# Single technology appraisal (STA)

# Specification for manufacturer/sponsor submission of evidence for pixantrone for the treatment of adults with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma [ID414]

**28 November 2012**

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# Executive summary

Non-Hodgkin lymphoma (NHL) is a cancer of the lymphoid tissue, the most common form being diffuse large B-cell lymphoma (DLBCL). In the UK approximately 12,000 patients a year are diagnosed with NHL, with a 5 year survival of approximately 60%. Upon diagnosis, patients receive standard chemotherapy of rituximab + CHOP (R-CHOP), which results in the majority of patients achieving remission. Should patients relapse, they will be offered a stem cell transplant, or a variety of established second line chemotherapy combinations, including ESHAP, ICE, and DHAP (all administered with or without rituximab). Should patients relapse following second line therapies however, they have a poor prognosis with expected survival of less than one year and limited treatment options – a variety of off-label treatments are used, but without strong evidence for their efficacy.

Pixantrone is a novel aza-anthracenedione specifically designed to reduce cardiac toxicity without compromising anti-tumour activity. It is also the only salvage therapy to be licensed for the treatment of patients with multiply relapsed or refractory aggressive B-cell NHL in whom there is no standard of care, and no licensed therapies. Pixantrone was evaluated in the only randomised study with an active control conducted in this patient population. This trial population is representative of the target population.

The evidence supporting the licensing of pixantrone is taken from study PIX301. As no standard of care exists in these patients, and there is debate amongst clinicians on which off label therapy is the most effective, a trial was conducted in 140 patients against 'physicians choice', a choice of 7 chemotherapy agents often used in this area. In PIX301, pixantrone showed a significant increase in median progression free survival (PFS) of 2.7 months (5.3 vs. 2.6), and an increase in median overall survival of 2.6 months (10.2 vs. 7.6), despite this being an active comparator trial (not placebo controlled). In the trial, adverse event rates were low, and an additional study (PIX203) provides supporting evidence on cardiotoxicity. Pixantrone has a lower cardiotoxic potential than equipotent doses of doxorubicin. The mean cumulative doxorubicin-equivalent dose in the PIX301 study reached 527 mg/m$^2$ at the end of the study. No patient treated with pixantrone developed congestive heart failure that is typical for anthracyclines, and no grade IV declines in LVEF were observed.

In order to demonstrate the economic benefits of pixantrone, a semi-Markov model was built, using data from the PIX-301 study. Patients started in a pre-progression state, before experiencing progression and death. The base case presented is for the aggressive B-cell NHL population, as this most closely resembles the licenced indication of pixantrone; results for the ITT and DLBCL are also presented. Extrapolating the outcomes from the clinical trial, pixantrone is expected to provide an additional 8.52 months of survival (29.04 vs. 20.52) and a QALY gain of 0.62 (1.75 vs 1.13) at a cost of £17,638 (£86,288 vs. £68,650), resulting in an

ICER of £28,423 per QALY gained. Sensitivity analyses demonstrated the model was most sensitive to the methods of extrapolation, patient weight, and utilities used.

Pixantrone offers an unprecedented level of evidence in late line disease area (where other companies frequently conduct single arm uncontrolled studies, or placebo controls), and provides a cost-effective option, for patients who currently have a high level of unmet need, and no standard of care. Based on the eligible patient population of approximately 1,650 per year, the budget impact of pixantrone is estimated to be £955,583 in year 1, rising to £4,218,973 in year 5.

Pixantrone fulfils the criteria for end of life medicines as it is indicated for patients with life expectancy less than 24 months (relapsed or refractory aggressive B-cell non-Hodgkin lymphoma patient have less than 1-year expected survival), extended life by more that 3 months (mean additional OS estimated to be 8.42 months) in a small patient population estimated to be 1,650 whom have no licenced treatment option. We ask therefore that the innovation provided by pixantrone be recognised by approving the drug as an end of life medicine.

**Table 1: Base-case cost-effectiveness results**

| | **Pixantrone** | **Comparator arm** |
|---|---|---|
| Technology acquisition cost | £16,793 | £1,175 |
| Other costs | £69,494 | £67,474 |
| Total costs | £86,288 | £68,650 |
| Difference in total costs | N/A | £17,638 |
| LYG | 2.42 | 1.71 |
| LYG difference | N/A | 0.71 |
| QALYs | 1.75 | 1.13 |
| QALY difference | N/A | 0.62 |
| ICER | N/A | £28,423 |

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

**Table 2: ITT subgroup cost-effectiveness results**

| | Pixantrone | Comparator arm |
|---|---|---|
| Technology acquisition cost | £15,219 | £1,137 |
| Other costs | £61,723 | £55,996 |
| Total costs | £76,942 | £57,132 |
| Difference in total costs | N/A | £19,809 |
| LYG | 2.03 | 1.47 |
| LYG difference | N/A | 0.56 |
| QALYs | 1.45 | 0.99 |
| QALY difference | N/A | 0.46 |
| ICER | N/A | £43,102 |

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

**Table 3: DLBCL subgroup cost-effectiveness results**

| | Pixantrone | Comparator arm |
|---|---|---|
| Technology acquisition cost | £14,186 | £1,072 |
| Other costs | £48,608 | £51,882 |
| Total costs | £62,794 | £52,953 |
| Difference in total costs | N/A | £9,841 |
| LYG | 1.70 | 1.26 |
| LYG difference | N/A | 0.44 |
| QALYs | 1.25 | 0.83 |
| QALY difference | N/A | 0.42 |
| ICER | N/A | £23,699 |

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

# Section A – Decision problem

## 1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand Name: PIXUVRI

Generic Name: Pixantrone

Therapeutic class: Aza-anthracenedione

1.2 What is the principal mechanism of action of the technology?

Pixantrone is a novel aza-anthracenedione related to anthracyclines and anthracenediones such as doxorubicin and mitoxantrone. The antineoplastic activity of these drugs is linked to the inhibition of topoisomerase II and DNA intercalation. In contrast to other agents in this class, Pixantrone has shown significant activity as an alkylating agent. Although anthracyclines are effective for use in the treatment of lymphoma and other cancers, they can cause cumulative heart damage that may result in congestive cardiac failure (CCF) many years post-treatment. Pixantrone was rationally designed to improve the efficacy and reduce the toxicity associated with anthracyclines and anthracenediones by reducing the potential for the formation of oxygen-free radicals and toxic drug–metal complexes. Furthermore, unlike other anthracycline and anthracycline-like agents, Pixantrone is not associated with alcohol metabolite production which may lead to long-term cardiotoxicity.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Pixantrone was granted Market Authorisation by the European Medicine Agency (EMA) in May 2012.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The CHMP considered that the risk-benefit balance of pixantrone in the indication 'the treatment of adult patients with multiply relapsed or refractory aggressive 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' was favourable[1]. Given the lack of standard of care and the poor prognosis for patients with multiple relapses or refractory aggressive NHL, the improvement in complete response/unconfirmed complete response (CR/CRu) supported by the results of the secondary endpoints of progression-free survival (PFS) and overall survival (OS) noted in the pivotal Phase III pixantrone trial, PIX301[2], was considered meaningful and to outweigh the risks of treatment. The CHMP concluded that pixantrone fulfils an unmet medical need.

The CHMP has granted pixantrone a conditional marketing authorisation. It determined that the benefits to public health of the immediate availability on the market of pixantrone outweighed any risk inherent in the fact that additional data are still required. It also agreed that the Risk Management Plan (RMP) for pixantrone in the approved indication was adequate to address any unidentified and unknown risks.

Details of the conditions and requirements of the marketing authorisation are specified below:

*Pharmacovigilance requirements*

The CHMP required a system of pharmacovigilance to be in place and functioning before and whilst the product is on the market. In addition to 'routine' pharmacovigilance, a non-clinical in vivo phototoxicity study is to be conducted as part of the RMP to determine the clinical risk of a positive non-clinical phototoxicity assay. No additional risk minimization activities were required by the CHMP. The CHMP agreed that the RMP presented for pixantrone in the approved indication was adequate to address any identified and unknown risks.

*Specific Obligation to complete post-authorisation measures*

In the PIX301 Phase III pivotal trial, although response rates to pixantrone were superior to comparator irrespective of prior rituximab use, the benefit of pixantrone in patients who had received prior treatment with rituximab was not as favourable as in the patients without prior rituximab. The CHMP felt that additional efficacy data would be needed to confirm the benefit of pixantrone in the subgroup of patients pre-treated with rituximab. A Specific Obligation was required for CTI Life Sciences Ltd (CTI) to conduct a randomised, controlled Phase III study (PIX306) of pixantrone-rituxumab vs. gemcitabine-rituximab in patients with aggressive NHL, who failed front-line CHOP-R who are not eligible for autologous stem cell transplant (ASCT) (second-line) or failed ASCT (third- or fourth-line). This study will support the efficacy of pixantrone in patients who had already received prior rituximab and will include patients with Diffuse Large B-cell Lymphoma (DLBCL) or Follicular grade III Lymphoma (FL) who had previously been treated with at least one rituximab containing multi-agent regimen. The trial is due to complete in June 2015.

**Comments on study design**

*The use of CR/CRu as primary endpoint*

The CHMP stated that although the choice of complete response (CR) as a primary endpoint is not usually considered acceptable for a single Phase III trial and progression-free survival (PFS) and overall survival (OS) would have been more appropriate, this point was not of major concern due to the positive

results of pixantrone on the heavily pre-treated population of the study. The primary endpoint was met in the study, and the CHMP also remarked that PFS showed consistent statistical significance across all analysis. OS was prolonged with pixantrone treatment although no statistical significant difference was observed. Other variables which did not show statistical significance also favoured pixantrone, except for time to response, which was equal in both groups.

*Choice of comparators*

The choice of single arm comparator from a pre-defined list according to physician preference was considered acceptable.

**Additional issues**

The clinical safety profile of pixantrone in the proposed indication was considered acceptable by the CHMP. Use of anthracyclines is known to lead to cardiac damage. Pixantrone was specifically designed to reduce cardiotoxicity associated with anthracyclines, without compromising tumour activity. Therefore, cardiac toxicity was closely monitored in the PIX301 pivotal Phase III study. In this trial, a higher incidence of cardiac events was seen in the pixantrone group (35% vs. 21%). However, only 9 cases of cardiac events were considered related to pixantrone (13%) and all were asymptomatic decreases of LVEF.

Overall events observed were relatively mild and asymptomatic and there were no clear cases of pixantrone-associated chronic heart failure (CHF). There was no demonstrable relationship between cumulative pixantrone dose to symptomatic declines in left ventricular ejection fraction (LVEF) or CHF; nor was a relationship seen with prior doxorubicin equivalent cumulative exposure. This is in marked contrast to anthracyclines, which have limited use in salvage regimens due to causing cumulative, dose-related progressive myocardial damage, leading to an unacceptable incidence of congestive heart failure[3].

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The indication is as follows:

Pixantrone 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 treatment with Pixantrone has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.

Currently, there is a lack of consensus and standard of care for this difficult-to-treat group and pixantrone is the only regulatory approved product (approved by the European Medicines Agency for use in the EU [European Union] in May 2012) for this patient population.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are no on-going studies that will produce additional evidence in the next 12 months. The primary objective of the post-approval commitment study is to evaluate the efficacy (as measured by overall survival) of pixantrone plus rituximab compared to gemcitabine plus 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 stem cell transplant.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The anticipated date of availability in the UK is 6 November 2012.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Pixantrone is available in Germany, Holland, Austria, Denmark, Sweden and Finland.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Pixantrone will be submitted to Scottish Medicines Consortium (SMC) for health technology assessment in January 2013.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

**Table 4: Unit costs of technology being appraised**

| **Pharmaceutical formulation** | Pixantrone |
|---|---|
| **Acquisition cost (excluding VAT)** | £1,660.50/dose (based on an average of 3 vials per dose) |
| **Method of administration** | IV Infusion |
| **Doses** | 50 mg/$m^2$ |
| **Dosing frequency** | Days 1, 8 and 15 of a 28-day cycle for up to 6 cycles |
| **Average length of a course of treatment** | The median length of treatment in the PIX301 pivotal study was 4 cycles |
| **Average cost of a course of treatment** | £19,926.18/cycle (Calculated 4 over cycles) |
| **Anticipated average interval between courses of treatments** | Re-treatment with pixantrone is not anticipated. |
| **Anticipated number of repeat courses of treatments** | Zero |
| **Dose adjustments** | Please see below for guidelines on dose adjustments for pixantrone |
| IV = intravenous | |

Dose modification and the timing of subsequent doses should be determined by clinical judgement depending on the degree and duration of myelosuppression. For subsequent courses, the prior dose can usually be repeated if white blood cell and platelet counts have returned to acceptable levels.

If on Day 1 of any cycle the Absolute Neutrophil Count (ANC) is $<1.0 \times 10^9$/L or platelet count is $<75 \times 10^9$/L it is recommended to delay treatment until ANC recovers to $\geq 1.0 \times 10^9$/L and platelet count to $\geq 75 \times 10^9$L.

