysis planned by the protocol, which was carried out at the time of the core database lock. At the time of the first interim analysis, 177 deaths had occurred: 94 (60.6%) in the pixantrone + rituximab group and 83 (52.9%) in the gemcitabine + rituximab group.

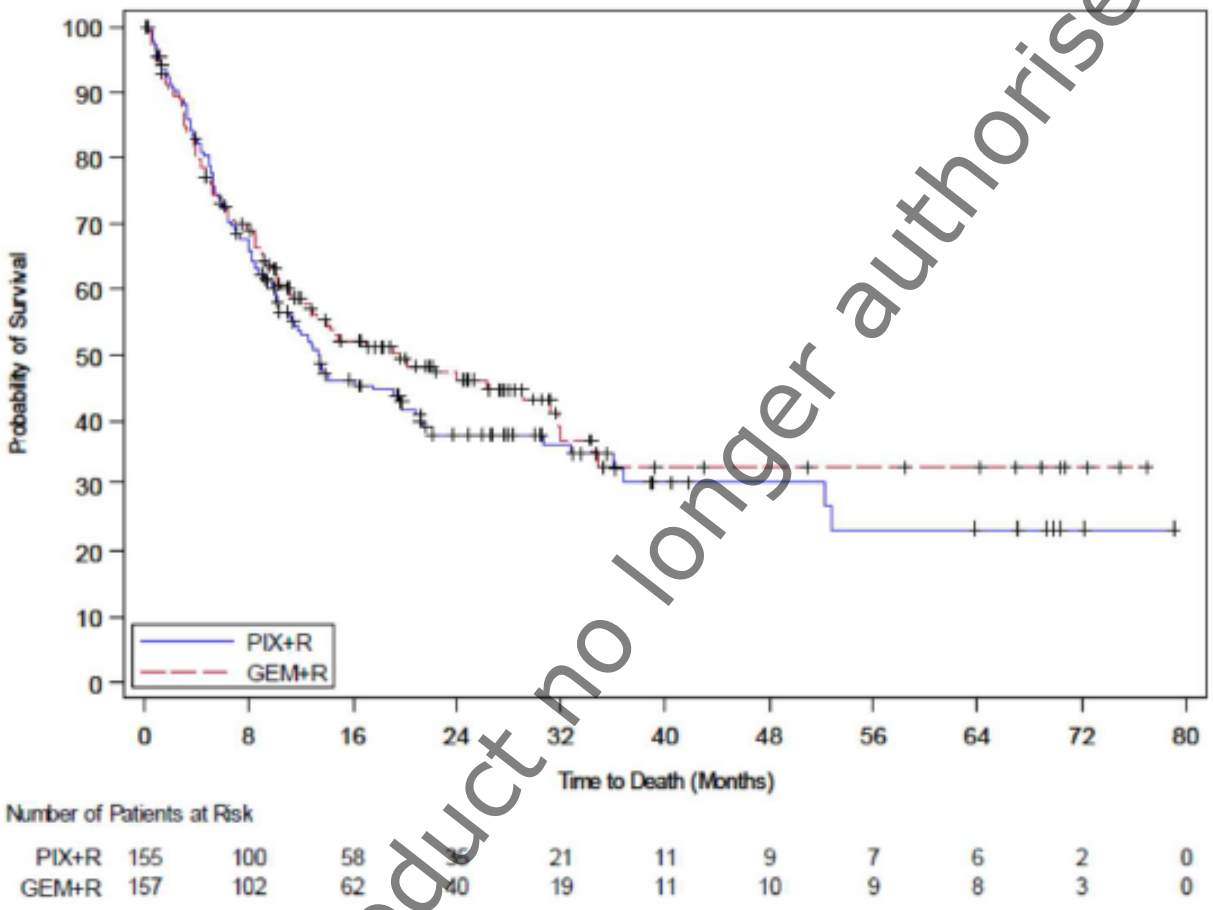
The median (95% CI) OS was 13.3 (10.1, 19.8) months in the pixantrone + rituximab group versus 19.6 (12.4, 31.9) months in the gemcitabine + rituximab group. The adjusted HR (95% CI) of OS in the pixantrone + rituximab group compared to the gemcitabine + rituximab group was 1.13 (0.83, 1.53).

Table 21 Overall survival in the ITT population (Study PIX306)

	Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)
Number (%) of patients who died	**94 (60.6)**	**83 (52.9)**
Number (%) of patients censored	**61 (39.4)**	**74 (47.1)**
Alive	52 (33.5)	64 (40.8)
Discontinued Study (including lost to follow-up)	9 (5.8)	10 (6.4)
Median OS (95% CI) (Month)[1]	**13.3 (10.1, 19.8)**	**19.6 (12.4, 31.9)**
OS Rate (95% CI)/Number of patients at risk[1]		
At 2 months	92 (87, 95) / 140	90 (84, 94) / 138
At 4 months	83 (76, 88) / 125	80 (73, 86) / 123
At 6 months	72 (64, 79) / 109	73 (65, 80) / 110
At 9 months	62 (54, 70) / 92	66 (58, 73) / 96
At 12 months	54 (45, 61) / 72	59 (50, 66) / 74
At 18 months	45 (36, 53) / 52	51 (43, 59) / 57
At 24 months	38 (30, 46) / 35	46 (37, 54) / 40
At 36 months	34 (26, 43) / 16	32 (22, 43) / 13
At 48 months	30 (21, 40) / 9	32 (22, 43) / 10
Stratified Log-rank Test p-value[2]	0.4326	
Adjusted Hazard Ratio (95% CI)[3]	1.13 (0.83, 1.53)	

[1] Median OS and OS rate were estimated using Kaplan-Meier method.
[2] Exploratory p-value from stratified log-rank test, adjusted for randomization stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse).
[3] Hazard ratio and 95% CIs were calculated using the Cox proportional hazards model, adjusted for randomization stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse).

Figure 5 Kaplan-Meier curve of the OS in the ITT population (Study PIX306)



Due to the limited sample sizes and exploratory nature, subgroup analyses should be interpreted cautiously.

Table 22 Subgroup analysis of OS in the ITT-population (Study PIX306)

	Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)
Number of Prior Lines of Therapy for DLBCL or FG3		
0-2		
Number of patients	136	138
Median OS (95% CI) (in Months)	13.5 (10.3, 21.4)	22.1 (12.7, 34.4)
Hazard Ratio (95% CI)	1.19 (0.86,1.64)	
≥ 3		
Number of patients	19	19
Median OS (95% CI) (in Months)	10.1 (2.6, 36.7)	8.6 (4.4, 29.1)
Hazard Ratio (95% CI)	0.87 (0.40,1.90)	
Number of Prior Lines of Therapy for DLBCL or FG3		
0-1		
Number of patients	102	104
Median OS (95% CI) (in Months)	13.8 (11.1, 32.7)	31.3 (12.9, NA)
Hazard Ratio (95% CI)	1.28 (0.87, 1.88)	
≥ 2		
Number of patients	53	53
Median OS (95% CI) (in Months)	10.1 (6.0, 19.1)	10.5 (6.5, 26.4)
Hazard Ratio (95% CI)	0.98 (0.61, 1.56)	
IPI Score		
0-2		
Number of patients	73	73
Median OS (95% CI) (in Months)	36.7 (17.6, NA)	34.8 (29.1, NA)
Hazard Ratio (95% CI)	1.37 (0.82, 2.29)	
≥ 3		
Number of patients	82	84
Median OS (95% CI) (in Months)	8.0 (5.4, 10.1)	6.8 (4.4, 10.5)
Hazard Ratio (95% CI)	1.01 (0.71, 1.46)	
Time from Start of 1st Line Therapy To 1st Relapse		
< 1 year		
Number of patients	58	58
Median OS (95% CI) (in Months)	8.6 (5.8, 13.3)	9.7 (4.8, 14.8)
Hazard Ratio (95% CI)	1.10 (0.71, 1.69)	
≥ 1 year		
Number of patients	97	99
Median OS (95% CI) (in Months)	21.2 (12.6, 36.7)	31.3 (17.0, NA)
Hazard Ratio (95% CI)	1.18 (0.79, 1.77)	
Age		
< 65 years		
Number of patients	36	30
Median OS (95% CI) (in Months)	32.7 (11.6, NA)	24.0 (12.9, NA)
Hazard Ratio (95% CI)	0.90 (0.44, 1.85)	
≥ 65 years		
Number of patients	119	127
Median OS (95% CI) (in Months)	11.7 (8.7, 16.1)	14.8 (10.1, 32.0)
Hazard Ratio (95% CI)	1.22 (0.88, 1.69)	

HR and 95% CIs were calculated using the Cox proportional hazards model

Subgroup analysis of OS in the ITT-population (Study PIX306) continued

	Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)
Gender		
Male		
Number of patients	69	67
Median OS (95% CI) (in Months)	11.7 (6.6, 21.2)	29.1 (10.2, NA)
Hazard Ratio (95% CI)	1.39 (0.88, 2.19)	
Female		
Number of patients	86	90
Median OS (95% CI) (in Months)	13.7 (1.1, 36.0)	19.1 (10.1, 31.3)
Hazard Ratio (95% CI)	1.00 (0.68, 1.48)	
Region		
North America		
Number of patients	51	53
Median OS (95% CI) (in Months)	10.7 (6.0, 21.4)	14.8 (6.5, NA)
Hazard Ratio (95% CI)	1.24 (0.76, 2.01)	
Europe		
Number of patients	104	104
Median OS (95% CI) (in Months)	14.2 (10.3, 22.0)	20.1 (12.7, 34.4)
Hazard Ratio (95% CI)	1.11 (0.76, 1.61)	
Ann Arbor Stage		
I-III		
Number of patients	81	76
Median OS (95% CI) (in Months)	19.1 (11.3, 52.3)	34.4 (22.1, NA)
Hazard Ratio (95% CI)	1.54 (0.98, 2.42)	
IV		
Number of patients	74	81
Median OS (95% CI) (in Months)	10.3 (6.4, 13.8)	10.2 (5.6, 14.3)
Hazard Ratio (95% CI)	0.92 (0.62, 1.37)	
ECOG PS		
0-1		
Number of patients	122	124
Median OS (95% CI) (in Months)	20.9 (13.5, 36.7)	22.1 (12.9, 34.8)
Hazard Ratio (95% CI)	0.99 (0.70, 1.40)	
≥ 2		
Number of patients	33	32
Median OS (95% CI) (in Months)	6.5 (4.9, 8.3)	10.5 (5.3, 24.0)
Hazard Ratio (95% CI)	2.40 (1.31, 4.41)	
Number of Extra Nodal Sites		
0		
Number of patients	57	60
Median OS (95% CI) (in Months)	19.7 (12.1, 30.7)	34.4 (17.0, NA)
Hazard Ratio (95% CI)	1.49 (0.88, 2.53)	
≥ 1		
Number of patients	98	97
Median OS (95% CI) (in Months)	11.3 (7.9, 13.8)	11.1 (6.8, 19.6)
Hazard Ratio (95% CI)	1.01 (0.71, 1.45)	

HR and 95% CIs were calculated using the Cox proportional hazards model

Analysis in patients with ≥ 2 prior lines of therapy for DLBCL or FL Grade 3

The median of OS in patients with ≥ 2 prior lines of therapy was also similar between the two treatment groups (10.1 months [6.0, 19.1] in the pixantrone + rituximab group versus 10.5 months [6.5, 26.4] in the gemcitabine + rituximab group, HR = 0.98 [0.61, 1.56]).

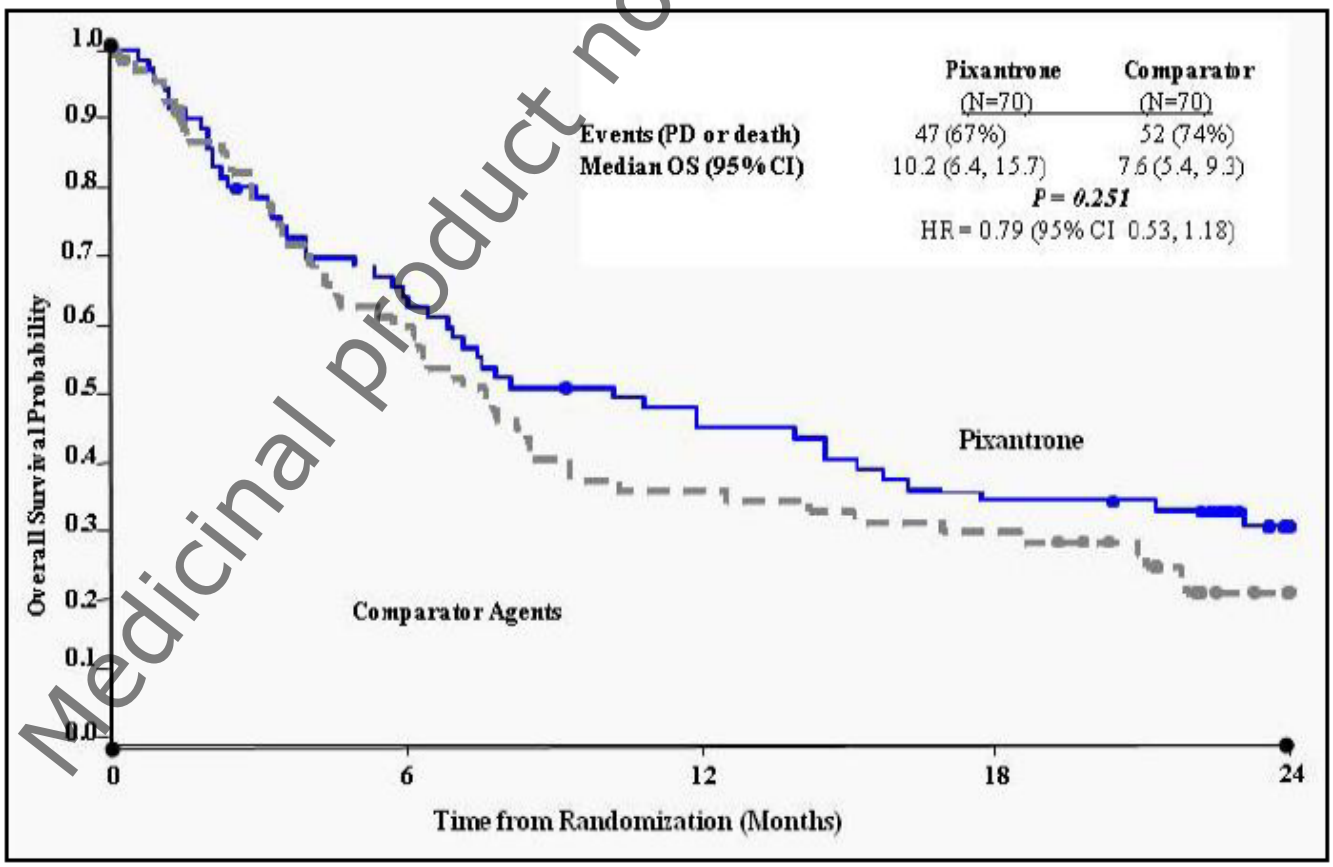
Table 23 OS in patients with ≥ 2 prior lines of therapy ITT population (Study PIX306)

	Pixantrone + R (N = 53)	Gemcitabine + R (N = 51)
Number of patients	53	53*
Median OS (95% CI) (in Months)	10.1 (6.0, 19.1)	10.5 (6.5, 26.4)
Hazard Ratio (95% CI)	0.98 (0.61, 1.56)	

**The discrepancy between the number of patients analyzed and the number of patients by subgroup is due to a different cut-off used by IDMC for OS analyses.*

For comparison, the OS-findings from study PIX301 are presented in Figure 5.6. The median survival advantage for patients randomized to pixantrone was 2.6 months (10.2 months vs. 7.6 months). Patients alive after 24 months were censored at 24 months.