Table 5 and Table 6 are recommended as guidelines to dosage adjustments for Days 8 and 15 of the 28-day cycles

**Table 5: Dose modifications for hematologic toxicity on Days 8 and 15 of any cycle**

| Grade | Platelet Count | ANC Count | Dose Modification |
|---|---|---|---|
| 1-2 | LLN – 50 x $10^9$/L | LLN – 1.0 x $10^9$/L | No change in dose or schedule. |
| 3 | <50 – 25 x $10^9$/L | <1.0 – 0.5 x $10^9$/L | Delay treatment until recovery to platelet count ≥50 x $10^9$/L and ANC ≥1.0 x 109/l. |
| 4 | <25 x $10^9$/L | <0.5 x $10^9$/L | Delay treatment until recovery to platelet count ≥50 x 109/l and ANC ≥1.0 x $10^9$/L.<br>Reduce the dose by 20%. |
| LLN: Lower Limit of the Normal range<br>ANC: Absolute Neutrophil Count | | | |

**Table 6: Treatment modifications for non-hematologic toxicities**

| Toxicity | Modification |
|---|---|
| Any Grade 3 or 4 drug-related non cardiac toxicity other than nausea or vomiting | Delay treatment until recovery to Grade 1.<br>Reduce the dose by 20%. |
| Any Grade 3 or 4 NYHA cardiovascular toxicity or persistent LVEF decline to ≥Grade 3 | Delay treatment and monitor until recovery. Consider discontinuation for persistent decline in LVEF of ≥15% of baseline value. |
| NYHA: New York Heart Association LVEF: Left Ventricular Ejection Fraction | |

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests are required for selection and no particular administration requirements are needed save for those for chemotherapy agents.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Cardiac function should be monitored before initiation of treatment with pixantrone and periodically thereafter. Multi gated acquisition (MUGA) scans and echocardiography (ECHO) have been used to monitor cardiac function during clinical trials. If cardiac toxicity is demonstrated during treatment, the risk versus benefit of continued therapy with pixantrone must be evaluated.

*Additional early trial data relating to cardiac function*

Pixantrone was rationally designed to retain the anti-tumour efficacy of anthracyclines while decreasing their potential to cause cardiotoxicity through the formation of free radicals by eliminating interactions with intracellular iron and the ability to form a retained alcohol metabolite responsible analogous to doxorubicin. Preclinical biochemical studies on isolated human myocardial strips verified that this goal was achieved. Studies in naïve and doxorubicin pre-treated mice demonstrated that pixantrone is substantially less cardiotoxic than either doxorubicin or mitoxantrone.

Clinical experience in over 300 patients with relapsed NHL, most of whom with had received approximately 300 mg/m$^2$ of prior doxorubicin, demonstrated that up to six cycles of pixantrone, as a single agent or in combination, could be administered in this setting, with an acceptably low incidence of severe cardiac adverse events and without evidence suggesting cumulative cardiotoxicity. In the PIX203 trial which compared CPOP-R to CHOP-R in high risk patients with newly diagnosed DLBCL, pixantrone patients had significantly lower incidence of troponin T elevations or >15% or >20% reductions in LVEF. No pixantrone treated patient developed chronic heart failure (CHF) versus 6.3% of doxorubicin treated patients.[4] On the basis of these data, CHMP has conditionally approved the use of pixantrone monotherapy in patients with relapsed aggressive NHL who have had up to the recommended lifetime limit of doxorubicin (450 mg/m$^2$ for up to six cycles).

**Table 7: Cardiac events – LVEF decreases from baseline by multi-gated acquisition Scan, development of congestive heart failure and Troponin T grade shifts**

| Parameter | CPOP-R | CHOP-R | P-value |
|---|---|---|---|
| All treated patients with events reported through end of study | N=59 | N=63 | |
| Patients with at least a 10% point drop in LVEF compared to baseline and to less than 50% | 9 (15.3%) | 17 (27.0%) | 0.394 |
| Patients with at least a 15% point drop in LVEF compared to baseline | 10 (16.9%) | 20 (31.7%) | 0.063 |
| Patients with at least a 20% point drop in LVEF compared to baseline | 1 (1.7%) | 11 (17.5%) | 0.004 |
| Patients who developed Grade 3 congestive heart failure during treatment | 0 (0%) | 4 (6.3%) | 0.120 |
| Number of patients with Baseline and End of Treatment Troponin T Results | N=43 | N=46 | |
| Patients with troponin T shifts to a higher toxicity grade from baseline to EOT | 3 (7.0%) | 15 (32.6%) | 0.003 |

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Pixantrone is being assessed for use as a monotherapy.

# 2 Context

| |
|---|
| In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem. |

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Non-Hodgkin lymphomas are a heterogeneous group of diseases originating in various cells within the lymphoid system. The REAL classification of lymphomas, proposed in 1994[5], represents a paradigm in lymphoma classification, consisting of a list of biologic entities defined by clinicopathologic and immunogenetic features. This conceptual grouping classifies NHL into three categories in terms of clinical behaviour (low grade/indolent, intermediate grade/aggressive, or high grade/very aggressive). The World Health Organization (WHO) classification of hematopoietic and lymphoid tumours, published in 2001[6], was a joint project of the Society for Haematopathology and European Association of Hematopathologists, under the auspices of the WHO. This classification includes not only lymphoid neoplasms, but also myeloid, histiocytic and mast cell neoplasms and does not maintain the conceptual grouping. The lymphoma component of the classification is merely an update of the REAL classification. In 2008 the IARC published the 4th Edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues[7]. The areas of modification relate to several discrete topics:

- A greater appreciation of early or in situ lesions that challenge definitions of the earliest steps in neoplastic transformation
- The recognition of age as a defining feature of some diseases, both in young and the elderly
- Further appreciation and recognition of site-specific impact on disease definition

- Recognition of borderline categories, in which current morphological, immunophenotypic, and genetic criteria do not permit sharp delineations into existing disease categories

Based on the recent evolution in classification, including the REAL and WHO classification systems, aggressive NHL was defined as including:

- DLBCL
- Follicular lymphoma grade III
- Mediastinal large B-cell lymphoma
- Anaplastic large cell lymphoma
- Peripheral T-cell lymphoma, not otherwise characterized
- Primary effusion lymphoma (includes previously called immunoblastic lymphoma)
- Transformed indolent lymphoma (areas of follicularity allowed)
- T/null cell, primary systemic type

Patients undergo staging to define prognosis and appropriate therapy. The staging system most often used in adults is the Ann Arbor staging system, which uses roman numerals I through IV. This has been further refined through use of the International Prognostic Index (IPI), which not only uses the Ann Arbor stage, but also includes the number of extranodal sites, age, performance status and lactate dehydrogenase (LDH) levels. IPI scores ≥2 predict a worse prognosis than scores of 0-1, and scores of ≥3 predict a poor outcome even with standard of care therapy.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Based on the incidence data from the EU cancer observatory 2008 we estimate that approximately 5,555 patients in the UK will suffer from aggressive NHL of which 1,830 patients are likely have multiply relapsed aggressive NHL of these we believe approximately up to 30-40% could be potentially eligible for treatment with pixantrone[8].

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Aggressive NHLs are defined as tumours that are likely to cause death in a short period of time if left untreated. Although aggressive NHLs have a cure rate of approximately 50-60%, relapse within the first 2 years following therapy is common[9]. Following relapse in patients with DLBCL, at least 60% of patients remain sensitive to conventional chemotherapy treatment, but less than 10% of patients experience prolonged disease-free survival with second-line treatments[10]. Despite a high response rate to these second-line therapies, studies suggest that as few as 10% of relapsed patients achieve long-term survival with conventional salvage chemotherapy and ASCT with a median survival after relapse of only 4–6 months[10].

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE has issued guidance on the use of:

- Rituximab for the treatment of relapsed or refractory Stage III or IV follicular non-Hodgkin lymphoma (TA137)[11]. CTI regards this guidance as relevant as Stage III and IV follicular lymphoma is regarded as a subgroup of aggressive NHL, and this group is represented in the pivotal PIX301 study.

- Rituximab for the first-line treatment of people with CD20-positive diffuse large-B-cell lymphoma at clinical Stage II, III or

IV as part of the R-CHOP regimen (TA65), however this does not overlap with the proposed indication for pixantrone.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The following flow chart (Figure 1) represents the treatment algorithm for patients with aggressive NHL for which pixantrone is indicated. There are currently no drug therapies licensed for use in this population in the UK. Figure 2 expands on this based on the publication by Friedburg[12].

**Figure 1: Treatment algorithm for aggressive NHL**

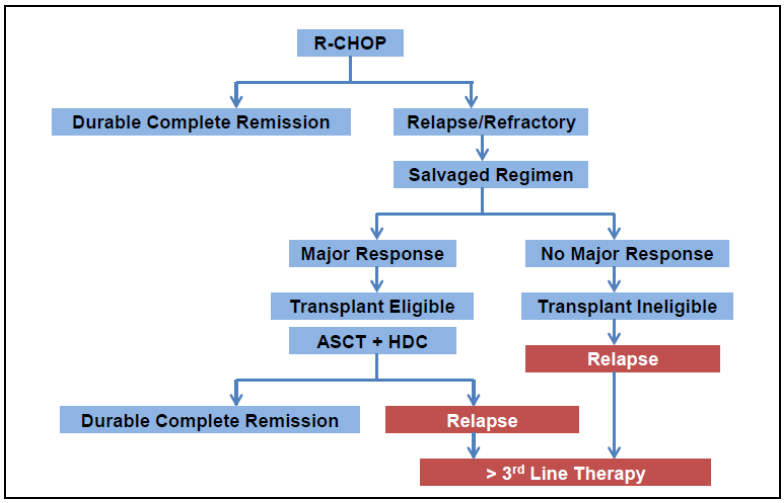
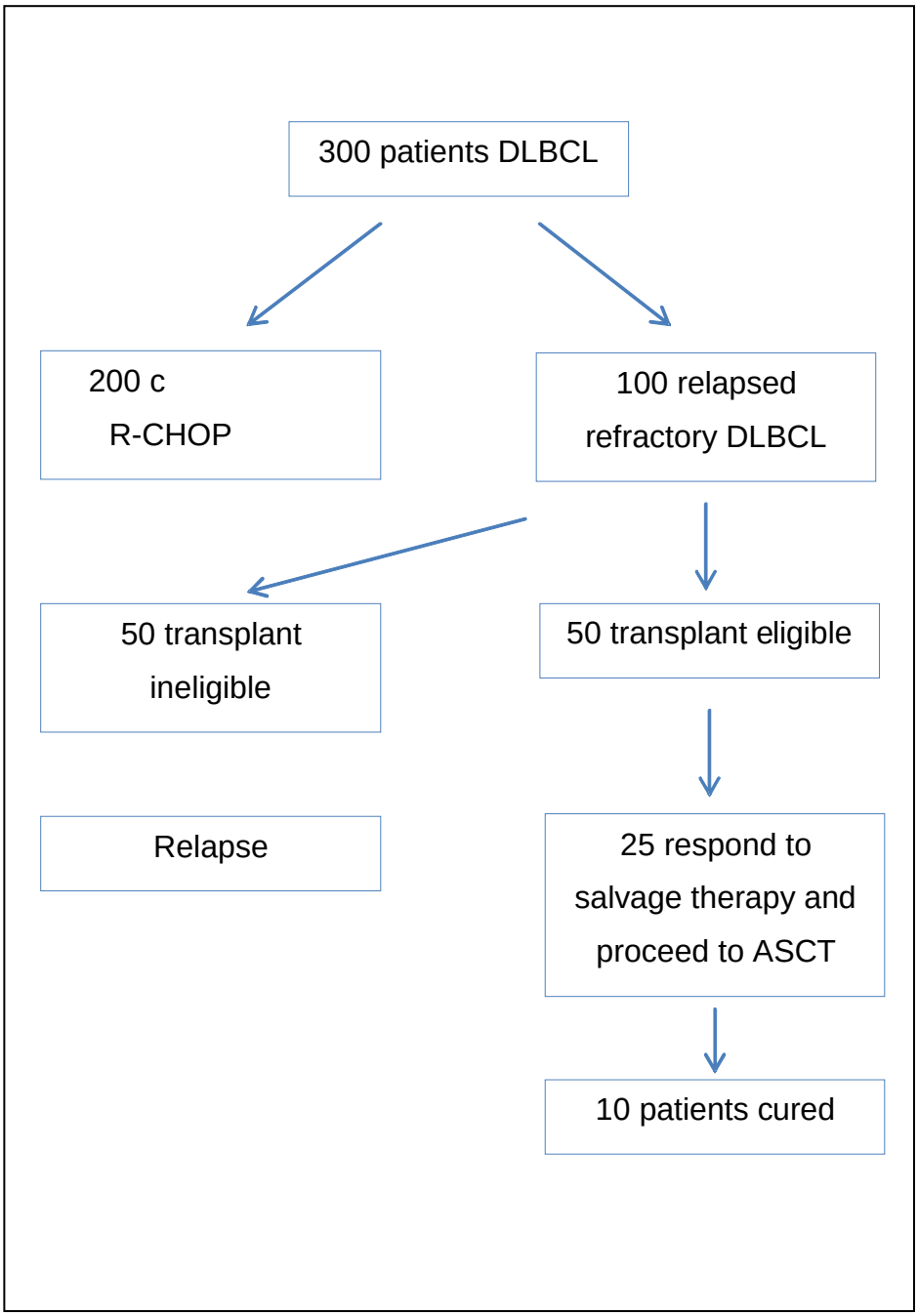


**Figure 2: DLBCL treatment pathway and expected patient flow**




For 300 patients diagnosed with DLBCL, 200 will be cured with up-front therapy. Of the 100 who relapse, at least half are unlikely to be eligible for aggressive approaches due to advanced age, comorbidities, social and access issues, or individual choice. Therefore, only 50 of these patients can be approached with curative intent. Based on the results of CORAL study, because these patients have had previous rituximab exposure, the response rate to salvage therapy is only 51%; therefore, at most, 25 patients will undergo ASCT. The 3-year PFS of those treated with ASCT is 40%, so only 10 patients of the original 300 de novo patients or the 100 relapsed patients are ultimately cured of lymphoma with HD-ASCT.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

There are limited treatment options for patients who relapse following R-CHOP first-line and fail second-line non-anthracycline containing regimens (R-DHAP, R-ICE). There are currently no approved therapies or agents for this population of patients and there is no clear consensus among physicians for how to treat this patient population.