Figure 6 OS by Kaplan-Meier estimation (Study PIX301)



comment

Result from the first interim analysis showed a median OS of 13.3 months in the pixantrone + rituximab group versus 19.6 months in the gemcitabine + rituximab group. This difference was not statistically significant with HR of 1.13 (95% CI: 0.655-1.260), unstratified log-rank test p= 0.4326). The results from the subgroup analysis of OS were consistent across most of the subgroups and with the results of the overall population analysis.

Basically, when PFS is chosen as the primary endpoint, a clear positive trend in OS is considered essential.

However, currently this is not the case. In this study both the primary efficacy endpoint PFS and key secondary endpoint OS, both failed to show superiority of the pixantrone + rituximab over gemcitabine + rituximab. In this respect, this is a failed study.

The median of OS in patients with ⩾ 2 prior lines of therapy (like in the population in the pivotal study PIX301) was 10.1 months in the pixantrone + rituximab group versus 10.5 months in the gemcitabine + rituximab group. This OS result, while taking into account of the indirect nature of the comparison, is in line with the median OS in the pixantrone alone group of 10.2 months in the study PIX301.

According to the MAH, following the analysis of the primary endpoint of this study, it was decided by the sponsor not to continue the study until the target 220 events for the OS analysis, but terminate it within 6 months of the data cut-off date (the actual date was 14 September 2018). The final OS analysis was done using the final cut-off date of September, 14 2018. Six (6) additional OS events (3 in each arm) are included in this final OS analysis; 183 deaths had occurred.

The OS trending in the wrong direction (HR 1.13) was initially a matter of concern. However, while the OS HR point estimate was on the wrong side of unity (HR 1.13), the confidence intervals are very wide. While information on post progression therapies is not available, there were no new safety concerns identified which would support a true detrimental effect on OS.

The ORR and CR rate were both significantly higher in the pixantrone + rituximab group compared to the gemcitabine + rituximab group (61.9% vs. 43.9%, p=0.0007, and 35.5% vs. 21.7%, p=0.0047). However, these differences in ORR and CR rate did not lead to improvement of PFS or OS over gemcitabine + rituximab group. The MAH has not been able to clarify the possible reasons behind the discrepancy and the clinical significance of the finding, that no correlation between ORR, CR, and OS were found.

Overall response rate

ORR per IRC assessment in the ITT population is presented in Table 5.22. A complete or partial response was reported by 61.9% [53.8, 69.6] in the pixantrone + rituximab group versus 43.9% [36.0, 52.1] in the gemcitabine + rituximab group. The estimate of the difference between the two groups was 18.0% [6.9, 28.6]. Similar results were observed in the sensitivity analyses.

Table 24 ORR (CR/PR) per IRC assessment - ITT-population (Study PIX306)

		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)
Best Overall Response			
Complete Response (CR)	n (%)	55 (35.5)	34 (21.7)
Partial Response (PR)	n (%)	41 (26.5)	35 (22.3)
Stable Disease (SD)	n (%)	12 (7.7)	29 (18.5)
Progressive Disease (PD)	n (%)	30 (19.4)	28 (17.8)
Not Evaluable	n (%)	17 (11.0)	31 (19.7)
ORR[1]	n (%)	96 (61.9)	69 (43.9)
	95% CI[2]	(53.8, 69.6)	(36.0, 52.1)
Difference in % ORR	(95% CI)[3]	18.0 (6.9, 28.6)	
	p-value[4]	0.0007	

[1] ORR = CR or PR as best overall response.
[2] 95% CI was based on the Clopper-Pearson method.
[3] 95% CI was based on the Agresti-Caffo method.
[4] Exploratory p-value from the exact Cochran-Mantel-Haenszel test for the treatment difference, adjusted for stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse)

Analysis in patients with ≥ 2 prior lines of therapy for DLBCL or FL Grade 3

The analysis of ORR in patients with ≥ 2 prior lines of therapy, per IRC assessment, showed a positive trend for pixantrone + rituximab in the subgroup of patients with ≥ 2 prior lines of therapy.

Table 25 ORR (CR/PR) per IRC in patients with ≥ 2 prior lines of therapy ITT population (Study PIX306)

		Pixantrone + R (N = 53)	Gemcitabine + R (N = 51)
ORR[1]	n/N (%)	25/53 (47.2)	15/51 (29.4)
	95% CI[2]	(33.3, 61.4)	(17.5, 43.8)
Difference in % ORR	(95% CI)[3]	17.8 (-1.0, 35.2)	

[1] ORR = CR or PR as best overall response.
[2] 95% CI for ORR based on the Clopper-Pearson method.
[3] 95% CI for treatment difference in ORR based on the Agresti-Caffo method.

The ORR was significantly higher in the pixantrone group at the EOT time-point, and this finding became more robust by EOS. During the follow-up period, two additional patients achieved a complete response, both of whom had been treated with pixantrone.

Table 26: ORR (CR/Cru/PR) by IAP review (Study PIX301)

	Pixantrone (N=70)	Comparator (N=70)
END OF TREATMENT		
CR/CRu/PR, n (%)	26 (37.1%)	10 (14.3%)
95% CI	(25.9%, 49.5%)	(7.1%, 24.7%)
	P = 0.003	
END OF STUDY		
CR/CRu/PR, n (%)	28 (40.0%)	10 (14.3%)
95% CI	(28.5%, 52.4%)	(7.1%, 24.7%)
	P = 0.001	

Complete response rate

CR per IRC assessment was higher in the pixantrone + rituximab group (35.5%) than in the gemcitabine + rituximab group (21.7%). The difference between the two groups was 13.8% with 95% CI [3.8, 23.5]. Similar results were observed in the sensitivity analyses.

Table 27 CR per IRC assessment in the ITT-population (Study PIX306)

		Pixantrone + R (N = 155)	Gemcitabine + R (N = 157)
Complete Response (CR)[1]	n (%)	**55 (35.5)**	**34 (21.7)**
	95% CI[2]	(28.0, 43.6)	(15.5, 28.9)
Difference in % CR	(95% CI)[3]	13.8 (3.8, 23.5)	
	p-value[4]	0.0047	

[1] CR was the percentage of patients who had CR as best overall response.
[2] 95% CI was based on the Clopper-Pearson method.
[3] 95% CI was based on the Agresti-Caffo method.
[4] Exploratory p-value from the exact Cochran-Mantel-Haenszel test for the treatment difference adjusted for stratification factors (number of prior therapies/IPI/time from start of 1st line therapy to 1st relapse)

Analysis in patients with ≥ 2 prior lines of therapy for DLBCL or FL Grade 3

The analysis of CR per IRC showed a positive trend for pixantrone + rituximab in the subgroup of patients with ≥ 2 lines of prior therapy.

Table 28: CR (CR/PR) per IRC in patients with ≥ 2 prior lines of therapy ITT population (Study PIX306)

		Pixantrone + R (N = 53)	Gemcitabine + R (N = 51)
Number of prior line ≥ 2			
CR	n/N (%)	12/53 (22.6)	4/51 (7.8)
	95% CI[1]	(12.3, 36.2)	(2.2, 18.9)
Difference in % CR	(95% CI)[2]	14.8 (0.5, 27.9)	

[1] 95% CI for CR, based on the Clopper-Pearson method.
[2] 95% CI for treatment difference in CR, based on the Agresti-Caffo method.

For comparison, the CR/Complete Response unconfirmed (Cru)-findings from study PIX301 are presented in Table 5.27. Of the 17 pixantrone patients who achieved a CR/CRu, 6 had stable or progressive disease as a response to their last regimen, 8 had a PR, and 3 had a CR/Cru.

Table 29: CR/Cru rate by IAP-review (Study PIX301)

	Pixantrone (N=70)	Comparator (N=70)
END OF TREATMENT		
CR/CRu, n (%)	14 (20.0%)	4 (5.7%)
95% CI	(11.4%, 31.3%)	(1.6%, 14.0%)
	P = 0.021	
END OF STUDY		
CR/CRu, n (%)	17 (24.3%)	5 (7.1%)
95% CI	(14.8%, 36.0%)	(2.4%, 15.9%)
	P = 0.009	

comment

The ORR and CR rate were both significantly higher in the pixantrone + rituximab group compared to the gemcitabine + rituximab group (61.9% vs. 43.9%, p=0.0007, and 35.5% vs. 21.7%, p=0.0047). However, these differences in ORR and CR rate did not lead to improvement of PFS or OS over gemcitabine + rituximab group.

In the pivotal study PIX301, the CR/CFu-rate was the primary efficacy endpoint, with CR/CFu-rate of 20%. In the subgroup of patients with ≥2 lines of prior therapy (study PIX306), the CR-rate was 22.6% in the pixantrone + rituximab group compared to 7.8% in the gemcitabine + rituximab group.

Reaching a CR is an important step before possibly curative treatment like intensive chemotherapy + ASCT. In patients with basically a palliative approach like treatment with pixantrone with no curative intention, reaching a CR does not seem have a long term benefit.

Exploratory endpoints

Duration of overall response

The median DOR (on KM analysis) was 10.0 months (95% CI [6.6, 17.3]) in the pixantrone + rituximab group versus 9.1 months (95% CI [6.5, 18.5]) in the gemcitabine + rituximab group. The estimated HR for DOR in the pixantrone + rituximab group was 0.96 (95% CI [0.63, 1.47]).

Duration of complete response

The median DCR (on KM analysis) was 13.0 months (95% CI [7.1, 30.7]) in the pixantrone + rituximab group versus 15.4 months (95% CI [7.5, not evaluable]) in the gemcitabine + rituximab group. The estimated HR for DCR in the pixantrone + rituximab group was 1.02 (95% CI [0.56, 1.88]).

Patients receiving SCT after start of study treatment

Four patients in the pixantrone + rituximab group (2.6%) and 2 patients in the gemcitabine + rituximab group (1.3%) required a SCT after start of study treatment.

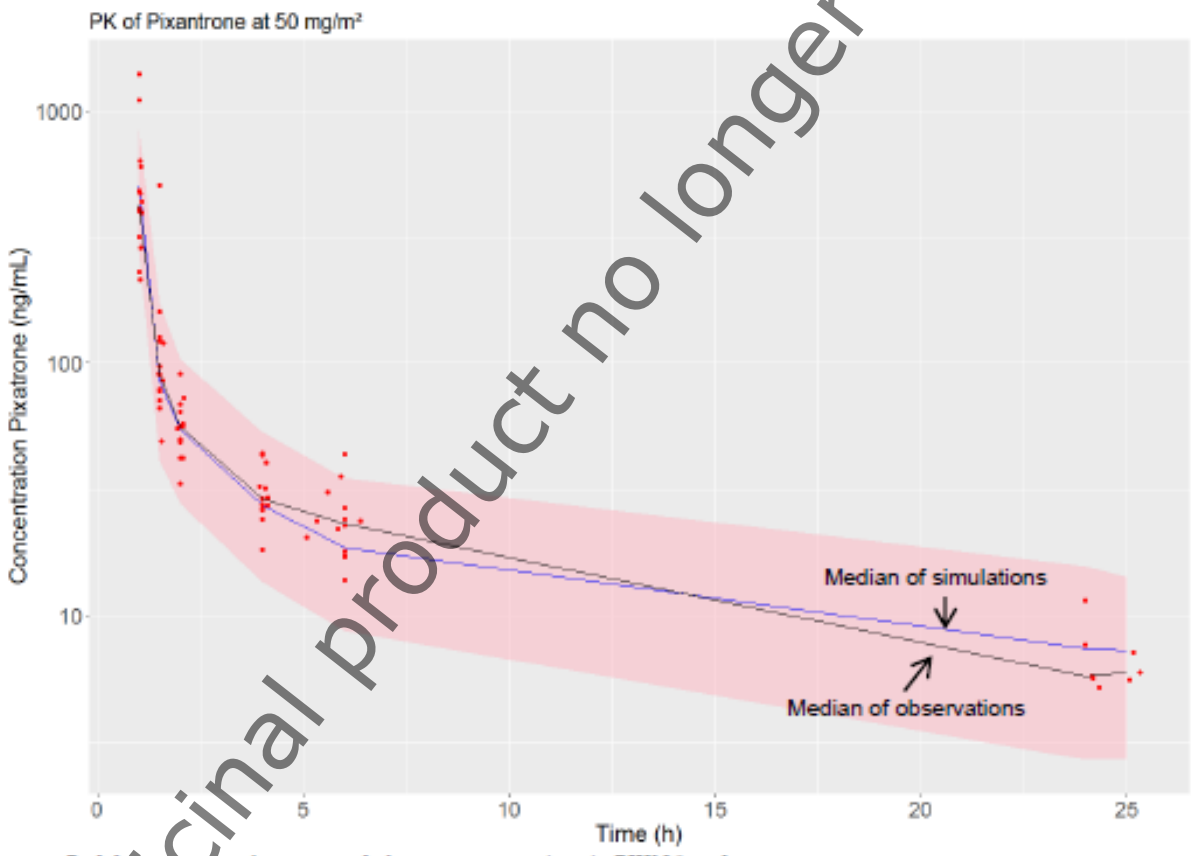
comment

There were no significant differences in the duration of overall response or duration of complete response between the two treatment groups.

PK-modeling

The aim of the PK substudy was to compare the pixantrone plasma concentrations measured during the current study (PIX306) in 14 patients, with the expected plasma concentrations predicted with the population PK model previously developed (Jumbe, Quantitative Solution Modeling and Simulation Report 2011). The measured concentrations are in agreement with the expected variability, and the median of the measured concentrations is in agreement with the simulated median profile.

Figure 7 Visual predictive check (VPC) obtained with the population PK model (Study PIX306)



Red dots represent the measured plasma concentrations in PIX306 study.
The pink area represents 90% confidence interval of the predictions.
Blue line represents the median of the simulations.
Black line represents the median of the observations.

comment

The agreement between the simulated data from a previously developed population PK model and the newly observed concentrations is summarized in Figure 5.7. Within the figure, red points indicate newly observed data from the PIX306 study and the pink area represents the 90% interval for the simulated values. The black line indicates the median of observed data and the blue line indicates the median of simulated data. Overall, there

is no visible difference between the concentrations observed in PIX306 study, and the simulations from the earlier developed population PK model; this indicates that pixantrone time-concentration data in patients receiving rituximab is not substantially different from the overall patient population characterised earlier and represented here by the population PK model.

Ancillary analyses

Not performed.

Safety

Safety exposure

A total of 302 patients received study drug: 153 patients in the pixantrone + rituximab group and 149 patients in the gemcitabine + rituximab group.

The median duration of treatment exposure was 17.0 weeks in the pixantrone + rituximab group versus 15.6 weeks in the gemcitabine + rituximab group. In the pixantrone + rituximab group, 50.3% of patients received all 6 cycles of study treatment versus 43.6% in the gemcitabine + rituximab group; the median number of cycles was 6.0 versus 5.0, respectively.

The median percentage of protocol dose was 66.7% in the pixantrone + R group versus 51.3% in the gemcitabine + R group, with a percentage of protocol dose ≥ 80% in 36.6% of patients versus 21.5%, respectively.

Table 30 Study drug exposure (pixantrone/gemcitabine) in the safety population (Study PIX306)

		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Duration of Exposure [1] to Pixantrone / Gemcitabine (weeks)			
	n	153	149
	Mean ± SD	15.8 ± 8.18	15.5 ± 8.56
	Median	17.0	15.6
	Q1, Q3	7.0, 23.1	7.1, 23.0
	Min, Max	1, 28	1, 31
Number of cycles of study drug received			
1	n (%)	14 (9.2)	17 (11.4)
2	n (%)	25 (16.3)	26 (17.4)
3	n (%)	13 (8.5)	11 (7.4)
4	n (%)	16 (10.5)	18 (12.1)
5	n (%)	8 (5.2)	12 (8.1)
6	n (%)	77 (50.3)	65 (43.6)
	n	153	149
	Mean ± SD	4.4 ± 1.87	4.2 ± 1.90
	Median	6.0	5.0
	Q1, Q3	2.0, 6.0	2.0, 6.0
	Min, Max	1, 6	1, 6
Total normalized dose (mg/m^2)			
	n	152	148
	Mean ± SD	568.5 ± 289.70	9373.1 ± 5158.94
	Median	600.0	9226.1
	Min, Max	50, 1295	898, 18026
Actual dose intensity [2] (mg/m^2/week)			
	n	152	148
	Mean ± SD	38.9 ± 12.22	650.3± 169.16
	Median	37.2	666.2
	Min, Max	17, 87	268, 1000
Percentage of protocol dose [3]			
	n	152	148
	Mean ± SD	63.2 ± 32.19	52.1 ± 28.66
	Median	66.7	51.3
	Q1, Q3	33.3, 88.9	27.8, 72.0
	Min, Max	6, 144	5, 100
< 70%	n (%)	83 (54.2)	109 (73.2)
[70 – 80%[	n (%)	14 (9.2)	8 (5.4)
[80 – 90%[	n (%)	22 (14.4)	13 (8.7)
≥ 90%	n (%)	34 (22.2)	19 (12.8)

[1] Defined as the time from the first study drug(s) dose date to the last day of study treatment.
[2] Actual dose intensity (mg/m^2/week) is calculated as the total normalized dose divided by the treatment duration.
[3] Percentage of protocol dose is calculated as the cumulative normalized dose divided by the total normalized dose as planned per protocol × 100%

Table 31 Study drug dose modifications (pixantrone/gemcitabine) in the safety population (Study PIX306)

		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Number of patients with at least one:			
Dose modification	n (%)	121 (79.1)	133 (89.3)
Dose reduction			
Adverse Event	n (%)	25 (16.3)	92 (61.7)
Other	n (%)	4 (2.6)	-
Dose delay			
Adverse Event	n (%)	44 (28.8)	54 (36.2)
For Patient Convenience	n (%)	4 (2.6)	2 (1.3)
Other	n (%)	6 (3.9)	4 (2.7)
Dose skipped			
Adverse Event	n (%)	102 (66.7)	82 (55.0)
Other	n (%)	2 (1.3)	1 (0.7)
Dose interruption			
Adverse Event	n (%)	4 (2.6)	-
Dose discontinuation			
Adverse Event	n (%)	17 (11.1)	18 (12.1)
Other	n (%)	9 (5.9)	8 (5.4)

Table 32 Study drug exposure (rituximab) in the safety population (Study PIX306)

		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Duration of Exposure [1] to Rituximab (weeks)	n	153	149
	Mean ± SD	14.9 ± 8.09	14.3 ± 8.34
	Median	18.0	16.0
	Q1, Q3	5.6, 21.4	5.3, 21.3
	Min, Max	1, 28	1, 29
Number (%) of cycles of rituximab received			
1	n (%)	14 (9.2)	17 (11.4)
2	n (%)	25 (16.3)	26 (17.4)
3	n (%)	13 (8.5)	11 (7.4)
4	n (%)	16 (10.5)	18 (12.1)
5	n (%)	8 (5.2)	12 (8.1)
6	n (%)	77 (50.3)	65 (43.6)
	n	153	149
	Mean ± SD	4.4 ± 1.87	4.2 ± 1.90
	Median	6.0	5.0
	Q1, Q3	2.0, 6.0	2.0, 6.0
	Min, Max	1, 6	1, 6
Total normalized dose (mg/m^2)			
	n	152	148
	Mean ± SD	1607.3 ± 707.72	1546.6 ± 716.07
	Median	1875.6	1705.9
	Min, Max	373, 2354	337, 2293
Actual dose intensity [2] (mg/m^2/week)	n	152	148
	Mean ± SD	139.9 ± 83.37	144.7 ± 88.13
	Median	107.2	108.0
	Min, Max	77, 395	75, 377
Percentage of protocol dose [3]	n	152	148
	Mean ± SD	71.4 ± 31.45	68.7 ± 31.83
	Median	83.4	75.8
	Q1, Q3	34.0, 100.0	33.4, 100.0
	Min, Max	17, 105	15, 102
< 70%	n (%)	72 (47.1)	75 (50.3)
[70 – 80%[	n (%)	1 (0.7)	-
[80 – 90%[	n (%)	8 (5.2)	12 (8.1)
≥ 90%	n (%)	72 (47.1)	62 (41.6)

[1] Defined as the time from the first study drug(s) dose date to the last day of study treatment.
[2] Actual dose intensity (mg/m^2/week) was calculated as the total normalized dose divided by the treatment duration.
[3] Percentage of protocol dose was calculated as the cumulative normalized dose divided by the total normalized dose as planned per protocol × 100%.

Table 33 Study drug dose modifications (rituximab) in the safety population (Study PIX306)

		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Number of patients with at least one :			
Dose modification	n (%)	68 (44.4)	51 (34.2)
Dose reduction	n (%)	-	-
Dose delay			
Adverse Event	n (%)	47 (30.7)	31 (20.8)
For Patient Convenience	n (%)	3 (2.0)	
Other	n (%)	6 (3.9)	6 (4.0)
Dose skipped	n (%)		
Adverse Event	n (%)	4 (2.6)	4 (2.7)
Dose interruption	n (%)		
Adverse Event	n (%)	5 (3.3)	12 (8.1)
Dose discontinuation			
Adverse Event	n (%)	7 (4.6)	4 (2.7)
Other	n (%)	3 (2.0)	1 (0.7)

comment

The pivotal study PIX301 for the CMA involved 68 subjects receiving pixantrone monotherapy. In Study PIX306 pixantrone was combined with rituximab for 153 patients, which slightly complicates the comparison of the adverse event profiles of pixantrone between the two studies.

In both studies, the pixantrone doses were reduced due to mainly tolerability issues. In PIX306 54.2% of patients received less than 70% of the protocol dose. Only 50.3% of the patients received 6 out of 6 study cycles as per protocol. For gemcitabine combined with rituximab, the dose reductions were even more frequently needed: 73.2 received less than 70% of the protocol dose and 43.6% of the patients went through 6 out of 6 study cycles.

The observed dose reductions of pixantrone in the clinical studies and clinical use and the consequences to efficacy/safety of pixantrone is being evaluated in the recently initiated legally binding procedure (LEG, see Section 6.5 of this AR).

Adverse events

Overall, the frequency of treatment emergent adverse events (TEAEs) was similar between groups except for the following (refer to Table 5.32):

- TEAEs leading to study drug reduction: reported in 23.5% in the pixantrone + rituximab group versus 65.1% of patients in the gemcitabine + rituximab group.
- TEAEs leading to rituximab dose interruption: reported in 41.2% of patients versus 28.9%, respectively.

Table 34 Overall summary of TEAEs - safety population (Study PIX306)

		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Any TEAE	**n (%)**	**153 (100)**	**146 (98.0)**
TEAE Related to Study Drug (pixantrone or gemcitabine)	**n (%)**	**140 (91.5)**	**140 (94.0)**
TEAE Leading to Study Drug Dose Reduction	n (%)	36 (23.5)	97 (65.1)
TEAE Leading to Study Drug Dose Interruption	n (%)	116 (75.8)	111 (74.5)
TEAE Leading to Study Drug Discontinuation	n (%)	33 (21.6)	36 (24.2)
TEAE Related to Rituximab	**n (%)**	**104 (68.0)**	**92 (61.7)**
TEAE Leading to Rituximab Dose Reduction	n (%)	-	-
TEAE Leading to Rituximab Dose Interruption	n (%)	63 (41.2)	43 (28.9)
TEAE Leading to Rituximab Discontinuation	n (%)	26 (17.0)	26 (17.4)
Any Grade 3/4 TEAE	**n (%)**	**130 (85.0)**	**132 (88.6)**
Grade 3/4 TEAE Related to Study Drug	n (%)	118 (77.1)	123 (82.6)
Grade 3/4 TEAE Related to Rituximab	n (%)	69 (45.1)	57 (38.3)
Serious AE (SAE)	**n (%)**	**59 (38.6)**	**57 (38.3)**
Serious AE Related to Study Drug	n (%)	30 (19.6)	22 (14.8)
Serious AE Related to Rituximab	n (%)	11 (7.2)	13 (8.7)
TEAE Leading to Death	**n (%)**	**14 (9.2)**	**8 (5.4)**

N: Number of patients by group.
n: Number of affected patients.
%: n/N x 100.

The overall incidence of TEAEs was similar in the pixantrone + rituximab and gemcitabine + rituximab groups (100% and 98.0%, respectively), refer to Table 5.33. The most frequently affected (> 50% of patients) SOCs were:

Blood and lymphatic system disorders: 79.7% in the pixantrone + R group versus 89.3% in the gemcitabine + R group.

- General disorders and administration site condition: 59.5% versus 56.4%, respectively.
- Gastrointestinal disorders: 56.2% versus 47.0%, respectively.

Other SOCs with differences in incidences between the 2 groups of 5% or more were:

- Skin and subcutaneous tissue disorders: 41.2% versus 30.2%, respectively.
- Infections and infestations: 39.9% versus 45.6%, respectively.
- Metabolism and nutrition disorders: 37.9% versus 29.5%, respectively.
- Nervous system disorders: 30.7% versus 22.1%, respectively.
- Musculoskeletal and connective tissues disorders: 28.1% versus 20.8%, respectively.
- Eye disorders: 10.5% versus 4.7%, respectively.

Table 35 TEAEs by SOC - safety population (Study PIX306)

System organ class		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Patients with ≥ 1 TEAE	**n (%)**	**153 (100)**	**146 (98.0)**
Blood and lymphatic system disorders	n (%)	122 (79.7)	133 (89.3)
General disorders and administration site conditions	n (%)	91 (59.5)	84 (56.4)
Gastrointestinal disorders	n (%)	86 (56.2)	70 (47.0)
Skin and subcutaneous tissue disorders	n (%)	63 (41.2)	45 (30.2)
Infections and infestations	n (%)	61 (39.9)	68 (45.6)
Metabolism and nutrition disorders	n (%)	58 (37.9)	44 (29.5)
Respiratory, thoracic and mediastinal disorders	n (%)	54 (35.3)	58 (38.9)
Nervous system disorders	n (%)	47 (30.7)	33 (22.1)
Investigations	n (%)	43 (28.1)	40 (26.8)
Musculoskeletal and connective tissue disorders	n (%)	43 (28.1)	31 (20.8)
Vascular disorders	n (%)	37 (24.2)	31 (20.8)
Cardiac disorders	n (%)	32 (20.9)	26 (17.4)
Renal and urinary disorders	n (%)	27 (17.6)	21 (14.1)
Psychiatric disorders	n (%)	22 (14.4)	17 (11.4)
Injury, poisoning and procedural complications	n (%)	21 (13.7)	15 (10.1)
Eye disorders	n (%)	16 (10.5)	7 (4.7)
Neoplasms benign, malignant and unspecified	n (%)	8 (5.2)	6 (4.0)
Immune system disorders	n (%)	5 (3.3)	2 (1.3)
Ear and labyrinth disorders	n (%)	4 (2.6)	4 (2.7)
Hepatobiliary disorders	n (%)	3 (2.0)	4 (2.7)
Reproductive system and breast disorders	n (%)	2 (1.3)	2 (1.3)
Endocrine disorders	n (%)	1 (0.7)	2 (1.3)

N: Number of patients by group.
n: Number of affected patients.
%: n/N x 100.
Note: Patients could have more than one AE per SOC. Within each SOC, a patient was counted only once if he experienced one or more AE.

The most commonly (≥ 20%) reported TEAEs in the treatment groups were:

In the pixantrone + rituximab group: neutropenia (69.3%), fatigue (29.4%), anaemia (27.5%), nausea (24.8%) and constipation (23.5%).

In the gemcitabine + rituximab group: thrombocytopenia (65.8%), neutropenia (59.1%), anaemia (50.3%), pyrexia (25.5%), fatigue (23.5%) and oedema peripheral (20.8%).

The incidence of the following TEAEs was numerically higher in the pixantrone + rituximab group than in the gemcitabine + rituximab group: neutropenia (69.3% versus 59.1%), constipation (23.5% versus 13.4%) and alopecia (19.0% versus 1.3%). Besides, the incidence of anaemia and thrombocytopenia was numerically lower in the pixantrone + R group than in the gemcitabine + R group (27.5% versus 50.3% and 16.3% versus 65.8%, respectively).

In addition, myelodysplastic syndrome was reported in 4 patients in the pixantrone + rituximab group versus none in the gemcitabine + rituximab group. Three of these events were reported as serious, and 2 had a fatal outcome.

The percentage of patients with at least one related TEAE was similar in both groups:

140 patients in the pixantrone + rituximab group (91.5%).

140 patients in the gemcitabine + rituximab group (94.0%).

A summary of the TEAEs that were considered as related to the study treatment (pixantrone or gemcitabine), in 2% or more patients in either group, is presented in Table 5.34.

The most frequently reported TEAEs considered to be related to rituximab were (in at least 10% of patients in any group): neutropenia (37.9% in the pixantrone + rituximab group versus 23.5% in the gemcitabine + R group), anaemia (11.1% versus 19.5%, respectively), thrombocytopenia (7.8% versus 24.2%) and fatigue (12.4% versus 9.4%).

comment

It is to be noted that myelodysplastic syndromes were reported only from patients receiving pixantrone.