Approximately 50% of patients do not achieve a major response to second-line therapy, and these patients, in addition to those who are ineligible for a stem cell transplant due to age, comorbidity, or inadequate stem cell collections, or who relapse after salvage therapy, have very few treatment options and none are curative[13].

Prior to the approval of pixantrone, no single agent or multi-drug regimen has demonstrated superiority or notable clinical value to another in patients with multiply relapsed or refractory aggressive NHL (see Section 6.1). At the present time, there is no clear consensus among physicians on how to treat these patients.

Market research conducted by CTI in 2012 in a group of 251 haemato-oncologists and oncologists in five EU countries demonstrated a wide variation in clinical practice. More than nine different regimens may be employed in the third- and fourth-line setting, see Table 8. Furthermore, some patients will not receive any active treatment; this may, in part, be due to the lack of effective therapies[13].

**Table 8: Current treatment approaches for aggressive B-cell lymphoma[13]**

| Regimen | Country |
|---|---|
| Bendamustine with or without rituximab | France, Germany, Italy, Spain, UK |
| Fludarabine + cyclophosphamide with or without rituximab | France, Germany, Italy, Spain, UK |
| Bortezomib with or without rituximab | France, Germany, Italy, Spain, UK |
| DHAP with or without rituximab | France, Germany, Italy, Spain, UK |
| ICE with or without rituximab | France, Germany, Italy, Spain, UK |
| CHOP with or without rituximab | France, Germany, Italy, Spain, UK |
| ESHAP with or without rituximab | France, Germany, Italy, Spain, UK |
| EPOCH with or without rituximab | France, Italy, Spain |
| HyperCVAD with or without rituximab | France, Italy, Spain |
| Other chemotherapy regimens, palliative care, or other modality treatment | France, Germany, Italy, Spain, UK |

Currently, treatment choice is based on physician preference and is determined by their clinical experience and evaluation of the limited available data. Choice among regimens is largely based upon side-effect profiles and clinical experience. Many agents that are used off-label demonstrate limited efficacy in this heavily pre-treated group. In addition they may be associated with toxicities, particularly when used as part of a multi-drug regimen[13].

2.7 Please identify the main comparator(s) and justify their selection.

No other agents are specifically licensed for treating multiply relapsed or refractory aggressive NHL. In the pivotal Phase III study PIX301, 7 single agent comparator agents were available in the control arm. This allowed physicians the flexibility to select the agent to which they felt the patient would be most likely to respond taking into consideration prior treatment regimes. All

comparator agents are among classes of agents known to have activity in aggressive NHL;

- Oxaliplatin, ifosfamide, vinorelbine, etoposide, mitoxantrone, gemcitabine and rituximab

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Granulocyte colony-stimulating factor (G-CSF) agents e.g. filgrastim may be required to manage haematologic toxicities associated with pixantrone use.

Anti-emetic therapy may be required, although pixantrone is associated with low rates of chemotherapy induced nausea and vomiting (CINV).

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The administration of pixantrone requires hospital setting by physicians who are familiar with the use of antineoplastic agents and have the facilities for regular monitoring of clinical, haematological, and biochemical parameters during and after treatment. It is to be given as a slow intravenous infusion using an in-line filter (over a minimum of 60 minutes) only after reconstitution with 5 mL sodium chloride 9 mg/mL (0.9%) solution for injection and after further dilution with sodium chloride 9 mg/mL (0.9%) solution for injection to a final volume of 250 mL according to the SPC[14]. Thus the administration costs would be the national average outpatient administration costs for the following:

- ‘Deliver simple Parenteral Chemotherapy at first attendance’ on the first day of the 4-weekly cycle with an average cost of £231 (code: SB12Z). This incorporates an overall time of 30 minutes nurse time and 30-60 minutes chair time.

- ‘Deliver subsequent elements of a Chemotherapy cycle’ on the 8th and 15th day of the four-weekly cycle with an average cost of £206 (code: SB15Z)[15].

In addition to the currently used disease monitoring, no additional tests are required for pixantrone during the treatment period. At treatment initiation baseline assessment of blood counts, serum levels of total bilirubin, serum levels of total creatinine, and cardiac function as measured by left ventricular ejection fraction (LVEF) are required[1]. The cost of the biochemistry tests done in outpatient setting is £1.26 per test (code: DAP841), while the cost of blood count is £3.36 (code: DAP823)[15]. The cost of a simple echocardiogram for cardiac monitoring is £86.31 using a weighted average with the activities in outpatient services, direct access and other (code: RA60Z) [15]. Thus the total cost of tests for treatment initiation is approximately £92.19 per patient.

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure – over that required for the reconstitution and administration of standard cytotoxic therapies – is needed for the reconstitution and administration of pixantrone.

# 3 Equality

## *3.1 Identification of equality issues*

3.1.1 Please let us know if you think that this appraisal would include equality issues

Not applicable, no equality issues are identified

3.1.2 How has the analysis addressed these issues?

Not applicable, no equality issues are identified

# 4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Pixantrone is the only regulatory approved product for the treatment of multiply relapsed or refractory aggressive NHL.

Pixantrone, a novel aza-anthracenedione, has been specifically designed to reduce the cardiotoxicity associated with anthracyclines, without compromising antitumor efficacy. It is the only anthracycline-like agent that can be used in patients who have received up to the recommended maximum lifetime dose of an anthracycline.

Pixantrone is the first aza-anthracenedione to reach advanced clinical development. The drug was rationally designed to improve efficacy and reduce the cardiotoxicity associated with anthracyclines and anthracenediones.

Anthracyclines are the cornerstone for the treatment of lymphoma, with R-CHOP being the standard of care for first-line treatment for aggressive DLBCL and one of the primary options for grade 3 FL[9]. While anthracyclines are effective as first-line treatment, as many as 50% of patients experience grade 3/4 toxicity and cumulative cardiac toxicity that may result in congestive cardiac failure (CCF). A retrospective analysis of three trials (involving 630 patients who received doxorubicin for the treatment of breast cancer or small cell lung cancer) estimated that 26% of patients would experience doxorubicin-related CCF at a cumulative dose of 550 mg/m$^2$ for up to six cycles.[3] In a study of elderly patients with DLBCL, any doxorubicin resulted in a 29% increase in the risk of CCF. Furthermore, the risk increased in older patients, pre-existing heart disease, comorbidities, diabetes and hypertension[16].

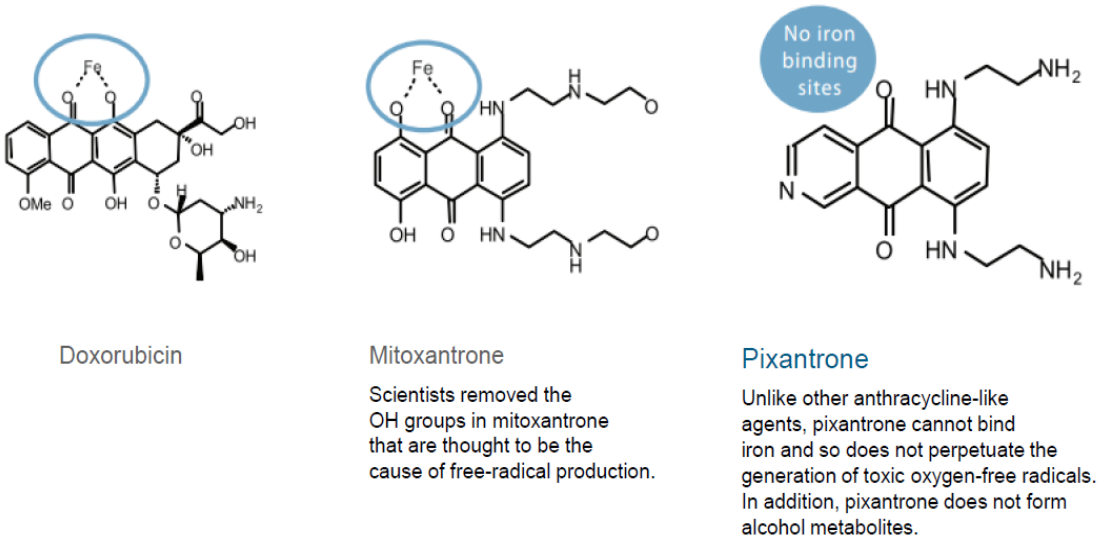
As a result, the number of anthracycline doses a patient can receive has a lifetime limit (450 mg/m$^2$ for up to six cycles), and most patients who previously have been treated with an anthracycline are not able to receive further anthracycline treatment if their disease relapses.

The unique molecular structure of pixantrone increases the stability of DNA adduct formation while reducing formation of oxygen-free radicals and toxic drug–metal complexes. Pixantrone lacks the 5,8-dihydroxy-substitution of mitoxantrone (an anthracenedione) and instead contains a nitrogen heteroatom. As shown in Figure 3, pixantrone lacks the quinine-hydroquinone site responsible for oxygen-free radical generation and iron binding in mitoxantrone and doxorubicin.

Furthermore, unlike other anthracycline and anthracycline-like agents, pixantrone is not associated with alcohol metabolite production which may lead to long-term cardiotoxicity. Pixantrone is associated with less cardiac toxicity than related anthracycline compounds and may therefore provide a unique alternative in heavily treated patients.

In addition, anthracyclines and anthracenediones are associated with tissue necrosis if they leach into peripheral tissues. Pixantrone is not a vesicant and can be given via a peripheral intravenous infusion over a 1-hour period, thus pixantrone is an effective and convenient treatment for both patients and healthcare professionals.

**Figure 3: Anthracycline and pixantrone molecular structure**




4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Not applicable

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable

# 5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

| | Final scope issued by NICE | Decision problem addressed in the submission | Rationale if different from the scope |
|---|---|---|---|
| **Population** | Adults with multiply relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. | Adult patients with multiply relapsed or refractory aggressive non-Hodgkin lymphoma. | Anticipated indication is 3rd line plus, since the available evidence from the Phase III registration trial (PIX301) applies only to patients who have had ≥2 prior lines of therapy. |
| **Intervention** | Pixantrone | Pixantrone | |
| **Comparator (s)** | • vinorelbine<br>• oxaliplatin<br>• ifosfamide<br>• etoposide<br>• mitoxantrone<br>• gemcitabine | • vinorelbine<br>• oxaliplatin<br>• ifosfamide<br>• etoposide<br>• mitoxantrone<br>• gemcitabine | It should be noted that whilst these comparator therapies are used in this patient group in the UK. They are older therapies and do not have a formally approved indication in adults with relapsed or refractory aggressive non-Hodgkin lymphoma whose disease is sensitive to treatment with anthracyclines and who would otherwise be treated with single-agent chemotherapy as a second or subsequent line of treatment. |
| **Outcomes** | • overall survival<br>• progression-free survival<br>• response rate<br>• adverse effects of treatment<br>• health-related quality of life | • overall survival<br>• progression-free survival<br>• response rate<br>• adverse effects of treatment<br>• health-related quality of life | The outcomes listed will be presented in the submission, however in this patient population reliable and robust utility data is scarce. However we did not measure HRQOL data in the pivotal trial |

| | | | |
|---|---|---|---|
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY<br><br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br><br>Costs will be considered from an NHS and Personal Social Services perspective. | The economic evaluation will be a cost effectiveness analysis, with the results presented as incremental cost per quality-adjusted life year gained.<br><br>Due to the chronic and advanced nature of the disease, lifetime horizon will be applied to account for any differences in costs and health outcomes between the technologies compared.<br><br>Costs will be considered from an NHS and Personal Social Services perspective. | |

| | | | |
|---|---|---|---|
| **Subgroups to be considered** | NA | Two subgroups of patients are considered:<br><br>Those with aggressive B-cell NHL<br><br>And those with DLBCL | These subgroups are considered as the aggressive B-cell NHL population described in the submission most closely resembles the licensed indication of pixantrone. DLBCL is considered as this represents the largest histologically confirmed group within PIX301. |

| | | | |
|---|---|---|---|
| **Special considerations, including issues related to equity or equality** | NA | Given that this is an end of life medicine, with small patient numbers, a demonstrable survival benefit and no alternative treatment with comparable benefits through the NHS, Pixantrone should be considered under the End of Life Policy. | Patient numbers are low, with an estimated 2,000 patients in the UK with multiply relapsed aggressive NHL based on a 2010 survey by the EBMT Activity Survey Office in Basel Switzerland.<br><br>Overall survival in the PIX301 trial for this patient population was less than a year (median overall survival was 10.2 (6.4, 15.7) vs.. 7.6 (5.4, 9.3) months for Pixantrone and standard care respectively) log rank p-value = 0.251; HR = 0.79 (95% CI: 0.53, 1.18), while median progression-free survival was less than 6 months; 5.3 (2.3, 6.2) vs.. 2.6 (1.9, 3.5) for pixantrone and standard care respectively) p = 0.005; HR = 0.60 (95% CI: 0.42, 0.86). In line with the fact that these are heavily-pre-treated patients, response rates in pixantrone-treated patients were consistent in those with and without previous rituximab. If this were to be considered an end of life medicine, because no combination or single-agent therapy is considered the standard of care for patients with relapsed or refractory NHL, and palliative care or clinical trials are often the only remaining treatment options, an effective salvage therapy is needed for these patients. The PIX301 study suggests that pixantrone is an effective single-agent treatment for patients with aggressive NHL and that it could fulfill the need as a standard salvage therapy that leads to improved outcomes with manageable toxicities.<br><br>Cardiac function. There is additional early data from trial PIX203 that due to pixantrone unique molecular structure and the lack of oxygen-free radical and alcohol metabolite production. Pixantrone is expected to have less cardiac toxicity than related anthracycline compounds and may therefore provide a unique alternative in heavily treated patients. For these reasons, cardiac function and toxicity were closely monitored in all clinical studies. that shows pixantrone could potentially be less cardio toxic than other anthracyclines |

## Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

| **Element of health technology assessment** | **Reference case** | **Section in 'Guide to the methods of technology appraisal'** |
|---|---|---|
| Defining the decision problem | The scope developed by NICE | 5.2.5 and 5.2.6 |
| Comparator(s) | Therapies routinely used in the NHS, including technologies regarded as current best practice | 5.2.5 and 5.2.6 |
| Perspective costs | NHS and PSS | 5.2.7 to 5.2.10 |
| Perspective benefits | All health effects on individuals | 5.2.7 to 5.2.10 |
| Type of economic evaluation | Cost-effectiveness analysis | 5.2.11 and 5.2.12 |
| Synthesis of evidence on outcomes | Based on a systematic review | 5.3 |
| Measure of health effects | QALYs | 5.4 |
| Source of data for measurement of HRQL | Reported directly by patients and carers | 5.4 |
| Source of preference data for valuation of changes in HRQL | Representative sample of the public | 5.4 |
| Discount rate | An annual rate of 3.5% on both costs and health effects | 5.6 |
| Equity weighting | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | 5.12 |

HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)

# 6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

## *6.1 Identification of studies*

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A literature review was completed to identify the clinical effectiveness of potential comparator agents that have been previously evaluated within the published literature. Searches were conducted of MEDLINE, EMBASE, Cochrane Central Register of Controlled trials (CENTRAL) and ClinicalTrials.gov.