Table 36 Analysis of TEAEs (pixantrone or gemcitabine) (in 2% or more patients in either group) – Safety Population (Study PIX306)

System Organ Class Preferred Term		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Patients with ≥ 1 TEAE related to study drug	**n (%)**	**140 (91.5)**	**140 (94.0)**
Blood and lymphatic system disorders	**n (%)**	**118 (77.1)**	**128 (85.9)**
Neutropenia	n (%)	105 (68.6)	88 (59.1)
Anemia	n (%)	35 (22.9)	65 (43.6)
Thrombocytopenia	n (%)	23 (15.0)	95 (63.8)
Leukopenia	n (%)	11 (7.2)	19 (12.8)
Gastrointestinal disorders	**n (%)**	**58 (37.9)**	**46 (30.9)**
Nausea	n (%)	27 (17.6)	23 (15.4)
Constipation	n (%)	17 (11.1)	6 (4.0)
Diarrhea	n (%)	15 (9.8)	10 (6.7)
Stomatitis	n (%)	15 (9.8)	7 (4.7)
Vomiting	n (%)	12 (7.8)	14 (9.4)
Abdominal pain	n (%)	3 (2.0)	-
General disorders and administration site conditions	**n (%)**	**53 (34.6)**	**57 (38.3)**
Fatigue	n (%)	35 (22.9)	29 (19.5)
Asthenia	n (%)	11 (7.2)	9 (6.0)
Pyrexia	n (%)	4 (2.6)	22 (14.8)
Oedema peripheral	n (%)	3 (2.0)	6 (4.0)
Malaise	n (%)	2 (1.3)	4 (2.7)
Skin and subcutaneous tissue disorders	**n (%)**	**49 (32.0)**	**17 (11.4)**
Alopecia	n (%)	28 (18.3)	2 (1.3)
Skin discoloration	n (%)	14 (9.2)	1 (0.7)
Night sweats	n (%)	4 (2.6)	1 (0.7)
Pruritus	n (%)	4 (2.6)	4 (2.7)
Nail discolouration	n (%)	3 (2.0)	-
Rash	n (%)	1 (0.7)	4 (2.7)
Infections and infestations	**n (%)**	**26 (17.0)**	**20 (13.4)**
Upper respiratory tract infection	n (%)	5 (3.3)	2 (1.3)
Oral candidiasis	n (%)	4 (2.6)	-
Pneumonia	n (%)	3 (2.0)	2 (1.3)
Metabolism and nutrition disorders	**n (%)**	**25 (16.3)**	**23 (15.4)**
Anorexia	n (%)	17 (11.1)	11 (7.4)
Decreased appetite	n (%)	5 (3.3)	3 (2.0)
Dehydration	n (%)	4 (2.6)	4 (2.7)
Hypomagnesaemia	n (%)	4 (2.6)	3 (2.0)
Hypokalaemia	n (%)	3 (2.0)	2 (1.3)

N: Number of patients by group.
n: Number of affected patients.
%: n/N x 100.
Notes: For each level (SOC and PT) a patient was counted only once if he experienced one or more AE at that level.

(Continued)

System Organ Class Preferred Term		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Nervous system disorders	**n (%)**	**23 (15.0)**	**11 (7.4)**
Dysgeusia	n (%)	11 (7.2)	2 (1.3)
Dizziness	n (%)	6 (3.9)	1 (0.7)
Headache	n (%)	5 (3.3)	-
Peripheral sensory neuropathy	n (%)	-	3 (2.0)
Investigations	**n (%)**	**22 (14.4)**	**26 (17.4)**
Ejection fraction decreased	n (%)	6 (3.9)	1 (0.7)
Neutrophil count decreased	n (%)	4 (2.6)	3 (2.0)
Weight decreased	n (%)	4 (2.6)	3 (2.0)
Troponin T increased	n (%)	3 (2.0)	-
C-reactive protein increased	n (%)	2 (1.3)	3 (2.0)
Gamma-glutamyltransferase increased	n (%)	1 (0.7)	4 (2.7)
Alanine aminotransferase increased	n (%)	-	9 (6.0)
Platelet count decreased	n (%)	-	9 (6.0)
Aspartate aminotransferase increased	n (%)	-	7 (4.7)
Blood alkaline phosphatase increased	n (%)	-	3 (2.0)
Cardiac disorders	**n (%)**	**15 (9.8)**	**7 (4.7)**
Atrial fibrillation	n (%)	4 (2.6)	1 (0.7)
Cardiac failure	n (%)	4 (2.6)	1 (0.7)
Renal and urinary disorders	**n (%)**	**11 (7.2)**	**11 (7.4)**
Chromaturia	n (%)	9 (5.9)	-
Respiratory, thoracic and mediastinal disorders	**n (%)**	**8 (5.2)**	**5 (3.4)**
Dyspnoea	n (%)	3 (2.0)	-
Neoplasms benign, malignant and unspecified	**n (%)**	**5 (3.3)**	**1 (0.7)**
Myelodysplastic syndrome	n (%)	4 (2.6)	-
Vascular disorders	**n (%)**	**5 (3.3)**	**5 (3.4)**
Musculoskeletal and connective tissue disorders	**n (%)**	**2 (1.3)**	**5 (3.4)**

N: Number of patients by group.
n: Number of affected patients.
%: n/N x 100.
Notes: For each level (SOC and PT) a patient was counted only once if he experienced one or more AE at that level.

The majority of patients experienced at least one Grade 3/4 TEAE, with similar frequencies in the two treatment groups (85.0% in the pixantrone + rituximab group and 88.6% in the gemcitabine + rituximab group), refer to Table 5.35.

The most frequently reported Grade 3/4 TEAEs in both groups were:

- Neutropenia: 63.4% in the pixantrone + rituximab group versus 55.7% in the gemcitabine + rituximab group.
- Anemia: 17.0% versus 37.6%, respectively.
- Thrombocytopenia: 11.1% versus 36.9%, respectively.

Table 37 Grade 3/4 TEAEs (in 5% or more patients in either group) - Safety Population (Study PIX306)

System Organ Class Preferred Term		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Patients with ≥ 1 CTCAE Grade 3/4 TEAE	**n (%)**	**130 (85.0)**	**132 (88.6)**
Blood and lymphatic system disorders	**n (%)**	**111 (72.5)**	**118 (79.2)**
Neutropenia	n (%)	97 (63.4)	83 (55.7)
Anemia	n (%)	26 (17.0)	56 (37.6)
Thrombocytopenia	n (%)	17 (11.1)	55 (36.9)
Leukopenia	n (%)	12 (7.8)	15 (10.1)
Lymphopenia	n (%)	9 (5.9)	3 (2.0)
Infections and infestations	**n (%)**	**24 (15.7)**	**30 (20.1)**
General disorders and administration site conditions	**n (%)**	**20 (13.1)**	**19 (12.8)**
Asthenia	n (%)	8 (5.2)	5 (3.4)
Fatigue	n (%)	5 (3.3)	9 (6.0)
Gastrointestinal disorders	**n (%)**	**17 (11.1)**	**9 (6.0)**
Respiratory, thoracic and mediastinal disorders	**n (%)**	**16 (10.5)**	**14 (9.4)**
Metabolism and nutrition disorders	**n (%)**	**15 (9.8)**	**14 (9.4)**
Cardiac disorders	**n (%)**	**13 (8.5)**	**6 (4.0)**
Vascular disorders	**n (%)**	**13 (8.5)**	**6 (4.0)**
Investigations	**n (%)**	**11 (7.2)**	**14 (9.4)**
Nervous system disorders	**n (%)**	**10 (6.5)**	**6 (4.0)**
Renal and urinary disorders	**n (%)**	**8 (5.2)**	**3 (2.0)**

N: Number of patients by group.
n: Number of affected patients.
%: n/N x 100.
Note: For each level (SOC and PT) a patient was counted only once if he experienced one or more AE at that level.

comment

The overall incidence of TEAEs in study PIX306 patients receiving pixantrone + rituximab was comparable to that of study PIX301 patients receiving pixantrone monotherapy, 91.5% vs. 97.1%. For grade 3 to 4 TEAEs the figures were 85.0% and 76.5% implying to a worse tolerability of the combination therapy. E.g., neutropenia 63.4% vs. 41.2%, anaemia 17.0% vs. 5.9%, or lymphopenia, 5.9% vs. 2.9%, in PIX306 vs. PIX301, respectively. However, these trends were reversed when looking at the SAEs, refer below to section "Serious adverse events".

There were some notable differences in the TEAE profiles between the treatments. Neutropenia was more common in pixantrone +rituximab group, and anaemia, thrombocytopenia, and leukopenia in gemcitabine + rituximab groups. These differences were also reflected to the number of transfusions the patients needed (any transfusion 8.5% vs 30.2%, platelets 0% vs 6.0%, RBCs 8.5% vs 28.9%, respectively) and to the use of growth factors (filgrastim was given to 66.0% and pegfilgrastim to 11.8% of pixantrone + rituximab patients, and to 47.7% and 4.7% of the gemcitabine + rituximab patients respectively).

Stomatitis, oral candidiasis, dysgeusia, and anorexia were more common in patients receiving pixantrone + rituximab. Skin discolouration affected 9.2% of pixantrone + rituximab patients and 0.7% of gemcitabine + rituximab patients. For the cardiovascular safety findings, refer to section "Other significant events" below.

The MAH has adjusted Section 4.8 of the Pixuvri SmPC proposal according to findings in Study PIX306. As this combination therapy has not been approved, this information must not be changed - to which the MAH as agreed.

Serious adverse event / deaths / other significant events

Deaths

An overall summary of on-treatment deaths (*i.e.*, deaths occurring on treatment and within 30 days of last dose of pixantrone or gemcitabine therapy), is presented in Table 5.36. Twelve patients in the pixantrone + rituximab group (7.8%) and 16 patients in the gemcitabine + rituximab group (10.7%) died within this timeframe.

Table 38 Overall summary of deaths during the treatment period - Safety Population (Study PIX306)

		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Number of on-treatment deaths	**n (%)**	**12 (7.8)**	**16 (10.7)**
Deaths by primary cause			
Adverse Event	n (%)	3 (2.0)	7 (4.7)
Disease Progression	n (%)	7 (4.6)	7 (4.7)
Other	n (%)	2* (1.3)	2** (1.3)

N: Number of patients by group; n: Number of affected patients; %: n/N x 100.
**viral pneumonia and asthenia*
***acute renal failure and sepsis*

TEAEs leading to death were reported in 14 patients (9.2%) in the pixantrone + rituximab group versus 8 patients (5.4%) in the gemcitabine + rituximab group.

TEAEs leading to death that were reported by at least 2 patients in either group were (pixantrone + rituximab group versus gemcitabine + rituximab group):

- Myelodysplastic syndrome and pneumonia (each reported in 2 patients versus none).
- Cardiac failure (none versus 2 patients).
- Cardiac failure acute (none versus 3 patients).

Table 39 Analysis of TEAEs leading to death by SOC and PT - safety population (Study PIX306)

System Organ Class Preferred Term		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Patients with ≥ 1 TEAE leading to death	**n (%)**	**14 (9.2)**	**8 (5.4)**
General disorders and administration site conditions	**n (%)**	**3 (2.0)**	-
Asthenia	n (%)	1 (0.7)	-
General physical health deterioration	n (%)	1 (0.7)	-
Multi-organ failure	n (%)	1 (0.7)	-
Neoplasms benign, malignant and unspecified	**n (%)**	**3 (2.0)**	-
Myelodysplastic syndrome	n (%)	2 (1.3)	-
Disseminated large cell lymphoma	n (%)	1 (0.7)	-
Cardiac disorders	**n (%)**	**2 (1.3)**	**5 (3.4)**
Atrial fibrillation	n (%)	1 (0.7)	-
Supraventricular tachycardia	n (%)	1 (0.7)	-
Cardiac failure	n (%)	-	2 (1.3)
Cardiac failure acute	n (%)	-	3 (2.0)
Infections and infestations	**n (%)**	**2 (1.3)**	**1 (0.7)**
Pneumonia	n (%)	2 (1.3)	-
Sepsis	n (%)	-	1 (0.7)
Renal and urinary disorders	**n (%)**	**2 (1.3)**	**1 (0.7)**
Cystitis hemorrhagic	n (%)	1 (0.7)	-
Renal failure acute	n (%)	1 (0.7)	1 (0.7)
Metabolism and nutrition disorders	**n (%)**	**1 (0.7)**	-
Lactic acidosis	n (%)	1 (0.7)	-
Nervous system disorders	**n (%)**	**1 (0.7)**	-
Cerebrovascular accident	n (%)	1 (0.7)	-
Respiratory, thoracic and mediastinal disorders	**n (%)**	**1 (0.7)**	**1 (0.7)**
Acute respiratory failure	n (%)	1 (0.7)	-
Aspiration	n (%)	-	1 (0.7)

N: Number of patients by group.
n: Number of affected patients.
%: n/N x 100.
Note: At each level (SOC and PT) a patient was counted only once if he experienced one or more AE at that level.

comment

The study groups were well balanced for the cardiac medical history and risk factors as well as for previous cardiotoxic treatments.

Deaths due to cardiovascular events were slightly more common in the gemcitabine arm. Cardiac arrhythmias were observed in similar extent in both study groups. Cardiac failure was reported more from the gemcitabine group. The cardiovascular adverse event potential of pixantrone does not raise concerns.

There were no other significant differences regarding deaths between the treatment groups, apart from 2 deaths due to myelodysplastic syndrome (and two further cases of myelodysplastic syndrome) in the pixantrone + rituximab group.

The percentage of on-treatment deaths was lower in PIX306 patients receiving pixantrone + rituximab compared to PIX301 patients receiving pixantrone monotherapy.

Serious adverse events

At least one treatment-emergent SAE was reported by 59 patients (38.6%) in the pixantrone + rituximab group versus 57 patients (38.3%) in the gemcitabine + rituximab group.

The most frequently reported events were (pixantrone + rituximab versus gemcitabine + rituximab)

- Pneumonia: 8 patients (5.2%) versus 4 patients (2.7%), respectively.
- Anaemia: 5 patients (3.3%) versus 8 patients (5.4%), respectively.
- Febrile neutropenia: 5 patients (3.3%) versus 1 patient (0.7%), respectively.
- Pyrexia: 4 patients (2.6%) versus 8 patients (5.4%) respectively.

At least one treatment-emergent SAEs considered as treatment-related was reported in 30 patients (19.6%) in the pixantrone + rituximab group versus 22 patients (14.8%) in the gemcitabine + rituximab group.

Table 40 Serious TEAEs by SOC and PT (in 2 or more patients in either group) - Safety Population (Study PIX306)

System Organ Class Preferred Term		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Patients with ≥ 1 SAE	**n (%)**	**59 (38.6)**	**57 (38.3)**
Infections and infestations	**n (%)**	**18 (11.8)**	**23 (15.4)**
Pneumonia	n (%)	8 (5.2)	4 (2.7)
Sepsis	n (%)	2 (1.3)	1 (0.7)
Septic shock	n (%)	2 (1.3)	-
Urinary tract infection	n (%)	2 (1.3)	3 (2.0)
Staphylococcal bacteremia	n (%)	1 (0.7)	2 (1.3)
Cellulitis	n (%)	-	2 (1.3)
Erysipelas	n (%)	-	3 (2.0)
Upper respiratory tract infection	n (%)	-	2 (1.3)
Blood and lymphatic system disorders	**n (%)**	**12 (7.8)**	**11 (7.4)**
Anemia	n (%)	5 (3.3)	8 (5.4)
Febrile neutropenia	n (%)	5 (3.3)	1 (0.7)
Thrombocytopenia	n (%)	2 (1.3)	3 (2.0)
Cardiac disorders	**n (%)**	**10 (6.5)**	**10 (6.7)**
Cardiac failure	n (%)	3 (2.0)	2 (1.3)
Atrial fibrillation	n (%)	2 (1.3)	2 (1.3)
Cytotoxic cardiomyopathy	n (%)	2 (1.3)	-
Supraventricular tachycardia	n (%)	2 (1.3)	-
Cardiac failure acute	n (%)	-	3 (2.0)
Cardiac failure congestive	n (%)	-	2 (1.3)
General disorders and administration site conditions	**n (%)**	**10 (6.5)**	**15 (10.1)**
Pyrexia	n (%)	4 (2.6)	8 (5.4)
Asthenia	n (%)	2 (1.3)	1 (0.7)
Chest pain	n (%)	2 (1.3)	1 (0.7)
Generalized edema	n (%)	-	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**n (%)**	**10 (6.5)**	**11 (7.4)**
Acute respiratory failure	n (%)	2 (1.3)	-
Dyspnea	n (%)	2 (1.3)	3 (2.0)
Pleural effusion	n (%)	1 (0.7)	2 (1.3)
Gastrointestinal disorders	**n (%)**	**6 (3.9)**	**7 (4.7)**
Diarrhea	n (%)	1 (0.7)	2 (1.3)
Nausea	n (%)	-	2 (1.3)
Neoplasms benign, malignant and unspecified	**n (%)**	**6 (3.9)**	**1 (0.7)**
Myelodysplastic syndrome	n (%)	3 (2.0)	-
Nervous system disorders	**n (%)**	**6 (3.9)**	**3 (2.0)**
Syncope	n (%)	3 (2.0)	-
Renal and urinary disorders	**n (%)**	**5 (3.3)**	**5 (3.4)**
Hematuria	n (%)	2 (1.3)	-
Renal failure acute	n (%)	2 (1.3)	2 (1.3)
Hydronephrosis	n (%)	-	2 (1.3)
Vascular disorders	**n (%)**	**5 (3.3)**	**4 (2.7)**
Injury, poisoning and procedural complications	**n (%)**	**4 (2.6)**	**1 (0.7)**
Metabolism and nutrition disorders	**n (%)**	**4 (2.6)**	**6 (4.0)**
Dehydration	n (%)	2 (1.3)	3 (2.0)
Skin and subcutaneous tissue disorders	**n (%)**	-	**3 (2.0)**

N: Number of patients by group; n: Number of affected patients; %: n/N x 100.

SAEs leading to treatment withdrawal were reported in 11 patients in the pixantrone + rituximab group (7.2%) versus 16 patients in the gemcitabine + rituximab group (10.7%).

comment

The incidences of serious treatment emergent adverse events did not differ significantly between the treatment groups in study PIX306, including cardiotoxicity.

In study PIX301 51.5% of the patients receiving pixantrone monotherapy experienced SAEs vs. 38.6% in PIX306: Blood and lymphatic system 22.1% vs. 7.8%, Infections and infestations 20.6% vs. 11.8%, Cardiac disorders 8.8% vs. 6.5%, etc. From this point of view, pixantrone + rituximab appears not less tolerable treatment than plain pixantrone.

Other significant events

Cardiovascular safety

Overall, cardiac events were reported with similar frequencies in each treatment group: 60 patients (39.2%) in the pixantrone + rituximab group versus 55 patients (36.9%) in the gemcitabine + rituximab group, refer to Tables 5.39 and 5.40.

The most frequently reported events were (pixantrone + rituximab group versus gemcitabine + rituximab):

- Edema peripheral: 12.4% versus 20.8%, respectively.
- Atrial fibrillation: 4.6% versus 4.7%, respectively.
- Cardiac failure: 3.3% versus 4.0%, respectively.
- Ejection fraction decreased: 5.2% versus 0.7%, respectively.
- Syncope: 3.9% versus 1.3%, respectively.
- Tachycardia: 2.0% versus 3.4%, respectively.

Heart failure (congestive or not, acute or not) was reported by 6 patients (3.9%) in the pixantrone + rituximab group versus 11 patients (7.4%) in the gemcitabine + rituximab group. There was no emergent cardiac failure or cardiac failure acute leading to death in the pixantrone + rituximab group, while it was reported in 2 patients and 3 patients, respectively, in the gemcitabine + rituximab group.

Cytotoxic cardiomyopathy was reported in 3 patients in the pixantrone + rituximab group (versus none) and cardiomegaly in 2 patients in the pixantrone + rituximab group (versus none). One patient recovered from cytotoxic cardiomyopathy.

Table 41 Summary of cardiac TEAEs (in 2 or more patients in either group) - safety population (Study PIX306)

System Organ Class Preferred Term		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Patients with ≥ 1 Cardiac (SMQ) TEAE	**n (%)**	**60 (39.2)**	**55 (36.9)**
Cardiac disorders	**n (%)**	**23 (15.0)**	**22 (14.8)**
Atrial fibrillation	n (%)	7 (4.6)	7 (4.7)
Cardiac failure	n (%)	5 (3.3)	6 (4.0)
Tachycardia	n (%)	3 (2.0)	5 (3.4)
Cardiomegaly	n (%)	2 (1.3)	-
Supraventricular tachycardia	n (%)	2 (1.3)	1 (0.7)
Cardiac failure congestive	n (%)	1 (0.7)	2 (1.3)
Cardiac failure acute	n (%)	-	3 (2.0)
General disorders and administration site conditions	**n (%)**	**20 (13.1)**	**32 (21.5)**
Edema peripheral	n (%)	19 (12.4)	31 (20.8)
Investigations	**n (%)**	**17 (11.1)**	**2 (1.3)**
Ejection fraction decreased	n (%)	8 (5.2)	1 (0.7)
Troponin T increased	n (%)	5 (3.3)	-
Troponin increased	n (%)	3 (2.0)	1 (0.7)
Electrocardiogram QT prolonged	n (%)	2 (1.3)	-
Nervous system disorders	**n (%)**	**9 (5.9)**	**3 (2.0)**
Syncope	n (%)	6 (3.9)	2 (1.3)
Vascular disorders	**n (%)**	**5 (3.3)**	**9 (6.0)**
Deep vein thrombosis	n (%)	1 (0.7)	3 (2.0)
Thrombophlebitis	n (%)	1 (0.7)	2 (1.3)
Embolism	n (%)	-	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**n (%)**	**3 (2.0)**	**5 (3.4)**
Pulmonary embolism	n (%)	2 (1.3)	2 (1.3)
Pulmonary edema	n (%)	-	3 (2.0)

N: Number of patients by group.
n: Number of affected patients.
%: n/N x 100.

Cardiac TEAEs of grade 3 or 4 were reported by 28 patients (18.3%) in the pixantrone + rituximab group versus 12 patients (8.1%) in the gemcitabine + rituximab group. The most frequently reported events were:

- Atrial fibrillation: 4 patients (2.6%) versus 3 patients (2.0%), respectively.
- Syncope: 5 patients (3.3%) versus 2 patients (1.3%), respectively.
- Ejection fraction decreased: 4 patients (2.6%) versus 1 patient (0.7%), respectively.

Grade 3/4 cardiac (SMQ) TEAEs over time were reported at higher incidence rates in the pixantrone + rituximab group than in the gemcitabine + rituximab group, especially over week 1 to week 28.

Table 42 Grade 3 to 4 cardiac TEAEs (in 2 or more patients in either group) - safety population (Study PIX306)

System Organ Class Preferred Term		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Patients with ≥ 1 Grade 3/4 Cardiac (SMQ) TEAE	**n (%)**	**28 (18.3)**	**12 (8.1)**
Cardiac disorders	**n (%)**	**11 (7.2)**	**6 (4.0)**
Atrial fibrillation	n (%)	4 (2.6)	3 (2.0)
Cardiac failure	n (%)	3 (2.0)	-
Cardiac failure congestive	n (%)	1 (0.7)	2 (1.3)
Myocardial infarction	n (%)	1 (0.7)	1 (0.7)
Supraventricular tachycardia	n (%)	1 (0.7)	1 (0.7)
Tachycardia	n (%)	1 (0.7)	1 (0.7)
Acute myocardial infarction	n (%)	1 (0.7)	-
Atrial thrombosis	n (%)	1 (0.7)	-
Stress cardiomyopathy	n (%)	1 (0.7)	-
Nervous system disorders	**n (%)**	**8 (5.2)**	**3 (2.0)**
Syncope	n (%)	5 (3.3)	2 (1.3)
Cerebrovascular accident	n (%)	1 (0.7)	1 (0.7)
Lacunar infarction	n (%)	1 (0.7)	-
Syncope vasovagal	n (%)	1 (0.7)	-
Investigations	**n (%)**	**6 (3.9)**	**1 (0.7)**
Ejection fraction decreased	n (%)	4 (2.6)	1 (0.7)
Electrocardiogram QT prolonged	n (%)	1 (0.7)	-
Troponin increased	n (%)	1 (0.7)	-
Vascular disorders	**n (%)**	**4 (2.6)**	-
Axillary vein thrombosis	n (%)	1 (0.7)	-
Deep vein thrombosis	n (%)	1 (0.7)	-
Jugular vein thrombosis	n (%)	1 (0.7)	-
Subclavian vein thrombosis	n (%)	1 (0.7)	-
Thrombosis	n (%)	1 (0.7)	-
Respiratory, thoracic and mediastinal disorders	**n (%)**	**3 (2.0)**	**3 (2.0)**
Pulmonary embolism	n (%)	2 (1.3)	2 (1.3)
Pulmonary thrombosis	n (%)	1 (0.7)	-
Pulmonary oedema	n (%)	-	1 (0.7)
General disorders and administration site conditions	**n (%)**	**2 (1.3)**	**1 (0.7)**
Edema peripheral	n (%)	2 (1.3)	1 (0.7)
Injury, poisoning and procedural complications	**n (%)**	**1 (0.7)**	-
Thrombosis in device	n (%)	1 (0.7)	-

N: Number of patients by group.
n: Number of affected patients.
%: n/N x 100.

Patients who were found to have a post-baseline LVEF value ≤ 50% or absolute decrease from baseline ≥ 10% were more frequent in the pixantrone + rituximab group (36 patients, 23.5%) than in the gemcitabine + rituximab group (17 patients, 11.4%). Refer to Table 5.41.

Table 43 Summary of Post-baseline LVEF (%) categories - safety population (Study PIX306)

		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Patients with any post-baseline LVEF values that were:			
LVEF [40% - 50%], or an absolute decrease* [10% - 19%]	n (%)	31 (20.3)	17 (11.4)
LVEF [20% - 39%], or an absolute decrease* ≥ 20%	n (%)	9 (5.9)	2 (1.3)
LVEF < 20%	n (%)	1 (0.7)	-
Total number of patients meeting at least one post-baseline LVEF category**	**n (%)**	**36 (23.5)**	**17 (11.4)**

*from baseline
**Patients could be counted in more than one category if they met the criteria at any post-baseline visit. The 'Total' displays distinct number of subjects meeting at least one of the LVEF categories

comment

As already stated above, the study groups were well balanced for the cardiac medical history and risk factors as well as for previous cardiotoxic treatments. Deaths due to cardiovascular events were slightly more common in the gemcitabine arm. Cardiac arrhythmias were observed in similar extent in both study groups. Cardiac failure was reported more from the gemcitabine group. The cardiovascular adverse event potential of pixantrone does not raise concerns.

Conversely, there seems to be no advantage of pixantrone over the comparator treatments (in both studies PIX301 and PIX306) regarding the cardiovascular safety or tolerability.

Laboratory findings

The most frequent emergent biochemical abnormalities of grade 3 or 4 (in at least 2% of patients in any group) were hyperglycaemia (8.5% in the pixantrone + rituximab group versus 4.0% in the gemcitabine + rituximab group), hyponatremia (2.0% versus 0.7%, respectively), hypophosphatemia and AST increased (each in 2.0% versus 1.3%, respectively).

Grade ≥ 3 abnormal laboratory values were sparse in both groups and for each parameter, see Table 5.42.

Hy's law criteria was defined as AST or ALT > 3 x ULN, total bilirubin > 2 x ULN, and alkaline phosphatase < 2 x ULN at the same visit. No patient met the Hy's Law criteria.

Table 44 Shift from baseline to worst CTCAE toxicity grade (Grade ≥ 3, only worsening) - safety population (Study PIX306)

Parameter	Post-baseline grade	NCI CTCAE Baseline Grade							
		Pixantrone + R				Gemcitabine + R			
		0	1	2	3	0	1	2	3
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sodium	3	1 (0.7)	2 (15.4)	-	-		1 (10.0)	-	-
	4	-	-	-	-	-	-	-	-
Potassium	3	2 (1.4)	-	-	-	2 (1.5)	-	-	-
	4	1 (0.7)	-	-	1(100)	1 (0.8)	-	-	-
Calcium	3	-	-	-	-	-	-	1 (16.7)	-
	4	-	-	-	-	-	-	-	-
Magnesium	3	-	2 (9.1)	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-
Phosphate	3	2 (1.4)	-	1 (25.0)	-	1 (0.7)	-	-	1 (50.0)
	4	-	-	-	-	-	-	-	-
Glucose	3	2 (1.6)	1 (14.3)	7 (53.8)	3 (42.9)	-	1 (12.5)	4 (20.0)	1 (50.0)
	4	1 (0.8)	-	-	1 (14.3)	-	-	-	-
Creatinine	3	-	-	-	-	1 (0.9)	-	-	-
	4	-	-	-	-		-	-	-
Bilirubin	3	-	-	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-
Albumin	3	-	-	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-
ALT/SGPT	3	1 (0.7)	-	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-
AST/SGOT	3	1 (0.7)	2 (20.0)	-	-	-	2 (10.5)	-	-
	4	-	-	-	-	-	-	-	-
Alkaline phosphatase	3	-	-	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-

n: Number of patients with value at baseline: grade ≤ 3 or missing and worst post-baseline ≥ 3
*%: n/(number of patients with Grade concerned at baseline) *100;* Grade 0=none, 1=mild, 2=moderate, 3=severe, 4=life threatening
There were no patients having missing baseline grades with post-baseline grades 3 or 4.

The most frequent emergent grade 3 or 4 haematological abnormalities, which were also more frequently reported in the pixantrone + rituximab group than in the gemcitabine + rituximab group, were: low white blood cell (WBC) counts (66.7% versus 43.0%, respectively), low neutrophil counts (62.7% versus 44.3%) and low lymphocytes counts (58.2% versus 38.9%).