Other sources that were hand-searched for relevant data were the websites of the following organisations:

- American Society of Clinical Oncology (ASCO; http://www.asco.org/);
- European Association for Cancer Research (EACR; http://www.eacr.org/);
- European Society for Medical Oncology (ESMO; http://www.esmo.org/);
- National Cancer Research Institute (NCRI; http://www.cancerportfolio.org);
- National Comprehensive Cancer Network (NCCN; http://abstracts.hematologylibrary.org);

- Health Technology Assessments via the Cochrane Library (HTAs; http://onlinelibrary.wiley.com/o/cochrane/cochrane_clhta_articles_fs.html); and
- Websites of the manufacturers of the current treatment options for relapsed or refractory aggressive NHL, detailed in Table 9 below

**Table 9: Manufacturer websites that were hand-searched for data**

| Product | Manufacturer | Website |
|---|---|---|
| pixantrone dimaleate | Cell Therapeutics Inc. | www.celltherapeutics.com/clinical_trials |
| bendamustine | Cephalon Inc. | www.cephalon.com |
| bortezomib | Janssen-Cilag Ltd. | www.janssen.co.uk |
| etoposide | Bristol-Myers-Squibb Pharmaceutical Ltd. | www.bms.com |
| gemcitabine | Accord Healthcare Ltd.<br>Actavis UK Ltd.<br>Hospira UK Ltd. | www.accord-healthcare.eu<br>www.actavis.co.uk<br>www.hospira.com |
| ifosfamide | Baxter Healthcare | www.baxterhealthcare.co.uk |
| lenalidomide | Celgene Ltd. | www.celgene.com |
| mitoxantrone | Hospira UK Ltd. | www.hospira.com |
| oxaliplatin | Sanofi Aventis | www.en.sanofi.com |
| rituximab | Roche Products Ltd. | www.rocheuk.com |
| vinorelbine | Hospira UK Ltd. | www.hospira.com |

The reference lists of the included primary studies and relevant systematic reviews and meta-analyses retrieved from the electronic database search were also hand-searched for additional relevant studies. A full list of electronic databases and other sources searched is also provided in section 10.2 (Appendix 2).

To ensure identification of all relevant studies for the population of interest (aggressive B-cell non-Hodgkin lymphoma), search terms that related to any

type of non-Hodgkin lymphoma were used (for example, lymphoma; lymphoma, high-grade; lymphoma, non-Hodgkin; and lymphoma, large-cell). These terms were combined with search terms relevant to the intervention, pixantrone (for example, pixantrone; Pixuvri; and BBR 2778) and relevant comparator drug therapies for this population. The search was limited to clinical trials as this was the study design of interest; and to English language papers. The full search strategy and search restrictions are provided in section 10.2, Appendix 2.

## *6.2 Study selection*

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The criteria used to select studies for inclusion in the review are detailed in Table 10. In summary, studies were selected for inclusion because they were relevant to the subpopulation of interest, namely patients undergoing third-line therapy for relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Interventions were selected as being licensed for, or widely used for treatment of non-Hodgkin lymphoma. Studies were included if they were comparative trials, so that the effectiveness of the intervention could be determined, which included both randomised and non-randomised controlled trials. As the number of relevant RCTs was expected to be very low for the small population of interest, non-randomised controlled trials were also included, to increase the likelihood of finding useful data.

In order to focus the review on those studies of most relevance to current clinical practice in the UK, studies were included if they were published in 1995 onwards, and in English. However, because few clinical trials were expected to be identified, studies from any country were included in the review if they met the other inclusion criteria.

Study selection was accomplished through 2 levels of study screening. A Level I screening was performed on title and abstracts. Full articles of

accepted titles and abstracts that passed Level I screening were retrieved for further review, i.e., Level II screening. Studies rejected at Level II screening required the consensus of second reviewer. All studies accepted at Level II studies were eligible for preliminary data extraction.

**Table 10: Eligibility criteria used in search strategy**

| | Inclusion criteria | Rationale |
|---|---|---|
| Population | Adults with relapsed or refractory aggressive non-Hodgkin lymphoma who have had at least two therapies. | Pixantrone is licensed for use in this population. |
| Intervention | • Bendamustine<br>• Bortezomide<br>• Etoposide<br>• Gemcitabine<br>• Ifosfamide<br>• Lenalidomide<br>• Mitoxantrone<br>• Oxaliplatin<br>• Pixantrone dimaleate<br>• Rituximab<br>• Vinorelbine | These are pharmacological interventions that can be used to treat this population or for which clinical trials are still ongoing. |
| Comparison | • Head-to-head<br>• Placebo<br>• Combination therapy including the intervention compared with combination therapy without the intervention. | Comparative studies are necessary to understand how effective these drugs are compared with each other or with placebo. |
| Outcomes | • Overall survival<br>• Progression-free survival<br>• Response rate<br>• Adverse effects of treatment<br>• Health-related quality of life<br>• Stable disease<br>• Progressive disease | These outcomes are most relevant for the population group and will provide the best data to demonstrate the clinical effectiveness of the pharmacological interventions. |
| Study design | • RCT<br>• Non-randomised controlled trials: a trial with a concurrent control | As the majority of studies in this population are not RCTs, non-randomised controlled |

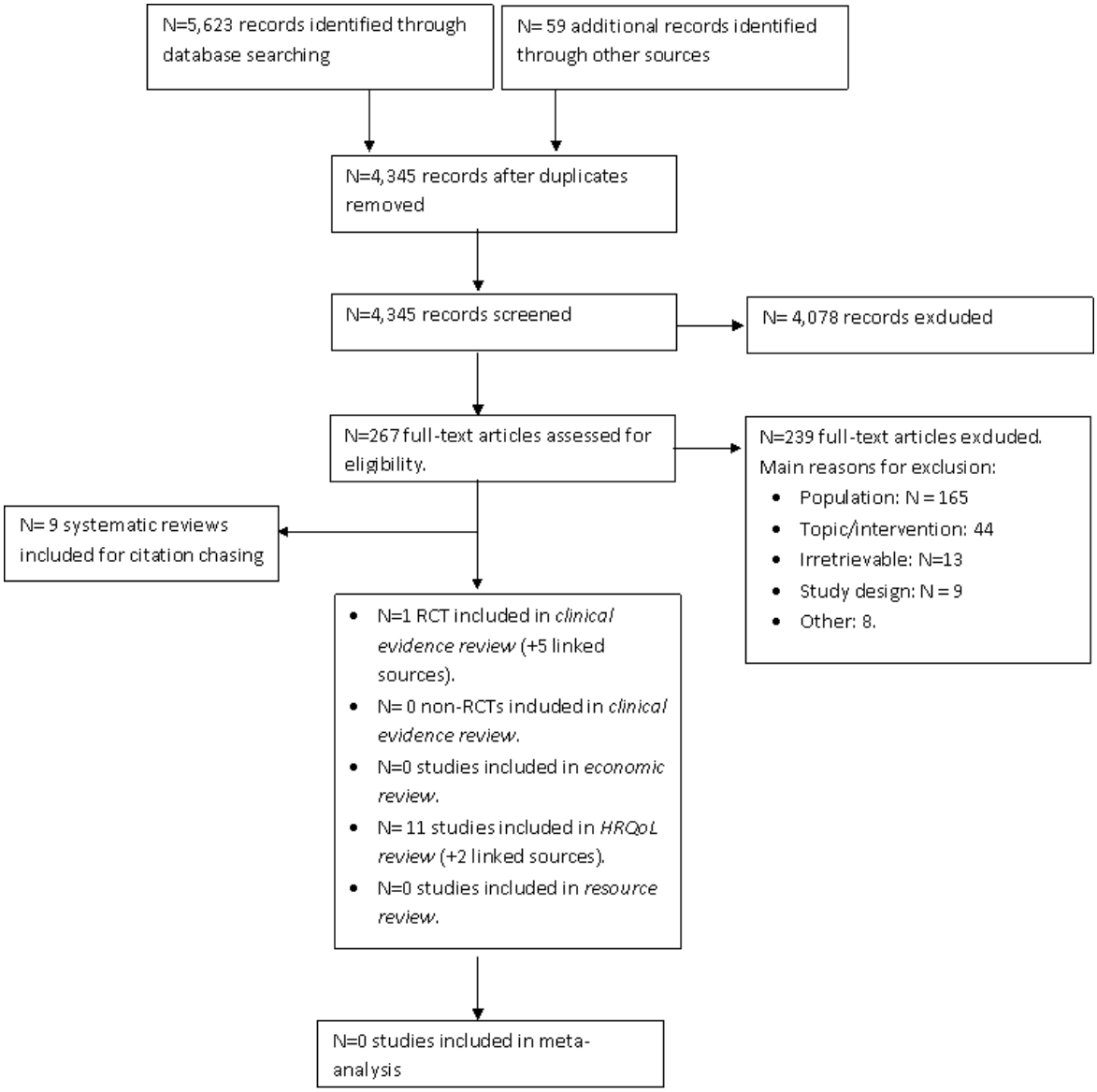
| | Inclusion criteria | Rationale |
|---|---|---|
| | group where participants were assigned by investigators non-randomly to treatment groups. | trials were also included. |
| Country | Any | Studies carried out in any country are relevant to the review. |
| Language | English | English language studies are most likely to be relevant to the UK context. |
| Publication year | 1995 to present | Rapid changes in cancer research may mean studies published before 1995 are of little relevance to current practice. |

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

The flow of literature for the searches conducted for the search for clinical evidence is described below in Figure 5. Due to the small number of total hits, the CONSORT flow of literature for the clinical evidence review, HRQL review (see section 7.4.5), economic evidence review (see section 7.1.2), and resource review (7.5.3) is presented in a combined fashion, including a summary of the results of each individual search.

A total of 4,345 records were screened based on titles and abstracts; 267 full texts were retrieved and screened; and 6 studies that provided data on one single RCT were included for the clinical effectiveness review. Despite broadening the study methodology to include non-randomised controlled trials, no studies were identified that were relevant to the population or interventions.

**Figure 4 Flow of Literature**



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Six sources[17,18,2,19,20,21] provided evidence on the single RCT Phase III trial of pixantrone compared with other third-line, single agent treatments of relapsed aggressive NHL[18].

Of these studies, four were published as conference abstracts[17,18,20,21] with limited reporting of methodology and data; one was the manufacturer's registration of the methodology of the PIX301 trial, which was first published in 2004 and updated in 2011 at the end of the trial[2]; and one was a summary of the two Pettengell abstracts [19]. The two conference abstracts by van der Jagt et al[20,21] also described other Phase II and III trials of pixantrone involving patients with indolent NHL or as first-line therapy in aggressive NHL, but these population groups and data relevant to them have not been included in this report.

Methodological details and outcomes reported in the six papers are summarised in Table 11**.**

**Table 11: Summary of papers reporting data from the PIX301 trial.**

| **Publication** | **Pettengell *et al.,* 2010** | **Pettengell *et al.,* 2009** | **PIX301 CSR, 2010** | **Horizon Scanning Centre, 2009** | **Van der Jagt *et al.,* 2009a** | **Van der Jagt *et al.,* 2009b** |
|---|---|---|---|---|---|---|
| Location | International | As Pettengell et al. 2010 | US, Argentina, Bulgaria, Costa Rica, Ecuador, Estonia, France, Germany, Hungary, India, Italy, Mexico, Panama, Peru, Poland, Romania, Russian Federation, Ukraine, UK, Uruguay | EU (incl UK), USA and other countries | NR | NR |
| Design | Randomised, controlled, multicentre open label study | As Pettengell et al. 2010 | Study protocol only: as Pettengell et al. 2010 | Randomised, open-label, active control | NR | NR |
| Study duration | Treatment period and end of study (18 month follow-up) | Treatment period and ≥9 months' follow-up | July 2004 – July 2010 | 24 weeks treatment period plus 18 weeks follow-up | 18 months follow-up | 18 months follow-up |
| Randomisation method | NR | NR | NR | NR | NR | NR |
| Method of blinding (care provider, patient and outcome assessor) | Open label | NR | Open label | Open-label | NR | NR |

| **Publication** | **Pettengell *et al.,* 2010** | **Pettengell *et al.,* 2009** | **PIX301 CSR, 2010** | **Horizon Scanning Centre, 2009** | **Van der Jagt *et al.,* 2009a** | **Van der Jagt *et al.,* 2009b** |
|---|---|---|---|---|---|---|
| Intervention(s) (n = ) and comparator(s) (n = ) | Pixantrone n=70;<br>choice of comparators included vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine or rituximab, n=70 | As Pettengell et al. 2010 | As Pettengell et al. 2010 | As Pettengell et al. 2010 | As Pettengell et al. 2010 | As Pettengell et al. 2010 |
| Primary outcomes (including scoring methods and timings of assessments) | CR/CRu | As Pettengell et al. 2010 | Response (time frame: 84 days) | Complete remission (CR) or unconfirmed remission (CRu) rates | Tumour response during/ after treatment;<br>Overall response lasting ≥4 months | Tumour response during/ after treatment;<br>Overall response lasting ≥4 months |
| Secondary outcomes (including scoring methods and timings of assessments) | Overall response rate (CR, CRu or PR);<br>Response duration;<br>Progression-free survival (PFS);<br>Overall survival (OS);<br>Safety | As Pettengell et al. 2010 | Toxicity (time frame: 21 days) | Overall response rate; response lasting ≥4 months; PFS;<br>OS;<br>Safety. | PFS;<br>OS;<br>Cardiac safety | PFS;<br>Cardiac safety |
| Duration of follow-up | 18 months | ≥9 months | NR | 18 months | 18 months | 18 months |

**NR=Not reported**

**Complete list of relevant RCTs**

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

The PIX301 trial directly compared the intervention of interest, pixantrone, with appropriate comparators, other active treatments for patients with aggressive NHL as chosen by the physician. Comparators were one of the following: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine, or rituximab. The patient population was adult patients with relapsed/refractory NHL who have had at least two prior drug therapies. More details of the methodology of this RCT are reported in Table 12.

**Table 12: List of relevant RCTs**

| Trial no. (acronym) | Intervention | Comparator | Population | Primary study ref. |
|---|---|---|---|---|
| PIX301 | Pixantrone | Choice of comparators included: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine or rituximab | Heavily pretreated patients with relapsed or refractory aggressive non-Hodgkin lymphoma | Pettengell 2010[18] and Pettengell 2012[22] |

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The only RCT to compare pixantrone directly with one or more of the appropriate comparators is the PIX301 trial, described in this document.

Rituximab is commonly used in UK clinical practice as a single agent to treat patients with relapsed or refractory NHL when all alternative treatment options have been exhausted. NICE also recommends the use of rituximab for the treatment of relapsed or refractory Stage III or IV FL in combination with chemotherapy to induce remission or alone as maintenance therapy during remission[11].

Based on discussion with clinical experts, other comparator options in the PIX301 trial, including gemcitabine, mitoxantrone, etoposide, and ifosfamide, are also commonly used in English clinical practice either as part of combination chemotherapy regimens or as a monotherapy[23-25].

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No additional studies were identified but subsequently excluded from further discussion.

**List of relevant non-RCTs**

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

The review searched for non-RCTs but did not identify any trials that met the inclusion criteria.

## *6.3 Summary of methodology of relevant RCTs*

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to

14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

**Scientific background and explanation of rationale:**

Currently, there is no approved treatment or established standard of care for the estimated 12,000 individuals in the European Union who fail first- and second-line treatment. Existing treatment options for multiply relapsed or refractory disease do not adequately address the key aims of extending life while maintaining quality of life. Treatment of relapsed or refractory aggressive NHL thus represents a strong unmet medical need.

Pixantrone, a novel aza-anthracenedione, has been specifically designed to reduce the cardiotoxicity associated with anthracyclines, without compromising antitumor efficacy. It is the only anthracycline-like agent that can be used in patients who have received up to the recommended maximum lifetime dose of an anthracycline.

A Phase II study (AZA II-01) in heavily pretreated patients with aggressive NHL or mantle cell lymphoma found pixantrone elicited a high rate and durability of complete responses[26]. The Phase III trial, PIX301, was therefore conducted to evaluate the safety and efficacy of pixantrone as a single-agent therapeutic in multiply-relapsed patients with aggressive NHL and is the pivotal trial addressing the decision problem.

**Specific Objectives**

The primary study objective was to compare the efficacy of pixantrone to a selection of single agents in terms of CR and CRu rate according to the report of the International Workshop to Standardize Response Criteria for NHL.

Secondary objectives were to compare the efficacy of pixantrone to a selection of single agents as demonstrated by overall survival, CR/CRu rate in histologically confirmed patients, objective overall response lasting at least 4 months, and progression-free survival.

Additional objectives were to compare pixantrone with other chemotherapy agents as demonstrated by overall response rate, time to initial response, time to complete response, duration of response, dose intensity, cardiac function, and safety. The pharmacokinetics parameters of pixantrone were also to be studied in patients randomized to the pixantrone group who voluntarily provided a separate consent to participate in this parallel study.

**Trial design**

This was a Phase III, multi-centre, open-label, single-blind, randomised (1:1), controlled trial in patients 18 years or older with aggressive NHL who have relapsed after two or more previous regimens of chemotherapy[22].

**Changes to trial design**

Major amendments in the conduct of the study or planned analysis included a modification to inclusion criteria in October 2004 to state patients must be sensitive to their last anthracycline/anthracenedione regimen. In March 2005, gemcitabine and rituximab were added as options for comparator treatments, and dosage specifications for oxaliplatin were removed. Follicular lymphoma grade III was also removed from eligible disease types. In February 2006, the statement ‘with evidence of disease progression’ was added to inclusion criteria requiring relapse after 2 or more prior regimens and ‘(confirmed or unconfirmed PR or CR)’ was added to inclusion criteria requiring prior response to anthracycline/anthracenedione. The expected accrual time was changed from 12 months to 36 months to reflect lower than anticipated enrolment. Furthermore, the geographical region for stratification previously defined as ‘Eastern Europe’ was amended to ‘Rest of World’. Text was added to indicate the stratification covariables will be investigated as covariates for the primary and secondary analyses. A further amendment in December 2006 was a change of the secondary endpoint time to progression (TTP) to PFS.

Finally, in June 2007, follicular lymphoma (grade III) was added to the inclusion criteria[1].

**Eligibility criteria for participants**

Eligible participants were patients 18 years or older with aggressive de novo or transformed NHL (according to the Revised European-American Lymphoma and WHO classification) who had relapsed after two or more previous regimens of chemotherapy, including at least one standard anthracycline-containing regimen with a response that had lasted at least 24 weeks. Patients were required to have a life expectancy of at least 3 months.

Patients were not eligible if they had received a cumulative dose of doxorubicin or equivalent of 450 mg/m$^2$ or if they were classed as having New York Heart Association Grade 3 or 4 cardiovascular abnormalities, among other exclusion criteria[22].

**Settings and locations where the data were collected**

PIX301 recruited patients in 66 academic and community-based hospitals across Europe, India, Russia, South America, the UK and the USA[22].

**Interventions**

Pixantrone was supplied in 50 mg vials (equivalent to 29 mg of pixantrone in its base form). Patients randomly assigned to the pixantrone group were given pixantrone, intravenously infused over 1 h at a dose of 85 mg/m. (equivalent to 50 mg/m$^2$ of pixantrone in its base form) on Days 1, 8, and 15 of a 28-day cycle, for up to six cycles. One reduction in dose was allowed for patients who had neutropenia during treatment. Patients randomly assigned to the comparator group received their physician's choice of a comparator agent at pre-defined standard doses and schedules.

**Outcomes**

*Primary Endpoint*

Complete Response/Complete Response unconfirmed (CR/CRu rate),

defined as the proportion of patients with CR or CRu as assessed by an independent assessment panel (IAP).

*Secondary Endpoints*

Overall Survival (OS): The time between the date of randomization and the date of death due to any cause.

Response Rate Lasting at Least 4 months: The total proportion of patients with CR, CRu, or PR with a difference from the first documented objective response to disease progression or death of at least 4 months.

Progression-Free Survival (PFS): The time between the date of randomization and the date of the initial documentation of progressive/relapsed disease or death due to any cause.

*Other Pre-defined Endpoints*

Overall Response Rate (ORR): The total proportion of patients with CR, CRu, or PR as assessed by the IAP.

Time to Response: The time between the date of randomisation and the date of the initial response independent of the duration.

Time to Complete Response: The time between the date of randomisation and the date of the initial CR or CRu.

Duration of Response: The time from the first documented objective response to disease progression/relapse or death.

Relative Dose Intensity: The proportion (%) of the actual dose intensity divided by the planned dose intensity for that same period of time[2].

**Sample size**

With enrolment of 140 patients, the study was considered sufficiently powered (about 80%) to detect a 15% difference in the CR/Cru rate, assuming a ≥18% CR/Cru rate in the pixantrone arm[22].

**Randomisation and blinding**

Patients were randomly assigned (1:1) to the pixantrone or comparator group by an interactive voice response system (IVRS). The randomisation schedule was created by the IVRS vendor.

The study was an open label study, but the Independent Assessment Panel and Independent Radiological Committee were masked to the treatment assignment and to the tumour response assessments made by the investigators. The success of masking was confirmed by external audit of the independent assessment panel[1,22].

**Statistics**

The Fisher exact test was used to compare the CR/CRu rate and the ORR between the two treatment groups. The OS and PFS were analysed using Kaplan-Meier methods and the differences in PFS and OS between treatment groups were assessed by un-stratified log-rank test[22].

**Additional analyses**

*Pre-defined subgroup analysis*

In addition to the ITT (primary analysis) study population, histologically-confirmed aggressive NHL population (HITT) by retrospective independent central pathology assessment was a second pre-defined ITT study population[1].

*Post-hoc subgroup analysis*

Post-hoc subgroup analysis evaluated:

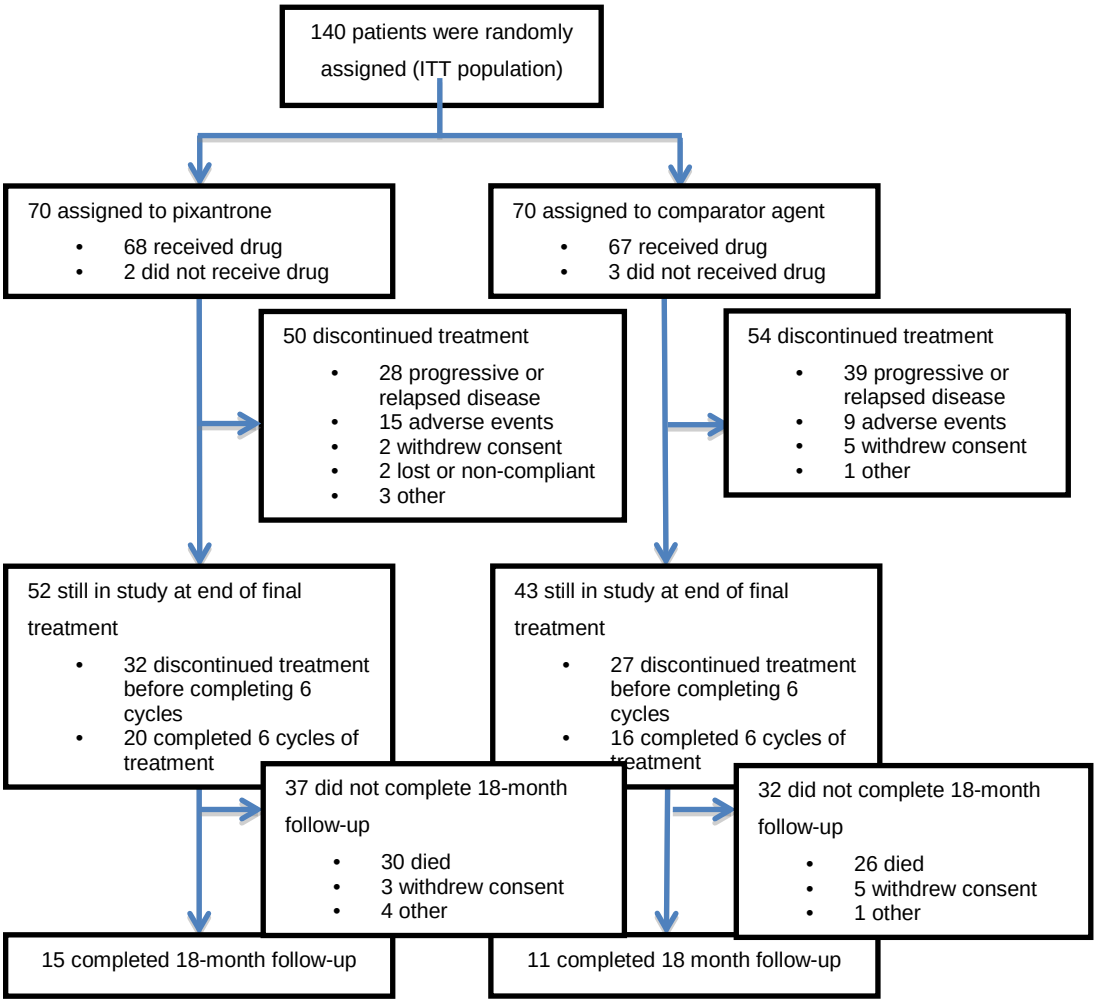
1. The effect of rituximab on the efficacy of pixantrone
2. Efficacy in aggressive B-cell lymphoma (classed as DLBCL, transformed indolent lymphoma, or follicular lymphoma, grade III)
3. Efficacy in patients with prior stem cell transplantation

4. Efficacy in European patients

5. Efficacy in older adults and women[22]

## Participant flow

**Figure 5: PIX301 trial profile flow chart**




## Losses and exclusions

In the PIX301 trial, 104 of 140 patients discontinued early, five before the drug was given. The most common reason for early discontinuation was disease progression or relapse.