Treatment emergent low platelet counts of grade 3 or 4 were less frequent in the pixantrone + rituximab group than in the gemcitabine + rituximab group (9.2% versus 27.5%)

Table 45 summary of treatment-emergent laboratory abnormalities* - safety population (Study PIX306)

Parameter CTCAE Grade at post-baseline**		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Leukocytes (WBC decreased)			
1-4	n (%)	140 (91.5)	124 (83.2)
3-4	n (%)	102 (66.7)	64 (43.0)
Neutrophils (Neutrophil count decreased)			
1-4	n (%)	140 (91.5)	120 (80.5)
3-4	n (%)	96 (62.7)	66 (44.3)
Lymphocyte (Lymphocyte count decreased)			
1-4	n (%)	147 (96.1)	134 (89.9)
3-4	n (%)	89 (58.2)	58 (38.9)
Hemoglobin (Anemia)			
1-4	n (%)	133 (86.9)	139 (93.3)
3-4	n (%)	12 (7.8)	17 (11.4)
Platelets (Platelet count decreased)			
1-4	n (%)	97 (63.4)	128 (85.9)
3-4	n (%)	14 (9.2)	41 (27.5)

** defined as an abnormality that, compared to baseline, worsened by ≥ 1 grade in the period from the first dose of study treatment to 30 days after the last dose of study treatment.*
*** worst CTCAE grade at post baseline, Grade 1=mild, 2=moderate, 3=severe, 4=life threatening.*
N: Number of patients by group, n: Number of affected patients, %: n/N x 100.

comment

There were no significant differences in the blood chemistry abnormalities between the treatment groups in PIX306. No Hepato-renal toxicity was reported.

Discontinuation due to adverse events

The percentage of patients who withdrew due to TEAE was similar between groups: 33 patients (21.6%) in the pixantrone + rituximab group and 36 patients (24.2%) in the gemcitabine + rituximab group, refer to Table 5.X.

Overall, the most frequent TEAEs that led to study drug withdrawal in the pixantrone + rituximab group versus gemcitabine + rituximab group were neutropenia in 8 patients (5.2%) versus 2 patients (1.3%), respectively, ejection fraction decreased in 5 patients (3.3%) versus none, respectively, and thrombocytopenia in 4 patients in each group (2.6% versus 2.7%, respectively).

Table 46 Analysis of TEAEs leading to study treatment discontinuation - safety population (Study PIX306)

System Organ Class Preferred Term		Pixantrone + R (N = 153)	Gemcitabine + R (N = 149)
Patients with ≥ 1 TEAE leading to discontinuation	**n (%)**	**33 (21.6)**	**36 (24.2)**
Blood and lymphatic system disorders	**n (%)**	**13 (8.5)**	**7 (4.7)**
Neutropenia	n (%)	8 (5.2)	2 (1.3)
Thrombocytopenia	n (%)	4 (2.6)	4 (2.7)
Anemia	n (%)	2 (1.3)	-
Investigations	**n (%)**	**6 (3.9)**	**2 (1.3)**
Ejection fraction decreased	n (%)	5 (3.3)	-
Platelet count decreased	n (%)	-	2 (1.3)
Infections and infestations	**n (%)**	**5 (3.3)**	**6 (4.0)**
Gastrointestinal disorders	**n (%)**	**4 (2.6)**	**4 (2.7)**
General disorders and administration site conditions	**n (%)**	**4 (2.6)**	**5 (3.4)**
Asthenia	n (%)	2 (1.3)	1 (0.7)
Mass	n (%)	-	2 (1.3)
Pyrexia	n (%)	-	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**n (%)**	**4 (2.6)**	**5 (3.4)**
Pleural effusion	n (%)	-	2 (1.3)
Cardiac disorders	**n (%)**	**2 (1.3)**	**3 (2.0)**
Renal and urinary disorders	**n (%)**	**2 (1.3)**	**5 (3.4)**
Nephropathy	n (%)	-	2 (1.3)
Nervous system disorders	**n (%)**	**1 (0.7)**	**2 (1.3)**
Metabolism and nutrition disorders	**n (%)**	-	**4 (2.7)**

N: Number of patients by group.
n: Number of affected patients.
%: n/N x 100.

In the Safety Population the incidence of TEAEs that led to study drug dose reductions was lower in the pixantrone + rituximab group (23.5%) than in the gemcitabine + rituximab group (65.1%).

Dose reductions were mainly due to neutropenia (18.3% versus 33.6%, respectively) and thrombocytopenia (1.3% versus 43.6%, respectively). Except for febrile neutropenia, reported in 2 patients in the pixantrone + rituximab group (versus none in the gemcitabine group), no other events leading to dose reduction in the pixantrone + rituximab group were reported in more than 1 patient.

In the Safety Population, the incidence of TEAEs leading to study drug dose interruptions was similar in the pixantrone + rituximab group (75.8%) and the gemcitabine + rituximab group (74.5%).

In the pixantrone + rituximab group, drug interruptions were mostly due to neutropenia (56.2% versus 34.2% in the gemcitabine + rituximab group). In the gemcitabine + rituximab group, drug interruptions were mostly due to thrombocytopenia (40.9% versus 9.8% in the pixantrone + rituximab group), neutropenia (see above), and anaemia (12.8% versus 2.0%, respectively).

comment

The rate of discontinuations due to TEAEs was lower in study PIX306 patients receiving pixantrone + rituximab compared to study PIX301 patients receiving only pixantrone (42.6% vs. 21.6%), which implies to not worse tolerability of the combination treatment compared to monotherapy.

5.3. Other clinical studies of relevance

PIX203 Cyclophoshpamiede, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R) and cyclophosphamide, pixantrone, vincristine, prednisone plus rituximab (CPOP-R) in patients with diffuse large B-cell lymphoma: A phase II, randomised, multicentre, comparative trial

This study took place between 28 November 2005 and 20 August 2008. The study report was finalised on 15 April 2011. The primary objective of this study was to compare the response rate of the cyclophosphamide, pixantrone, vincristine, and prednisone + rituximab (CPOP-R) regimen with the standard cyclophosphamide, doxorubicin, vincristine, and prednisone + rituximab (CHOP-R) regimen and to show that the response rate for CPOP-R was not inferior to that of CHOP-R.

The secondary objectives were to compare the OS, PFS, and safety and tolerability of the two treatment regimens, including cardiac function. Other comparisons included duration of response (DOR), ORR, and time to treatment failure (TTF).

Patients who discontinued treatment for disease progression, withdrawal of consent, or unacceptable toxicity continued in the follow-up period and were monitored for up to 36 months after EOT. AEs were monitored throughout treatment. Follow-up therapies and cardiac history were monitored during follow-up. Cardiac function was assessed by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO) at baseline, after cycles 2, 4, and 6, at EOT, and 6, 12, and 24 months after EOT.

Study enrolment was terminated for business reasons, not safety concerns, on 31 January 2008 with 124 patients enrolled in the study. 61 patients in the CPOP-R arm and 63 patients in CHOP-R arm.

The main inclusion criteria: Patients aged ≥18 years with untreated, histologically confirmed, CD20-positive, DLBCL NHL according to Revised European-American Lymphoid Neoplasm/World Health Organization (REAL/WHO) classification were included. Additional requirements for inclusion were stage II, III, or IV disease; adequate organ function and ECOG performance status (PS) ≤2.

Experimental group: On Day 1 of each 21-day cycle, patients received pixantrone (active ingredient: pixantrone dimaleate) 150mg/m2 IV, cyclophosphamide (750 mg/m^2 IV), vincristine (1.4 mg/m^2 IV), and rituximab (375 mg/m^2 IV). Prednisone (100 mg) was administered orally once daily on days 1 to 5 of each cycle.

Comparator group: On Day 1 of each 21-day cycle, patients received doxorubicin (50 mg/m2 IV), cyclophosphamide (750mg/m^2 IV), vincristine (1.4 mg/m^2 IV), and rituximab (375 mg/m^2 IV). Prednisone (100 mg) was administered orally once daily on days 1 to 5 of each cycle.

The primary endpoint was CR/CRu rate, defined as the total proportion of patients in the intent-to-treat population with a CR or complete response unconfirmed (CRu) as assessed by the IAP according to the International Workshop to Standardize Response Criteria. Secondary endpoints were OS, PFS, ORR, duration of response, and TTF.

Safety parameters included AEs and their severity, duration, and relationship to treatment. AE severity was defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

version 3.0. AEs of particular interest were grade 3 and 4 cardiac events, whether considered related to study drug or not, and left ventricular ejection fraction (LVEF) decreases.

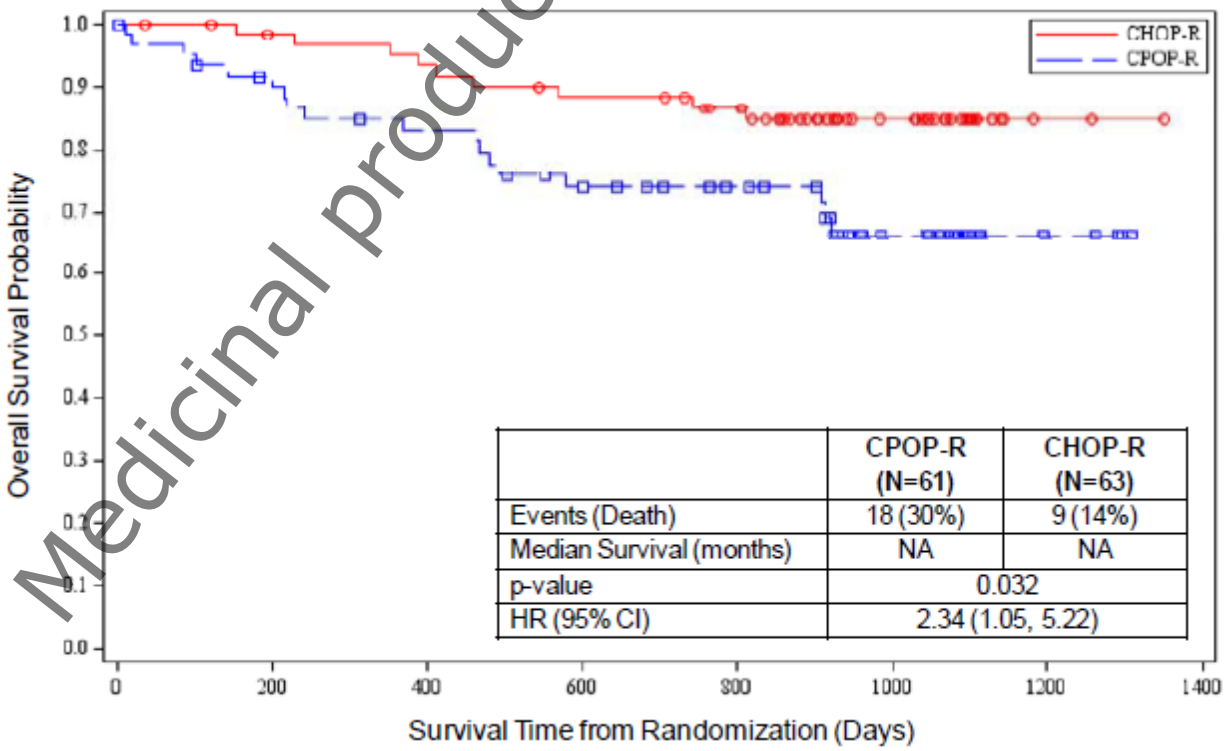
As of the final Statistical Analysis Plan (SAP), the required total sample size for at least 80% power, assuming a 15% non-inferiority margin, was 138 patients per arm, assuming a 5% dropout rate. Given a total of 124 patients as the final sample size, this study was not sufficiently powered to detect statistical significance. OS and other time to event endpoints were analysed K-M methods. The unstratified log-rank test was used to compare the K-M curves across the two arms. Descriptive statistics were provided for baseline and demographic characteristics, efficacy endpoints, and safety. Where appropriate, 95% CIs were calculated under the assumption. The primary analysis was based on the IAP assessment of the ITT population; supportive analyses were performed in the histologically confirmed intent-to-treat (HITT) and the per-protocol (PP) populations.

Demographic characteristics were generally well-balanced between treatment groups for mean age, age group, gender, distribution of race, mean weight, smoking status, and ECOG PS. No statistically significant differences were observed between treatment groups for any demographic variable. Baseline disease characteristics were well balanced between the two treatment groups for type of biopsy, current Ann Arbor stage of NHL, current International Prognostic Index (IPI) and distribution, and number of extranodal sites. All patients had DLBCL according to the investigator's assessment.

The ORR for the CPOP-R arm was 82% compared to 87% for the CHOP-R arm. The PFS analysis demonstrated a hazard ratio (HR) of 1.03 (95% CI = 0.55, 1.91). Median PFS was not reached for the CPOP-R arm.

OS was significantly better for patients treated with CHOP-R compared to those treated with CPOP-R (p = 0.032). The HR was 2.34 (95% CI = 1.05, 5.22). Median OS was not reached for either arm.

Figure 8: OS by Kaplan-Meier estimation (Study PIX203)



CPOP-R produced a CR/CRu rate of 72% and an ORR of 82% compared to 79% and 87% for CHOP-R. The PFS analysis demonstrated a HR of 1.03 (95% CI = 0.55, 1.91). OS for CHOP-R patients was better (for unknown reasons) than for CPOP-R patients and was also higher than that reported in recent large randomized studies.

Similar proportions of patients experienced SAEs, treatment related AEs, and AEs leading to treatment discontinuation or interruption. The incidence of neutropenia, febrile neutropenia, and sepsis, including grade 3/4 events, was comparable between arms. More CHOP-R than CPOP-R patients had congestive heart failure (CHF), >20% declines in LVEF, and increases in troponin T levels.

There were more deaths in the CPOP-R group; three occurred during the treatment period, one of which was related to study drug. There were no deaths in the CHOP-R arm during the treatment period. Of 14 deaths on the CPOP-R arm and 9 deaths on the CHOP-R that occurred more than 30 days after study treatment, most were in the context of progressive disease and in elderly patients with IPI scores ≥3.

comment

In study PIX203, the non-inferiority assumption of R-CPOP treatment compared to R-CHOP (the established, standard first-line treatment) was not met. OS was significantly higher in the CHOP-R treatment group compared to CPOP-R treatment group.

In the first-line treatment of DLBCL, like in this study, the efficacy of the treatment is of foremost interest. Today most of the DLBCL patients can be cured with CHOP-R treatment. However, despite of this effective treatment option, at least 30% will eventually relapse. If the long-term efficacy of the proposed alternative treatment (replacing doxorubicin with pixantrone) is not at least at the same level, then there is no possibility or need to change the established first line treatment.

The result from this study imposes some question marks also on the potential efficacy of pixantrone after the use of CHOP-R therapy, like in the approved indication. However, the dose of pixantrone was not the same (it was much higher than in studies PIX301 or PIX306) and the patient population was different (first line vs. second or later lines).

AZA302 An open-label, randomized, phase III comparative trial of BBR 2778 + rituximab versus rituximab in the treatment of patients with relapsed or refractory indolent non-Hodgkin's lymphoma (NHL)

This study took place between 11 August 2004 and 19 January 2005. The study report was finalised on 05 September 2007.

The primary objective was to compare the time to tumour progression (TTP) of the combination of BBR 2778 (pixantrone) + rituximab with that of rituximab alone.

Secondary objectives were to compare between the objective overall response rate (ORR; CR + PR), objective complete response rate (CRR), rate of molecular remission, time to response, time to complete response, duration of response, time to tumour progression requiring treatment, quality-adjusted time to progression (QATTP), overall survival, disease-specific survival, and safety/tolerability with a particular focus on cardiac safety.