## Recruitment

Between October 12, 2004 and March 17, 2008, 140 patients were randomly

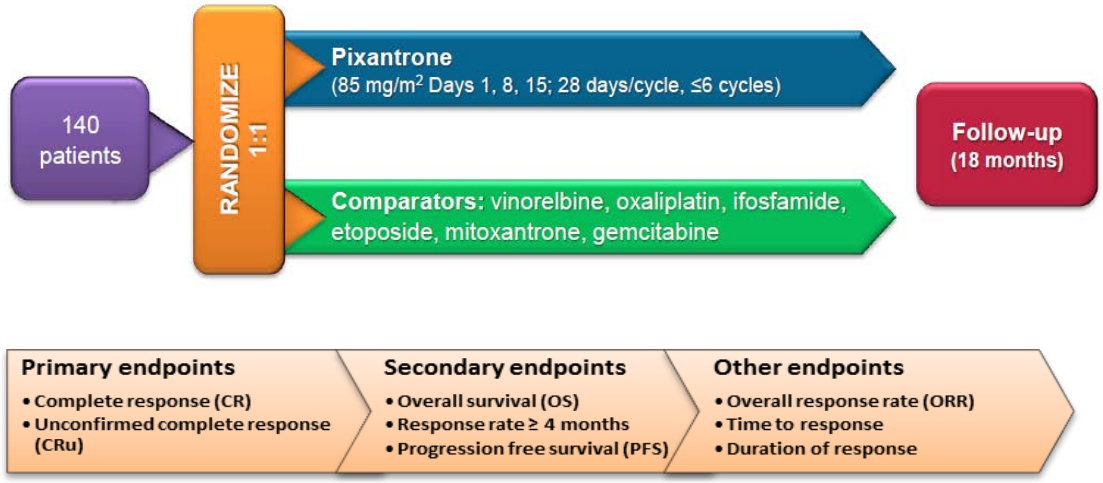
assigned to either the pixantrone group or the comparator group (ITT; n=70 in both groups). The last patient completed protocol-defined therapy on August 28, 2008. The data cutoff for the end of treatment analysis was September 30, 2008. The last follow-up assessment took place on February 16, 2010[22].

## Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.

*Study design and patients*

**Figure 6: PIX301 study plan and main study endpoints**




Pixantrone dose is expressed as pixantrone dimaleate.

The pivotal PIX301 study is the key clinical trial addressing the decision problem. The study was a Phase III, multi-centre, open-label, randomised trial in patients aged 18 years or older with aggressive de novo or transformed NHL (according to the Revised European–American Lymphoma and WHO classification) who had relapsed after two or more previous regimens of chemotherapy, including at least one standard anthracycline-containing regimen with a response that had lasted at least 24 weeks. Patients were required to have a life expectancy of at least three months. The trial was

performed at 66 study sites in 17 countries in academic and community-based hospitals across Europe, India, Russia, South America, the UK, and the USA. Patients living in a country where rituximab was available were only eligible if they had received rituximab therapy (when their neoplastic cells expressed CD20). Patients with NHL that had relapsed after stem-cell transplantation were also eligible[22].

*Randomisation and masking*

Patients were randomly assigned (1:1) to the pixantrone or comparator group by an interactive voice response system (IVRS). The randomisation schedule was created by the IVRS vendor. Stratified blocked randomisation was used with a block size of two within each of the 18 unique stratification combinations. There were three stratification factors: region (North America vs. Western Europe vs. rest of world), International Prognosis Index score (0 or 1 vs. ≥2; an internationally accepted prognostic index for patients with aggressive NHL), and previous stem-cell transplantation (yes vs. no). The study was open label, but the independent assessment panel was masked to the treatment assignment and to the tumour response assessments made by the investigators. The sponsor was masked to the treatment assignment until the end of treatment, when the database was locked for analysis. The success of masking was confirmed by external audit of the independent assessment panel[22].

*Interventions*

Pixantrone was supplied in 50 mg vials (equivalent to 29 mg of pixantrone in its base form). Patients randomly assigned to the pixantrone group were given pixantrone, intravenously infused over 1 h at a dose of 85 mg/m$^2$ (equivalent to 50 mg/m$^2$ of pixantrone in its base form) on Days 1, 8, and 15 of a 28-day cycle, for up to six cycles. One reduction in dose was allowed for patients who had neutropenia during treatment. Patients randomly assigned to the comparator group received their physician’s choice of a comparator agent at pre-defined standard doses and schedules (Table 13).

**Table 13: Treatment regimens for study and comparator drugs**

| | Dose/Route of administration | Days of cycle* | Length of cycle/number of cycles |
|---|---|---|---|
| **Study drug** | | | |
| Pixantrone | 85 mg/m<br>IV | 1, 8, and 15 | 28 days<br>6 cycles |
| **Comparator drugs†** | | | |
| Vinorelbine[1] | 30 mg/m$^2$<br>IV | Day 1, 8, 15 and 22 | 4 weeks<br>6 cycles |
| Oxaliplatin[1] | 100 mg/m$^2$<br>IV | Day 1 | 3 weeks<br>6 cycles |
| Ifosfamide[1, 2] | 3000 mg/m$^2$<br>IV | Day 1 and 2 | 4 weeks<br>6 cycles |
| Etoposide[1, 2] | 100 mg/m$^2$<br>IV | Day 1, 2, 3, 4 and 5 | 4 weeks<br>6 cycles |
| Etoposide[1, 2] | 50 mg/m$^2$<br>PO | Daily for 21 days | 4 weeks<br>6 cycles |
| Mitoxantrone[1, 2] | 14 mg/m$^2$<br>IV | 1 | 3 weeks<br>6 cycles |
| Gemcitabine[1, 3] | 1250 mg/m$^2$<br>IV | Day 1, 8 and 15 | 4 weeks<br>6 cycles |
| Rituximab[4] | 375 mg/m$^2$ | Day 1, 8 and 15 of cycle 1 and Day 1 of cycle 2 | 3 weeks |

*Days of cycle on which dose was given

†Published studies of dose and responses were used to determine which comparator drugs to test.

1[27], 2[28], 3[29], 4[30].

*Additional procedures*

The study monitored cardiac function by assessment of LVEF with

echocardiography or a multiple-gated acquisition scan. Serious adverse events were reported from time of patient consent to 30 days after last study treatment. During the follow-up period, only new adverse events that were thought to be related to the study drug were reported.

*Losses and exclusions*

In the PIX301 trial, of 140 patients, 36 patients completed six cycles of protocol treatment, and 104 patients discontinued early. The most common reason for early discontinuation in both groups was disease progression or relapse. 95 patients entered the follow-up period after completing study treatment and 26 completed 18 months of follow-up.

*Duration of follow-up*

Patients were followed up for 18 months after last treatment for disease progression and survival. The last follow-up assessment took place on February 16, 2010.

*Primary Outcomes*

The primary objective of PIX301 was an analysis of the intent-to-treat (ITT) population at the end of treatment comparing the CR/CRu rate of pixantrone to that of single agents selected by physicians. The CR/CRu rate was defined as the proportion of patients with CR or CRu as determined by a blinded independent assessment panel (IAP)[2].

*Secondary Outcomes*

Secondary objectives were to compare the efficacy of pixantrone to a selection of single agents as demonstrated by overall survival, CR/CRu rate in histologically confirmed patients, objective overall response lasting at least 4 months, and progression-free survival.

Where:

- OS: defined as the interval between the date of randomisation and death from any cause
- CR/CRu rate in histologically confirmed patients
- ORR lasting at least 4 months, where ORR was defined as the percentage of patients who achieved CR, CRu, or partial response (PR)
- PFS: the interval between the date of randomisation and the first documented progression of disease (PD) or death[2].

Additional objectives were to compare pixantrone with other chemotherapy agents as demonstrated by overall response rate, time to initial response, time to complete response, duration of response, dose intensity, cardiac function, and safety.

**Participants**

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial.

A summary of inclusion and exclusion criteria are provide below, the complete criteria are found in Appendix Q.

*Inclusion criteria*

- Histologically confirmed aggressive [de novo or transformed] NHL according to REAL/WHO classification.
- At least one objectively measurable lesion as demonstrated by CT, spiral CT, or MRI and plain radiograph of the chest (chest x-ray, for chest lesions only) that can be followed for response as target lesion.
- Relapse after 2 or more prior regimens of chemotherapy
- ECOG performance status of 0, 1, or 2
- Adequate hematologic, renal and hepatic function
- LVEF ≥50% determined by MUGA scan

*Exclusion criteria*

- Prior treatment with a cumulative dose of doxorubicin or equivalent exceeding 450 mg/m²
- Prior allogenic stem cell transplant
- Histological diagnosis of Burkitt lymphoma, lymphoblastic lymphoma or Mantle cell lymphoma
- Active CNS lymphoma or HIV-related lymphoma.
- Any chemotherapy, radiotherapy, or other anticancer treatment (including corticosteroid, 10 or more mg/day of prednisone or equivalent) within the 2 weeks before randomization
- Pregnant women or nursing mothers

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

**Table 14: PIX301 Baseline demographic characteristics (ITT population)**

| | **Pixantrone** (N=70) | **Comparator** (N=70) |
|---|---|---|
| **Age at Randomisation (years)** | | |
| Mean (SD) | 58.2 (13.5) | 56.2 (12.9) |
| Median (range) | 60.0 (18-80) | 58.0 (26-82) |
| **Age Category at Randomisation, n (%)** | | |
| 18 to <30 | 5 (7.1%) | 2 (2.9%) |
| 30 to <40 | 2 (2.9%) | 9 (12.9%) |
| 40 to <50 | 9 (12.9%) | 7 (10.0%) |
| 50 to <60 | 18 (25.7%) | 21 (30.0%) |
| 60 to <70 | 20 (28.6%) | 21 (30.0%) |
| 70 to <80 | 15 (21.4%) | 9 (12.9%) |
| ≥80 | 1 (1.4%) | 1 (1.4%) |
| **Sex, n (%)** | | |
| Male | 46 (65.7%) | 40 (57.1%) |
| Female | 24 (34.3%) | 30 (42.9%) |
| **Race, n (%)** | | |
| Caucasian | 46 (65.7%) | 44 (62.9%) |
| Black | 0 | 0 |
| Asian | 10 (14.3%) | 13 (18.6%) |
| Hispanic | 7 (10.0%) | 6 (8.6%) |
| Native American | 1 (1.4%) | 1 (1.4%) |
| Other | 6 (8.6%) | 6 (8.6%) |
| **Baseline ECOG Performance Status, n (%)** | | |
| 0 | 26 (37.1%) | 23 (32.9%) |
| 1 | 30 (42.9%) | 32 (45.7%) |
| 2 | 14 (20.0%) | 14 (20%) |

| | | |
|---|---|---|
| 3 | 0 | 1 (1.4%) |
| **Geographic Region, n (%)** | | |
| North America | 4 (5.7%) | 4 (5.7%) |
| Western Europe | 19 (27.1%) | 19 (27.1%) |
| Rest of World | 47 (67.1%) | 47 (67.1%) |
| **Weight (kg)** | | |
| Mean (SD) | 70.9 (15.8) | 68.7 (15.3) |
| Median (range) | 70.0 (45-117) | 67.5 (37-115) |

SD=standard deviation
Fisher exact test was used to compare proportions between the group and a two-sided student's t-test was used in the comparison of means between treatment groups.
Source: 14.1.3 and 14.1.3.4 [PIX301 CSR 2010]

**Table 15: PIX301 Baseline history**

| | **Pixantrone** (n=70) | **Comparator** (n=70) |
|---|---|---|
| Diffuse large B-cell lymphoma | 53 (75.7%) | 51 (72.9%) |
| Transformed indolent lymphoma | 10 (14.3%) | 9 (12.9%) |
| Follicular lymphoma grade III | 1 (1.4%) | 2 (2.9%) |
| Peripheral T-cell lymphoma NOC | 3 (4.3%) | 7 (10.0%) |
| Anaplastic large cell lymphoma/null cell/primary systemic | 3 (4.3%) | 1 (1.4%) |

**Table 16: PIX301 Baseline disease characteristics**

| | **Pixantrone** (n=70) | **Comparator** (n=70) |
|---|---|---|
| **Duration of NHL (months)** | | |
| Mean (SD) | 43.6 (35.6) | 46.6 (51.7) |
| Median (range) | 32.0 (7-160) | 31.6 (0-333) |
| **Ann Arbor Stage of NHL, n (%)** | | |
| I/II | 19 (27.1%) | 14 (20.0%) |

| | | |
|---|---|---|
| III/IV | 51 (72.9%) | 56 (80.0%) |
| **International Prognostic Index, n (%)** | | |
| 0, 1 | 21 (30.0%) | 17 (24.3%) |
| ≥2 | 49 (70%) | 52 (74.3%) |
| Missing | 0 | 1 (1.4%) |
| **Number of Extranodal Sites, n (%)** | | |
| 0 | 35 (50%) | 35 (50%) |
| ≥1 | 34 (48.6%) | 33 (47.1%) |
| Missing | 1 (1.4%) | 2 (2.9%) |
| **Time from Last Chemotherapy to Randomisation (months)** | | |
| Mean (SD) | 13.6 (15.7) | 13.2 (23.5) |
| Median (range) | 9.0 (1-86) | 8.0 (1-190) |

SD=Standard deviation

Fisher exact test was used to compare proportions between the groups, and a two-sided student's t test was used in the comparison of means between treatment groups. P-values are for reference purposes only.

**Table 17: Prior NHL treatment**

| | **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 (a) | 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 (b) | 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 ($mg/m^2$) (b)** | | |
| Mean (SD) | 284.8 (98.1) | 321.9 (119.0) |
| Median (range) | 292.9 (51-472) | 315.5 (15-681) |

(a) Other topoisomerase inhibitors were etoposide and teniposide

(b) Other includes targeted therapies, non-classified anticancer therapies and supportive therapies

SD=Standard deviation

Fisher exact test was used to compare proportions between the groups, and a two-sided student's t test was used in the comparison of means between treatment groups.

Demographic characteristics of patients at baseline were well balanced, except for cardiac history. Three patients in the pixantrone group had a history of congestive heart failure and two had continuing cardiomyopathy, compared with no patients with either disorder in the comparator group. DLBCL was the most common histological subtype. At baseline, 46 (66%) of 70 patients in the pixantrone group and 44 (63%) of 70 in the comparator group had an International Prognostic Index score of 2 or lower. Both groups received the same median number of previous chemotherapy regimens, and the median

dose of doxorubicin dose-equivalent exposure was slightly lower in the pixantrone group than in the comparator group. A similar number of patients in each group had previously received rituximab, and the same number of patients in each group were refractory to their previous therapy[22].

Aggressive histological features were identified on site in all patients before treatment was given, and the central independent pathological review histologically confirmed aggressive NHL in 54 (77%) of 70 patients in the pixantrone group and 50 (71%) of 70 patients in the comparator group, retrospectively. Of the remaining 36 patients, reference pathologists did not achieve consensus for ten patients, but agreed that 13 had low-grade histological features and five had a nonaggressive subtype other than NHL. Two patients were reviewed by only one pathologist, and six did not have a review because of shortage of specimen[22].

**Outcomes**

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-defined outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).

*Primary outcomes*

The primary endpoint was assessed by an independent assessment panel of three experts (a radiologist, an oncologist, and a pathologist). The CT imaging of tumour response was also reviewed by an independent radiological review panel[22].

*Secondary outcomes*

Overall Survival (OS): The time between the date of randomization and the date of death due to any cause. If a patient was not known to have died, survival was censored at the time of last contact/last date patient was seen alive. Patients still alive at the end of the study were censored at that time.

Response Rate Lasting at Least 4 months: The total proportion of patients with CR, CRu, or PR with a difference from the first documented objective response to disease progression or death of at least 4 months. Patients who had a response and later underwent engraftment were censored at the start of the induction treatment.

Progression-Free Survival (PFS): The time between the date of randomization and the date of the initial documentation of progressive/relapsed disease or death due to any cause. PFS for patients who were alive without disease progression at their date of last tumor assessment was censored at the date of last tumor assessment[2].

*Other prespecified outcomes*

Overall Response Rate (ORR): The total proportion of patients with CR, CRu, or PR as assessed by the IAP.

Time to Response: The time between the date of randomization and the date of the initial response independent of the duration.

Time to Complete Response: The time between the date of randomization and the date of the initial CR or CRu.

Duration of Response: The time from the first documented objective response to disease progression/relapse or death. Patients who were still responding at the date of their last tumor assessment were censored at the date of last tumor assessment.

Relative Dose Intensity: The proportion (%) of the actual dose intensity divided by the planned dose intensity for that same period of time[2].

*CR/CRu as a surrogate endpoint for OS*

OS is the accepted standard for measurement of efficacy and patient benefit in oncology studies as it is straightforward to measure, interpret and explain and is clinically meaningful. However, measurement of OS requires large sample sizes and may require long follow-up periods. In order to bring novel therapies to patients in a timely manner, the oncology community has extensively researched measurable surrogate endpoints that can be used to predict OS in smaller, shorter studies.

To identify surrogate endpoints for OS in NHL, Lee and colleagues performed a meta-analysis that included a total of 58 randomised studies of first-line therapies conducted between 1978 and 2005[31]. The analysis demonstrated that CR was significantly correlated with both 3-year and 5-year survival in NHL, although the correlation was only moderate (correlation coefficient of 0.58 and 0.50 on 3-year and 5-year OS, respectively). However PFS was strongly correlated with OS in aggressive NHL patients. Using a linear regression analysis, they observed that a 10% improvement in CR corresponded to a 9% ± 1% improvement in 3-year PFS and also that a 10% improvement in PFS predicted a 7% improvement in 5-year survival.

The aggressive NHL patients included in the Lee et al meta-analysis were untreated; thus the interpretation of surrogacy of CR to OS was limited to the first-line patient population and did not consider the impact of salvage regimens. CTI performed a literature search (2012) to identify potential surrogacy for OS in relapsed or refractory aggressive NHL. The pre-defined criteria included: 20 or more patients with relapsed or refractory aggressive NHL receiving third-line or later therapy; both CR and 3-year OS results reported; and publication within the previous 15 years. The identified studies comprised three randomised studies[10,32,33] and nine single arm studies[34-42].

Using methods similar to Lee et al, CTI performed correlation and linear regression analyses for the randomised and single arm studies, respectively. The analysis of the randomised studies evaluated the effect of CR on 3-year OS. For the single arm studies, the six treatment groups in the three

randomised studies were added to the nine studies to yield a total of 15 data points. The CR rate was then compared to the 3-year OS rate.

The regression analysis of the 3 randomised studies, though likely under-powered, showed a trend towards a significant correlation ($r^2$ = 0.99, p=0.07) between CR and 3-year survival. This trend was further supported by evidence from the single arm studies where a strong and statistically significant correlation between CR and OS ($r^2$ = 0.81, p<0.001) was observed. These results in relapsed/refractory aggressive NHL taken together with those of Lee et al in untreated aggressive NHL provide evidence for the relationship between CR and OS and the appropriate use of CR as a surrogate measure in aggressive NHL studies.

**Statistical analysis and definition of study groups**

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).

*Hypothesis*

The primary aim of the PIX301 study was to determine whether pixantrone improved the CR or CRu rate in the ITT population compared with a physician's choice of comparator. Secondary aims were to determine whether pixantrone improved progression-free survival (PFS), response rate lasting at least 4 months and overall survival compared with a physician's choice of comparator. Additionally, the study aimed to observe whether pixantrone improved the ORR (total proportion of patients with a CR/CRu/PR as assessed by an independent assessment panel), the time to response, time to CR /CRu and duration of response compared with a physician's choice of comparator.

Efficacy analyses for the PIX301 trial were based on assessments, by an independent assessment panel, of the ITT population, which included all patients randomised to either the pixantrone or comparator group. The safety analyses consisted of data from patients who received any amount of protocol therapy. The study investigators used SAS version 9.2 for statistical analyses.

*Statistical analysis for the primary outcome*

The researchers analysed the primary outcome comparing the proportion of patients with a CR or CRu in the pixantrone or comparator groups at end of treatment. Analysis took place when the last patient finished their last treatment visit. An additional analysis was performed at the end of the study, when patients had finished 18-month follow-up. Fisher's exact test was used

*Statistical analysis for secondary outcomes*

In the analysis of progression-free survival, patients starting follow-up therapy were thought to have progressed, irrespective of whether progression had been confirmed radiologically. Patients were censored at their last tumour assessment. Progression-free survival and overall survival was assessed with Kaplan–Meier methods and the unstratified log-rank test. A Cox proportional hazards model was used to assess the significance of subgroups for the efficacy variables and to establish the hazard ratio (HR) and 95% CI for each subgroup.

*Sample size and power calculation*

With a final enrolment of 140 patients, the study was considered sufficiently powered (about 80%) to detect a 15% difference in the CR/CRu rate in the pixantrone arm[22].

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

The results for the subgroup of those patients with aggressive B-cell lymphoma (classed as DLBCL, transformed indolent lymphoma, or FL, grade

3) and those with DLBCL are presented in Section 6.5.

**Participant flow**

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

This data is presented in section 6.3.1 (Figure 5)

## *6.4 Critical appraisal of relevant RCTs*

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

**Table 18: Quality assessment results for RCTs**

| PIX301 study | | |
|---|---|---|
| **Study question** | **How is the question addressed in the study?** | **Grade (yes/no/not clear/N/A)** |
| Was randomisation carried out appropriately? | Patients were randomly assigned (1:1) by an interactive voice response system (IVRS). The randomisation schedule was created by the IVRS vendor. | Yes |
| Was the concealment of treatment allocation adequate? | The success of masking was confirmed by external audit of the independent assessment panel. | Yes |
| Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease? | With the exception of cardiac history, both groups were similar. Two patients in the pixantrone group had a history of congestive heart failure and two had continuing cardiomyopathy, compared with no patients with either disorder in the comparator group. | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? | The trial was open-label. Treatment assignments were known to the patients and investigators, but masked to the independent assessment panel and to the tumour response assessments made by the investigators, thus there was no risk of bias. | N/A |
| Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? | | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | | No |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | ITT analysis was used. There were no missing data. | Yes |
| Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See Section 10.3, appendix 3 for a suggested format.

As there was only one study, the complete quality assessment for that study is presented above (Table 18).

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Not applicable, as there was only one study.

## *6.5 Results of the relevant RCTs*

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

**Study PIX301 results summary**

- Pixantrone demonstrated statistically significantly higher rates of confirmed and unconfirmed complete response compared to other single agent therapies.
    - At end of treatment, CR/CRu (complete response/unconfirmed complete response) rates were 20.0% [95% CI 11.4-31.3] in the pixantrone group compared to 5.7% [1.6-14.0] in the comparator arm (*P*=0.021).
    - This figure rose to 24.3% [95% CI 14.8-36.0] for pixantrone and 7.1% [2.4-15.9] for the comparator at the end of study (*P*=0.009).
- Pixantrone provides a clinically significant increase in progression-free survival compared to single agent comparator therapies:
    - 5.3 months [95% CI 2.3-6.2] for pixantrone vs.. 2.6 months [1.9-3.5] for comparators (*P*=0.005).
- Pixantrone resulted in a numerical increase in overall survival (10.2 months [95% CI 6.4-15.7]) but this did not reach statistical significance

compared to the comparator arm (7.6 months [5.4-9.3], *P*=0.251).

- Patients who achieved a response (CR/CRu or partial response), were twice as likely to achieve a durable response (≥4 months) with pixantrone compared to the comparator agents (17.1% vs.. 8.6%).
- Of those who had a CR/CRu, 82% of patients (14/17) had a better response to pixantrone than they had experienced with their last multi-agent regimen.
    - Six of these patients were refractory to their last therapy.
- A sub-group analysis was performed in patients with aggressive B-cell lymphoma who received pixantrone (n=50) or comparator (n=49) as third- or fourth-line therapy. In this sub-group, pixantrone was associated with statistically and clinically relevant improvements in:
    - CR/CRu of 28.0% vs. 4.1% for pixantrone vs. control (*P*=0.002)
    - ORR of 48.0% vs. 12.2% for pixantrone vs. control (*P*<0.001)
    - PFS of 5.8 vs. 2.8 months for pixantrone vs. control (*P*=0.002)
- Similar to the overall study population, in those receiving third- or fourth-line therapy, OS showed a numerical trend in favour of pixantrone therapy which did not reach statistical significance.
    - OS of 13.9 vs. 7.8 months for pixantrone vs. control (*P*=0.275, HR 0.76 (0.47–1.24))

*Conclusion*

Pixantrone monotherapy has demonstrated efficacy in heavily pre-treated patients with aggressive NHL. It results in higher Cr/CRu rates and PFS than existing single therapy options, which are both statistically significant and clinically relevant.

*Efficacy*

The study achieved its primary endpoint, indicating that pixantrone is effective when compared to a physician's choice of single-agent comparators for treating relapsed or refractory aggressive NHL in a heavily pre-treated patient population[2].

*CR/CRu rate*

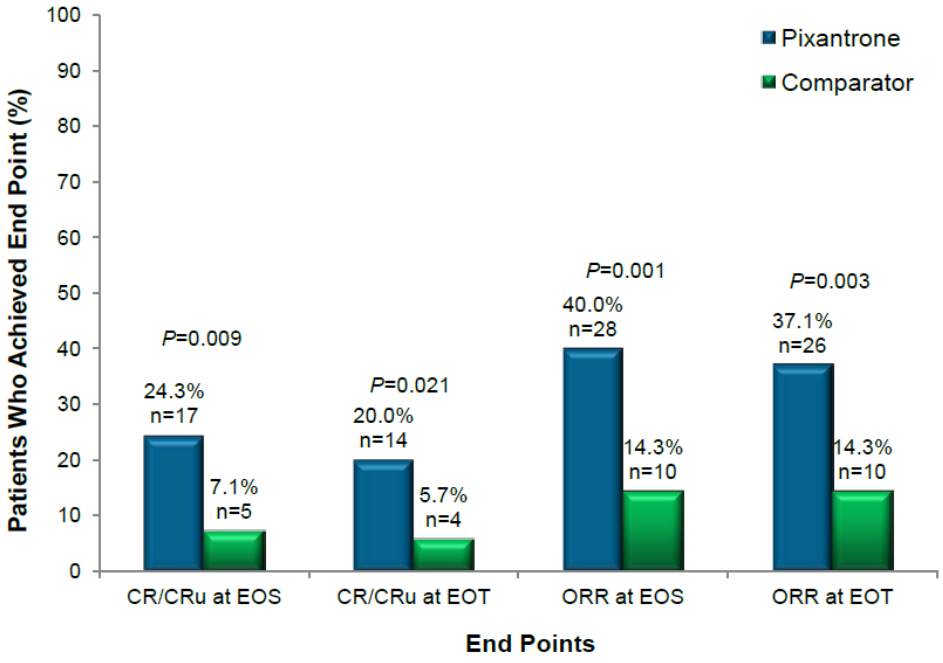
**Table 19: CR/Cru rates at the end of treatment and at the end of study[22]**

| | End of treatment | | | End of Study | | |
|---|---|---|---|---|---|---|
| | **Pixantrone (n=70)** | **Comparator (n=70)** | **p value** | **Pixantrone (n=70)** | **Comparator (n=70)** | **p value** |
| **CR/CRu** | 14 (20%, 11.4-31.3) | 4 (5.7%, 1.6-14.0) | 0.021 | 17 (24.3%, 14.8-36.0) | 5 (7.1%, 2.4-15.9) | 0.009 |
| **CR** | 8 (11.4%, 5.1-21.3) | 0 (0%, 0.0-5.1) | 0.006 | 11 (15.7%, 8.1-26.4) | 0 (0%, 0.0-5.1) | 0.001 |
| **CRu** | 6 (8.6%, 3.2-17.7) | 4 (5.7%, 1.6-14.0) | 0.075 | 6 (8.6%, 3.2-17.7) | 5 (7.1%, 2.4-15.9) | 1.000 |
| Data are presented as n (%, CI)<br>End of study refers to analyses of treatment and 18-month follow-up | | | | | | |

Of those who experienced a CR/CRu, 82% (14/17) had a better response to pixantrone than they had experienced with their last multi-agent regimen. Six of these patients were refractory to their last therapy[2].