This was a multinational, controlled, randomized, multi-centre, open-label study in patients with indolent NHL who had experienced up to 5 episodes of progressive disease after prior treatments. Patients were randomly assigned to receive pixantrone + rituximab (experimental group) or rituximab alone (control group). Chemotherapy was administered in cycles repeated every 21 days.

Patients in the experimental arm received rituximab on day 1, pixantrone on day 2, and rituximab and pixantrone on day 8 of cycle 1; rituximab and pixantrone on day 1 and day 8 of cycle 2; and single agent pixantrone on day 1 and day 8 of cycles 3 through 6.

Patients in the control arm received rituximab as directed by the rituximab label for indolent NHL, administered as 4 once-weekly infusions on days 1, 8, and 15 of cycle 1 and day 1 of cycle 2 (day 22). Patients could discontinue treatment for progressive disease, toxicity, protocol noncompliance, patient request, physician's decision, or administrative reasons.

Patients were treated for up to six 21-day cycles or until treatment was discontinued due to progressive disease, toxicity, protocol noncompliance, patient request, physician's decision, or administrative reasons.

A total of 800 patients (including drop-outs) were planned to be enrolled in this study. The study was closed early due to poor enrolment. All 38 patients who were enrolled were included in the efficacy and safety analyses.

Eligible patients had histologically-confirmed relapsed or refractory CD20+ indolent non-Hodgkin's lymphoma (NHL), were ECOG PS 0 or 1, ⩾18 years of age, and had measurable disease. Patients had to have adequate hematologic, cardiac, renal, and hepatic function at baseline. Patients were not eligible if they were resistant to rituximab or anthracycline during previous treatment cycles, had previous bone marrow or stem cell transplant, had prior treatment with a cumulative dose of doxorubicin equivalent exceeding 450 mg/m^2, or had clinically significant cardiac abnormalities.

Efficacy: Objective tumour assessments were to be made every other cycle and disease response was defined according to International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphomas. The objective tumour response (CR or PR) was to be confirmed in 2 consecutive instances performed not less than 1 month apart. Time to tumour progression was defined as the time from date of randomization to date of first objective disease progression or the last date the patient was assessed and found to be progression free. Objective tumour assessments were evaluated by the reporting investigator. Post hoc sponsor medical monitor review of the investigator reported efficacy was also performed to ensure uniform application of protocol definitions of confirmed response between investigative sites. No blind independent panel assessments were performed.

Safety: Adverse events were assessed throughout the study and graded according to NCICTC, v. 2 criteria. Safety parameters included laboratory evaluations including haematology, blood chemistry, urinalysis, and LVEF measured by MUGA. In addition, patients were followed for toxicity for 30 days following the off-treatment visit (approximately 127 days from the first infusion of study medication) or until recovery of abnormal results to baseline values. Toxicity assessment included clinically relevant laboratory and LVEF abnormalities. Cardiac safety was assessed with particular attention as all cardiac adverse events even those felt to be unrelated to study drug were reported in a similar time frame of a serious adverse event.

Patients were randomly assigned to receive pixantrone + rituximab or rituximab alone. Randomization was stratified at baseline by:

- International Prognostic Index (IPI) Score
- Number of prior episodes of disease progression
- Prior anti CD20 regimen

The efficacy analyses were based on the ITT population. TTP was the primary efficacy endpoint. The comparison of TTP between treatment groups was made using K-M survival curves and the log-rank test statistic.

ORR and CR were computed for both treatment groups. Safety variables (including toxicity assessments,

adverse events, laboratory values, and physical examination results) were summarized by descriptive statistics for patients who received any study treatments.

All 38 patients who were enrolled received study treatment, 20 in the experimental arm and 18 in the control arm. The treatment groups were generally well balanced in terms of baseline characteristics. The patients receiving pixantrone + rituximab were somewhat older (this is also reflected in the IPI scores, where age is one factor). The median age of the subjects in the experimental arm was 67.0 years (range 52.0-77.0), while in the control arm it was 58.5 (45.0-74.0). The comparator arm was predominately male (72%), whereas there was an equal number of males and females in the pixantrone arm. There were slightly more patients with high baseline IPI scores (>2) in the pixantrone arm (30%) than in the comparator arm (11%).

Estimated median TTP was 150 days longer in the experimental arm (395 vs. 245 days, p <0.001). Kaplan-Meier survival curve analysis predicted that 100% of patients treated with rituximab alone would have progressed within one year of treatment. By contrast, patients in the experimental arm had an estimated 32% probability of disease progression after 1 year (p < 0.001) and 55% at 2 years (p = 0.002).

Table 47: Efficacy results in AZA302

Statistics	Pixantrone + Rituximab	Rituximab	P-value*
N	20	18	
Number of documented events	6	10	
12 months progression rate (95% C.I.)	32% (5% , 59%)	100% (100%, 100%)	< 0.001
24 months progression rate (95% C.I.)	55% (25% , 86%)	100% (100%, 100%)	0.002
Median time to progression in days (95% C.I.)	395 (289 , NE)	245 (123 , 247)	
Log-rank test p-value		< 0.001	
Hazard ratio (95% C.I.)		0.14 (0.04 , 0.52)	

NE = Not estimable.
Hazard Ratio (Pixantrone + rituximab to rituximab) was estimated by Cox regression with treatment arm as a single covariate.
* P-value based on normal approximation.

The overall response rate assessed by the primary investigator was 75% in the experimental arm vs. 33% in the control arm (CR, CRu and PR; p = 0.038). Post hoc sponsor medical review of efficacy recorded similar results: experimental group ORR (65%) vs. control group ORR (33%) [p = 0.1013]. Four of 6 patients with a baseline IPI score of 3 or 4 achieved PR in the experimental arm. The two patients with IPI score 3 or 4 in the control arm failed to respond to treatment.

The only severe toxicity was neutropenia (12 grade 3/4 adverse events of neutropenia were reported in the experimental arm vs. 0 in the control arm). Cytopenias, GI symptoms, fatigue, alopecia, and LVEF declines of $\geqslant$ 10% were reported more commonly in the pixantrone and rituximab treatment group. Five patients in the experimental arm reported a decrease in LVEF $\geqslant$ 10% from baseline, compared to one patient treated with single agent rituximab. All reports of decreased LVEF were grades 1 or 2, were generally asymptomatic and most often returned toward baseline with continued dosing. Transient subacute congestive heart failure developed in a 70 year old male 5 days after receiving his first dose of pixantrone. The CHF resolved and the investigator attributed the CHF to underlying NHL. Following resolution of the CHF no additional cardiovascular adverse events were reported with continued dosing of pixantrone (six cycles) in this patient. Adverse events leading to premature discontinuation of study medication were seen only in the experimental arm (6 patients).

Two patients discontinued for severe neutropenia, 1 for febrile neutropenia, 1 for nausea (grade 2, with simultaneous grade 1 headache and dyspnoea), 1 for decreased LVEF (grade 2), and 1 for hepatitis (grade 2). The patient with decreased LVEF was asymptomatic and discontinuation was required per protocol (decline in LVEF $\geqslant$ grade 2). The patient with discontinuation attributed to hepatitis recorded no clinically significant abnormal liver function tests in available routine study chemistries. Four patients in the pixantrone group and 5 patients in the rituximab only group experienced

Serious Adverse Events; one of these (febrile neutropenia) in the experimental arm led to discontinuation. SAEs in the experimental arm were febrile neutropenia, thrombosis, abdominal distension, exertional dyspnea, peripheral oedema, neutropenia, and subacute cardiac failure (discussed above). In the control group, SAEs included headache, pyrexia/leukopenia, limb and neck pain, rigors with hypotension following initial dose of rituximab, infection following dog bite, LVEF decrease, and incidental anaplastic carcinoma (primary site unknown).

comment

The population recruited into study AZA302 consisted of relapsed follicular lymphoma patients. The prognosis and estimated treatment efficacy in second line is much higher compared to patients with relapsed, more aggressive lymphoma, DLBCL.

In this study, pixantrone + rituximab performed better than rituximab alone, which is hardly surprising.

It is difficult to draw any other conclusions from this very small study (38 patients) with different patient population than in studies PIX301 and PIX306.

5.4. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, new data regarding SOBs have emerged. The new data emerged data are compliant in terms of acceptability of data submitted.

6. Additional scientific data provided relevant for the assessment of the benefit / risk balance

6.1. Quality

From the last renewal to date, the following changes have been approved: change of specification for the Drug Product, and change in the specification parameters of the immediate packaging of the finished product (Deletion of the statement “treated with sulfate or equivalent”).

These quality changes do not impact the benefit/risk ratio of the product.

6.2. Non-clinical

No new data or updates have been submitted since the previous annual renewal.

6.3. Clinical pharmacology

The PK analysis in the sub-study of PIX306 is acceptable if the sponsor is able to demonstrate that the PK samples are stable over the storage period of 576 days. Overall, the probability of an interaction potential is low because according to *in vitro* investigations, pixantrone is primarily metabolised by N-acetyltransferase. Thus,

the potential of the monoclonal antibody rituximab to affect pixantrone PK is considered low.

The agreement between the simulated data from a previously developed population PK model and the newly observed concentrations was summarized. Overall, there was no visible difference between the concentrations observed in PIX306 study, and the simulations from the earlier developed population PK model; this indicated that pixantrone time-concentration data in patients receiving rituximab was not substantially different from the overall patient population characterised earlier and represented here by the population PK model. The comparison was visual, and the MAH was requested to provide more rigorous statistical tests to assess the lack of rituximab effect on PK of pixantrone. The MAH provided the requested statistical tests and no effect of rituximab on PK of pixantrone could be seen.

6.4. Clinical efficacy

No additional data have been made available/submitted since the previous annual renewal.

6.5. Clinical safety

Pixantrone is marketed in 25 countries during the review period, including Austria, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Norway, Poland, Slovakia, Slovenia, Spain, Sweden, United Kingdom and Israel.

The PDCO discussed the PIP modification request on 28 May 2018. Based on the high cure rate of disease with first line treatment, the modest activity of pixantrone in paediatric preclinical models, the high competitive environment with novel innovative drugs leading to feasibility challenges and the long-term cardiotoxicity of pixantrone, PDCO was on favour of granting a waiver for pixantrone for treatment of non-Hodgkin lymphoma. In second discussion, based on the review of the rationale submitted by the application for modifying the agreed paediatric investigation plan, the PDCO considered that the proposed changes could be accepted. The PDCO therefore adopted a favourable Opinion on the modification of the agreed PIP as set in the Agency's latest decision (P/0310/2016 of 4 November 2016) and on the granting of a product-specific waiver. The new PDCO Opinion on the modified agreed PIP supersedes the previous PDCO Opinion.

There have been no actions taken for safety reasons in this renewal period.

The SmPC dated 23 August 2018 is the RSI. The list of adverse events in the SmPc (section 4.8) was amended to identify 'Sepsis" as a commonly occurring event and "Hepatotoxicity" as uncommon occurring event. The RSI in the IB already notes Sepsis and Hepatotoxicity, hence no updates to the IB were warranted at this time.

The Investigational Brochure (IB) Version 18 and 19 were approved on 23 Feb 2018 and 13 Apr 2018, respectively. Administrative changes were made to the RSI per requests from Belgium (FAMHPS) regarding their recently issued guidance, Clinical Trial Facilitation Group (CTFG) Question and Answer Document – Reference Safety Information.

The MAH states that surveillance of adverse event data across commercial, medical information, product quality complaints, clinical and literature sources warrants no modification to the pixantrone risk assessment.

<u>Estimated exposure and use patterns</u>

Clinical trial exposure

Table 48 Cumulative subject exposure from completed controlled and uncontrolled pixantrone clinical studies*

Treatment	Number of subjects
PIX	560
Comparators	297
Total	857
*Includes patients as of August 31, 2018 Does not include patients treated under Investigator Sponsored Trials or Non-Interventional Studies	

Table 49 Cumulative and interval period of new patient starts from commercial, named patient program, non-interventional studies, registry, investigator sponsored trials, donation program and clinical studies

Source	Cumulative no of patients	Interval no of patients
Ongoing Data		
Commercial exposure	2479[a]	480
Donation program organized in Croatia	718	62
Donation program organized in Bulgaria		
Pixantrone completed clinical studies		
Mark study (IST)		
GOAL study (IST)		
PREBEN study (IST)		
PIVeR (IST)		
SOHAL study		
Total	**3197**	**542**
Completed Data		
Donation program organized in Estonia		
Medical need program in Belgium		
Named patient study organized in Israel		
Named patient study organized in Turkey		
Non-interventional study		
P14003 study (IST)		
Total	**120**	**6**

[a] *Commercial exposure includes the patients from market research program (DES95001058) [16 patients] and PIXA registry in Spain [79 patients]*

Marketing exposure

Cumulative and interval exposure is difficult to ascertain as the Marketing Authorization Holder (MAH) has little visibility into product utilization from the wholesaler or customer (e.g. Hospital or Pharmacy) given the indication for use and prescribed dosing regimen. CTI is informed indirectly of patient utilization only as a result of requests to refill orders; however, this data does not represent a direct correlation to single patient use. Commercial exposure has been estimated based on 1) historical data that describes the average patient

receiving 2 cycles of pixantrone; 2) Body Surface Area (BSA) calculations outlined in the SmPC for an average weight patient which estimate the number of vials/units used per infusion as 3; and 3) the assumption that one cycle (with 3 recommended infusions) requires between 9 and 12 units/vials per patient as a total of 59507 units of product.

Safety data

There was a total of 4 cases reported during the review period associated with cardiotoxicity which were assessed as serious and related to pixantrone across all sources; one report of tachycardia (grade 3); one report of cardiotoxicity (grade unknown), one report of cardiac failure (grade unknown) and one report of cytotoxic cardiomyopathy (grade 2). None of these cases represent an unforeseen risk nor occurred at an increased frequency or severity observed for this identified risk during the review period.

During the review period, 67 serious myelotoxic events considered related to pixantrone originating from across all sources and included events of anaemia, bicytopenia, febrile neutropenia, granulocytopenia, pancytopenia and haematoxicity originating from clinical and post marketing environment. The patients for whom these events were reported often times had myelosuppressive risk factors which might have played a key role in the events. Myelotoxicity is an expected side-effect of cytotoxic therapy. The key toxicities with pixantrone are associated with falls in white cell counts, particularly neutrophils and lymphocytes as well as falls in platelet counts and the reported cases during this review period are consistent with very commonly occurring events as per the SmPC.

Two unrelated SAEs of disease progression were reported which led to a fatal outcome. Given that Pixuvri is indicated for patients with relapsed, refractory NHL who have failed multiple lines of treatment, expected clinical outcomes include progressive disease and death. These types of events will still be monitored for increased frequency or change in pattern. Precluding increased frequency of this event type, progressive disease will be described only within the aggregated reports.

No reports of tumour lysis syndrome were received during the review period. One new case of acute myeloid leukaemia (grade 5) was received and a follow-up for cases and was also received adding information on prior NHL therapy and disease course and update to the verbatim term from leukaemia monocytic (grade 4) to acute myelomonocytic leukaemia (grade 4).

Sixteen cases were reported where in pixantrone was used in an off- label condition. Of these cases, events associate with off label usage included neutropenia (grade 4), pyrexia (grade unknown), febrile neutropenia (grade unknown), sepsis (grade unknown), thrombocytopenia (grade unknown), febrile neutropenia (grade unknown), diarrhoea (grade unknown); drug ineffective (grade unknown) was reported in two patients. Given the limited information available from the cases, notably related to current disease status, prior medical history and concomitant conditions, it is difficult to assess whether or not pixantrone was causally related to these events.

Other reported toxicities, including infections (pneumonia, bronchitis, cytomegalovirus infection and urinary tract infection), gastrointestinal events (rectal haemorrhage, stomatitis), respiratory events (atelectasis, pulmonary thrombosis and pneumonia aspiration) and general physical health deterioration (grade 4) while often serious varied in nature and were without any pattern or trend.

Safety continues to be monitored in elderly patients exposed to pixantrone. As of the data cut off, approximately 407 patients aged 65 years and above have been treated with pixantrone since the DIBD. Of these 407 patients, 160 originated from completed studies, approximately 247 from the PIX306 study. After further review of the

events experienced by the patients there is no pattern or trend in the cases suggesting any greater risks for any adverse event in this population.

In all, as of 31 August 2018, at least 724 patients have received Pixuvri alone or in combination with other agents in clinical trials, and 2479 patients are estimated to have been treated, mainly in Europe, since the first marketing authorisation in May 2012. A review of the adverse event profile for the compound, from data originating from the PIX306 clinical trial, post marketing sources, named patient programs, non-interventional studies and market research programs and donation programs has identified no new and/or unforeseen risks associated with pixantrone exposure.

Since the last annual reassessment, safety data from ongoing trials and post-marketing sources has been assessed in PSUR procedure EMEA/H/C/PSUSA/00009261/201805 (PSUR #12). Much of the data presented in this annual reassessment overlaps with that in the recent PSUR procedure(s).

PRAC is aware of more than anticipated cases of dose skipping due to adverse reactions associated to pixantrone treatment in the PIX Real study, which was terminated early in Feb 2016. It remains currently unknown whether the dose skipping due to adverse effects has influence on the efficacy of the product, and thus indicates dissimilar B/R profile compared to one expected based on the original pivotal clinical trial. The issue has been further elaborated in the PSUSA procedure, but at the time of finalisation of the PSUSA procedure in Dec 2018 PRAC meeting, there were still open questions. PRAC therefore considers that it is necessary to further explore this issue within a LEG procedure. In the LEG procedure initiated, the MAH should provide:

- For all phase III trials (including PIX306): number and proportion of patients with a) dose lowering (*i.e.*, dose given on schedule at a lower amount), b) dose omission/skipping. Reason for dose lowering/omission for each one of these patients (*i.e.*, toxicity/ADR or any other reason). Provide all relevant CIOMS forms, and provide an explanation for any instances where the reason for dose reduction is not known.
- For PIXreal: number and proportion of patients with a) dose lowering, b) dose omission/skipping. Reason for dose lowering/omission for each one of these patients. The MAH is asked to provide CIOMS forms for all patients within the PIXreal study regardless of whether doses were skipped or not), and provide an explanation for any instances where the reason for dose reduction is not known.
- For PIX306, please also provide a discussion of the rate of dose omission and reasons for it. Please also provide a rationale for the differences in dose modification criteria in this study compared to that in the pivotal studies and the SmPC guidance.
- A discussion of any impact of dose lowering, delay, or omission, on the safety or efficacy of pixantrone, in view of the totality of the data. The MAH should discuss whether changes to the product information or any other risk minimisation measures are warranted.

The search criteria and mechanisms used by the MAH to identify all relevant cases should be detailed in the responses.

comment:

It is notified that the above mentioned ongoing LEG procedure concerning more frequent than anticipated dose skipping due to adverse reactions associated to pixantrone treatment in the PIX Real study, and the possible influence on the efficacy of the product, may be seen remotely relevant also for this procedure in which B/R is scrutinized. However, as it is separate parallel ongoing procedure, it is not possible to incorporate any conclusions into this AR yet.

6.6. Pharmacovigilance inspections

A MHRA statutory inspection of the CTI pharmacovigilance system was conducted from October 23-26, 2017 which identified 5 major findings. A follow-up statutory inspection by the ANSM of the CTI pharmacovigilance system was conducted from June 12 – 15, 2018 to confirm CAPA implementation arising from the previous MHRA inspection. It allows further inspection of areas not reviewed during the previous inspection. One major finding specific to CTI practices and procedures in updating the PSMF was identified. The MAH stated that while these observations contributed to improve management of the pharmacovigilance system, neither the root cause analyses nor impact assessments for these findings identified gaps that adversely affected the risk/benefit profile of the compound, nor adversely affected the rights, safety or well-being of patients.

6.7. Discussion

A review of adverse events and other safety information from the ongoing PIX-306 clinical trial and post-marketing sources does not warrant modification to the risk assessment of pixantrone. No major issues have been identified during this review period.

7. Risk management plan

The MAH has submitted an updated RMP within the annual renewal procedure (RMP version 10.1, data lock point 31 August 2018).

Summary of significant changes in the RMP:

- Implementation of the new template (EMA GVP Module V, rev. 2, RMP template)
- Update with post marketing data (DLP 31 August 2018)
- Clinical data from PIX 306 study (specific obligation for condition MA of Pixuvri®)

Safety concerns

The MAH has revised safety specifications according to the guidance of new EMA GVP Module V rev. 2 (28 March 2017, EMA/838713/2011). In RMP revision from version 10 to version 10.1 the MAH suggests shortening of the safety specification to include above mentioned important identified risks. Deletion of all other risks is suggested (See Table 2 below).

Summary of the safety concerns as presented in the RMP version 10.0. Proposed deletions marked with strikethrough and red font.

Summary of the Safety Concerns

Summary of safety concerns (RMP version 10.0)	
Important identified risks	• Cardiotoxicity • Myelotoxicity • ~~Serious infections~~

	• Tumour lysis syndrome • ~~Development of secondary malignancies such as AML and MDS~~
Important potential risks	• ~~Reproductive toxicity (Pregnancy and effect on male fertility)~~ • ~~Photosensitivity~~ • ~~CYP1A2 and CYP2C8 inhibition~~
Missing information	• ~~Safety in children~~ • ~~Safety in people with significant hepatic and renal impairment~~ • ~~Safety in patients with severely abnormal cardiac function~~ • ~~Safety in patients with poor bone marrow reserve~~ • ~~Off-label use~~ • ~~Safety in Elderly patient > 65 years of age~~ • ~~Safety in non-Caucasians~~ • ~~Safety in patient with poor performance status~~ • ~~Safety in patient with prior mediastinal radiotherapy~~

The MAH's proposal for revised Safety Concerns (RMP version 10.1).

Summary of safety concerns	
Important identified risks	• Cardiotoxicity • Myelotoxicity • Tumour lysis syndrome
Important potential risks	• None
Missing information	• None

In general the deletions can be accepted since the safety concerns proposed to be removed are not critical for B/R; are not considered requiring additional RMMs beyond the routine RMMs (mainly SmPC text) and/or no additional PhV activities are indicated.

MAH has provided characterisation of the data and description of routine risk minimisation measures concerning three identified risks in the RMP. Based on the existing data the MAH has not specified any need for additional pharmacovigilance actions or additional risk minimisation measures to further characterise and/or minimise the risks in addition to routine pharmacovigilance.

Important Identified Risks Cardiotoxicity and Myelotoxicity are key risks with potentially critical impact on the benefit/risk. Therefore, they should remain as Important Identified Risks in the RMP at the moment, even if no additional PhV activities or additional RMMs are specified for them.

The MAH was asked to further justify the critical impact of suggested important identified risk Tumour lysis syndrome on risk benefit balance of the product and discuss the potential need of further additional pharmacovigilance activities and/or risk minimisation measures to address uncertainties related to this risk, or alternatively remove Tumour lysis syndrome from the list of important safety concerns.

The MAH responded that Tumour lysis syndrome should be removed from safety specifications, since no additional pharmacovigilance activities or additional risk minimisation measures are considered needed to further characterise or minimise this risk. The MAH will submit an updated RMP at the end of this renewal procedure.

Pharmacovigilance plan

The MAH states that important identified risks are well characterised and therefore, routine pharmacovigilance activities are deemed sufficient. There are no additional pharmacovigilance activities suggested.

In RMP v. 10 four studies were listed in PhV Plan. Three of these studies were paediatric studies that are considered to be part of paediatric investigation plan and may be deleted from the RMP in the update of RMP according to the guidance of new EMA GVP Module V rev. 2 (28 March 2017, EMA/838713/2011).

In more details, in the previous RMP version (version 10.0) the following on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan were listed; proposed deletions marked with strikethrough and red font:

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
~~PIX306~~ ~~A Randomized Multicenter Study Comparing Pixantrone + Rituximab with Gemcitabine + Rituximab in Patients with Aggressive B-cell Non-Hodgkin Lymphoma Who Have Relapsed after Therapy with CHOP-R or an Equivalent Regimen and are Ineligible~~	~~Primary~~ ~~To evaluate the efficacy (as measured by progression-free survival of pixantrone plus rituximab compared to gemcitabine plus rituximab in patients with relapsed or refractory DLBCL or DLBCL transformed from follicular lymphoma who have received 1-3 prior lines of therapy for aggressive NHL, including CHOP-R or an equivalen regimen, and are not currently eligible for high-dose (myeloablative) chemotherapy and stem cell transplant Secondary To compare the two treatment arms with regard to the following secondary endpoints:~~ ~~• Overall survival~~ ~~• Overall response rate~~ ~~• Complete response rate~~ ~~• Safety~~	~~Cardiotoxicity~~ ~~Myelosuppression~~ ~~Serious Infection~~ ~~Tumour lysis syndrome (TLS)~~ ~~Development of secondary malignancies such as acute myeloid leukaemia or myelodysplastic syndrome (MDS)~~	~~Ongoing~~	~~Study Finish - May 2018~~ ~~Final Report - December 2018~~
~~PIX111~~ ~~A Phase 1, Dose- Escalation~~	~~To assess activity measured by objective response~~	~~Cardiotoxicity~~ ~~Safety in children~~	~~Planned~~	~~Study Finish - December 2022~~

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
~~Study of Pixantrone Monotherapy in Pediatric Patients with Relapsed or Refractory Cancer~~	• ~~To determine the tolerability of pixantrone when substituted for an anthracycline in a standard combination chemotherapy regimen~~ • ~~To assess cardiac toxicity as measured by change in LVEF and biological markers (e.g., troponin)~~			
~~PIX311 An, randomised, activecontrolled, multi-centre trial to evaluate safety and efficacy of pixantrone in children from 5 years to less than 18 years with newly diagnosed non- Hodgkin lymphoma including lymphoblastic lymphoma, Burkitt lymphoma and diffuse large B-cell lymphoma~~	• ~~To assess the efficacy (as measured by Overall Response Rate [ORR]) of pixantrone when substituted for an anthracycline in a standard front line combination chemotherapy regimen.~~ • ~~To evaluate cardiac toxicity measured by change in LVEF and biological markers (e.g., troponin).~~ • ~~To determine the tolerability of pixantrone when substituted for an anthracycline in a standard combination chemotherapy regimen~~ • ~~To assess PFS and OS~~	~~Cardiotoxicity Safety in children~~	~~Planned~~	~~Study Finish – May 2026~~

In the current proposal (RMP version 10.1) no on-going or planned additional PhV studies/activities in the Pharmacovigilance Plan were proposed:

Table 3 On-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
Not Applicable				

Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

PIX306 study was included in the post-authorisation pharmacovigilance development plan in the previous version of RMP (v. 10). PIX306 study is specific obligation in context of a conditional marketing authorisation and the study has been recently completed. The final study report has been submitted as part of the annual renewal application. The MAH has replaced the PIX306 study into the post-authorisation efficacy development plan, including planned and ongoing post-authorisation efficacy studies in the revised RMP, since primary objective of this study is to evaluate the efficacy.

The following table has been included in the RMP under part IV Plans for Post-Authorisation Efficacy Studies

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
PIX306 A Randomized Multicenter Study Comparing Pixantrone + Rituximab with Gemcitabine + Rituximab in Patients with Aggressive B-cell Non-Hodgkin Lymphoma Who Have Relapsed after Therapy with CHOP-R or an Equivalent Regimen and are Ineligible for Stem Cell Transplant Under evaluation	**Primary** To evaluate the efficacy (as measured by progression-free survival of pixantrone plus rituximab compared to gemcitabine plus rituximab in patients with relapsed or refractory DLBCL or DLBCL transformed from follicular lymphoma who have received 1-3 prior lines of therapy for aggressive NHL, including CHOP-R or an equivalent regimen, and are not currently eligible for high-dose (myeloablative) chemotherapy and stem cell transplant **Secondary** To compare the two treatment arms with regard to the following secondary endpoints: Overall survival Overall response rate Complete response rate Safety	Based on the randomized controlled study presented in patients with multiply relapsed or refractory aggressive NHL (study PIX 301), the superiority of pixantrone was demonstrated compared to single chemotherapy agent with an increase in the response rate (20% versus 5.7%; p=0.02), an increase in median PFS (HR=0.60, 95% CI, 0.42 to 0.86, p=0.005) and a trend in longer overall survival (median 10.2 months versus 7.6 months; HR 0.79, 95% CI 0.53, 1.18, p=0.25) The benefit risk balance of pixantrone in patients with multiply relapsed or refractory aggressive NHL is therefore considered to be positive. From a quantitative point, of view, the benefit in the subgroup of patients previously treated with rituximab might be less as compared with what was observed in patients that had not received prior rituximab treatment. However, the efficacy of pixantrone in patients that had received prior rituximab therapy and up to 3 prior regimens was still superior to the comparator. In Europe most patients that had multiple relapse or are refractory to treatments are expected to have received prior rituximab. Therefore there is a need to further confirm the efficacy of pixatnrone in patients previously treated with rituximab.	Final report	December 2018 (submitted in November 2018 within the annual renewal procedure)

In conclusion:

- Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.
- Routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Routine risk minimisation activities are considered sufficient to manage the safety concerns of the medicinal product. No additional risk minimisation measures have been proposed.

Summary table of Risk Minimisation Measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Cardiotoxicity	Routine risk minimisation measures: SmPC section 4.2, 4.4, 4.8 SmPC section 4.2, PL section 2, 4. Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Myelotoxicity	Routine risk minimisation measures: SmPC section 4.2, 4.3, 4.4 , 4.8 PL section 2 , 4 Legal status: Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Tumour lysis syndrome	Routine risk minimisation measures: SmPC section 4.4 Legal status: Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

Elements for a public summary of the RMP

The elements for a public summary of the RMP require revision following the removal of Tumour lysis syndrome from safety specification. The MAH will submit updated RMP at the end of this renewal procedure.

Annexes

The RMP annexes have been updated appropriately.

7.1. Overall conclusion on the RMP

The RMP version 11, submitted in conclusion of this renewal procedure, is acceptable.

8. Changes to the Product Information

Changes to the Product Information (PI), based on the submitted data within the scope of this procedure, are introduced during the assessment of this renewal.

The final PI proposal is acceptable to the CHMP.

Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Pixuvri (pixantrone) is removed from the additional monitoring list as the condition(s) to the marketing authorisation have been fulfilled.

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.