Meanwhile, the ORR at EOT was also significantly higher in the pixantrone group relative to the comparators (n=26 vs.. 10; 37.1% vs.. 14.3% [95% CI 25.9-49.5 vs.. 7.1-24.7]; *P*=0.003), becoming even more robust by EOS (n=28 vs.. 10; 40.0% vs.. 14.3% [95% CI 28.5-52.4 vs. 7.1-24.7]; *P*=0.001; Figure 7)[22].

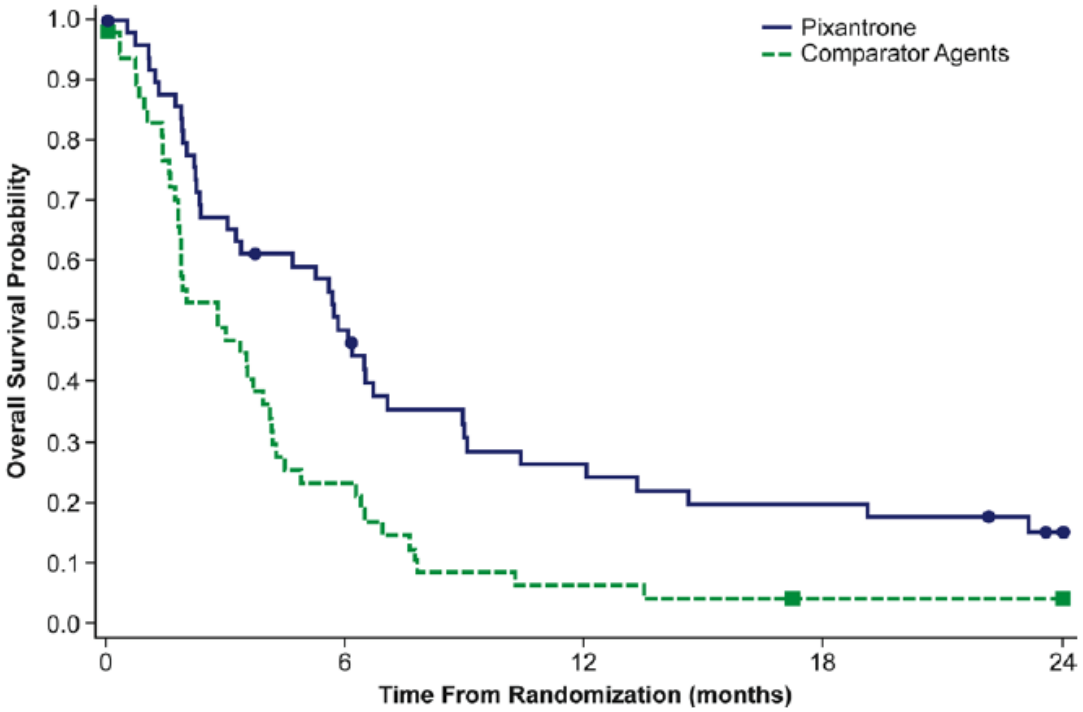
**Figure 7: IAP-assessed CR/CRu rate and ORR of the ITT populations[2]**




*Progression-free survival*

The median PFS of the ITT population was significantly longer for patients treated with pixantrone (5.3 months; 95% CI 2.3-6.2), than for those treated with comparators (2.6 months; 95%CI 1.9-3.5, HR [hazard ratio] 0.60 [95%CI 0.42-0.82]; log-rank *P*=0.005; Figure 8)[22].

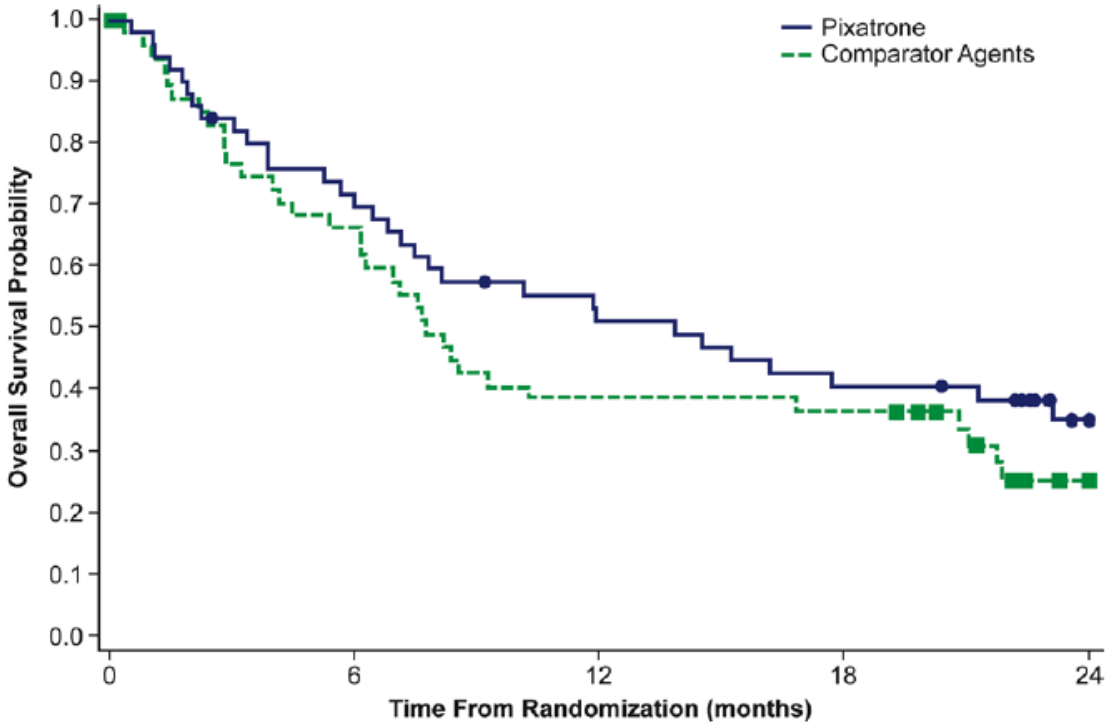
**Figure 8: Kaplan–Meier curve of PFS of the ITT population**




*Overall survival*

The median OS advantage for patients randomised to pixantrone was 2.6 months (10.2 months [95% CI 6.4-15.7] vs.. 7.6 months [95% CI 5.4-9.3]; HR 0.79 [95% CI .53-1.18]; log-rank *P*=0.251; Figure 9). Although this result is not statistically significant, it is suggestive of a trend in increased survival that requires further investigation[22].

**Figure 9: Kaplan–Meier curve of OS of the ITT population**




*Time to response*

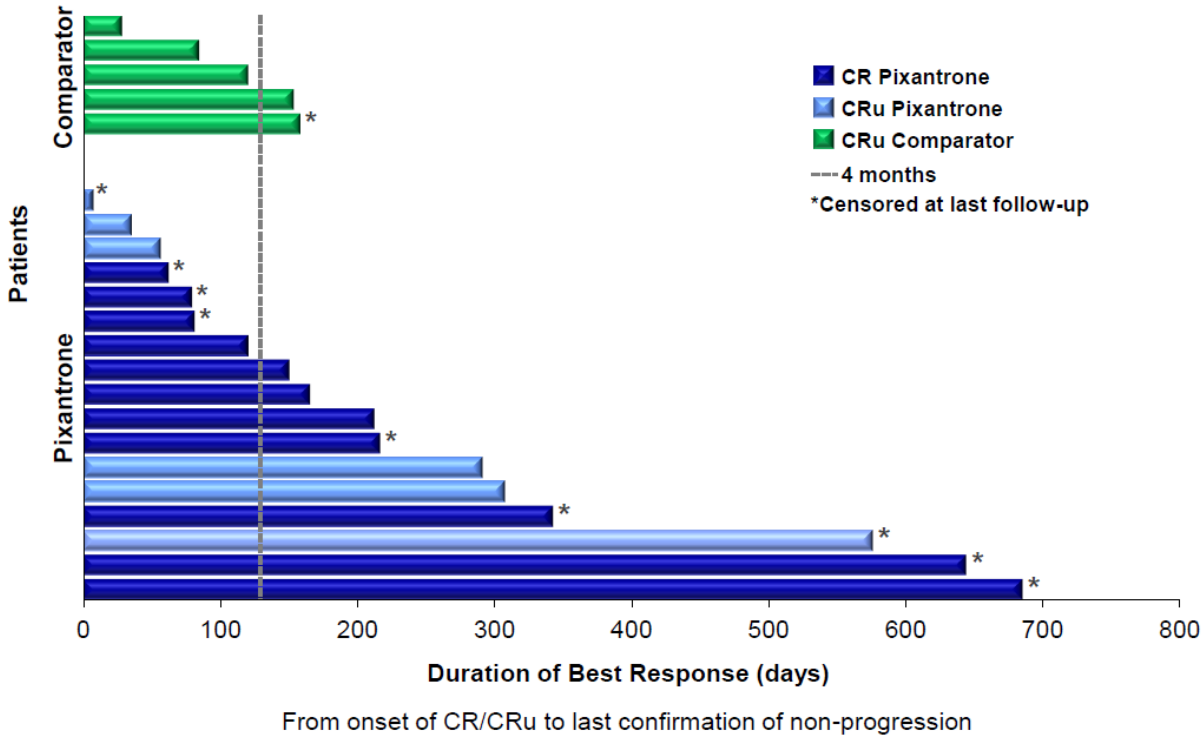
Time to initial overall response was similar, with a median of 1.9 months for both groups (95% CI 1.8–2.3 for pixantrone vs. 1.6–2.3 for comparator; HR 0.68 [95% CI 0.32–1.43]; p=0.304), including 28 patients in the pixantrone group and ten in the comparator. The median time to complete response was 2.0 months (95% CI 1.7–3.7) for the pixantrone group and 3.6 months (2.3–19.0) for the comparator (HR 1.92 [95% CI 0.64–5.77]; p=0.237)[22].

*Duration of response*

The median duration of CR/CRu for the pixantrone group was 9.6 months (95% CI 4.0−20.8). No patients in the comparator group had a CR, so the median duration of CRu-only was 4.0 months (95% CI 1.0−5.1; *P*=0.081, Figure 10)[2,22]. Furthermore, the percentage of patients with a response lasting at least 4 months (from CR/CRu/PR until disease progression) is a measurement of both frequency and durability of response. The responses

with pixantrone were more durable than those with comparators[2]; twice as many patients in the pixantrone arm had a response lasting ≥4 months (12 patients [17.1%] vs.. six patients [8.6%])[2,22].

**Figure 10: Duration of CR/CRu by IAP assessment[2]**




*Dose Intensity*

Median dose intensity for the pixantrone group was 55 mg/m per week (range 24–64) with a median relative dose intensity of 90.6% (range 20–102). Median relative dose intensity was greater than 93% for all patients in the comparator group, except for those who received vinorelbine.

## Subgroup analysis

*Aggressive B-cell lymphoma*

This population forms the basis for the base case presented for cost effectiveness analysis. This group of patients from the PIX301 study most closely resembles the population for the licensed indication of pixantrone.

According to baseline characteristics, 64 (91.4%) of 70 patients in the pixantrone group and 62 (88.6%) of 70 in the comparator group had aggressive B-cell lymphoma. In post-hoc analyses, the proportion of these patients with a CR/Cru and an ORR was significantly higher for those who received pixantrone than for those given a comparator agent. Median PFS was significantly longer in the pixantrone group (Table 20). In all histological subtypes, median OS in the pixantrone group was longer than in the comparator group, although the difference was not significant (10.2 months [95% CI 6.4–15.7] vs. 7.6 months [5.4–9.3]; HR 0.79 [95% CI 0.53–1.18]; log-rank p=0.251). Kaplan-Meier plots are shown in Figures 11& 12.

**Table 20: Summary of efficacy in patients with aggressive B-cell lymphoma*[22]**

| | **Pixantrone (n=64)** | **Comparator (n=62)** | **P value** | **HR (95% CI)** |
|---|---|---|---|---|
| **CR/CRu** | 15 (23.4%, 13.8-35.7) | 5 (8.1%, 2.7-17.8) | 0.027 | - |
| **OR†** | 26 (40.6%, 28.5-53.6) | 10 (16.1%, 8.0-27.7) | 0.003 | - |
| **Median PFS, months‡** | 5.7 (2.4-6.5) | 2.5 (1.9-3.5) | 0.002** | 0.56 (0.38-0.81) |

Data are n (%, 95% CI) or median (95% CI) unless specified otherwise

Efficacy was determined by an independent assessment panel after 18-month follow-up

ITT=intention-to-treat. HR=hazard ratio

*Patients with diffuse large B-cell lymphoma, transformed indolent lymphoma, and follicular lymphoma, grade 3, determined by on-site pathology

†Responses included patients with complete, unconfirmed complete, or partial response

‡Kaplan-Meier analysis

**Log-rank p value

Aggressive B-cell lymphoma analyses were exploratory and did not include median overall survival

**Figure 11: Overall survival for patients with aggressive B-cell lymphoma and 2 or 3 prior lines of therapy**

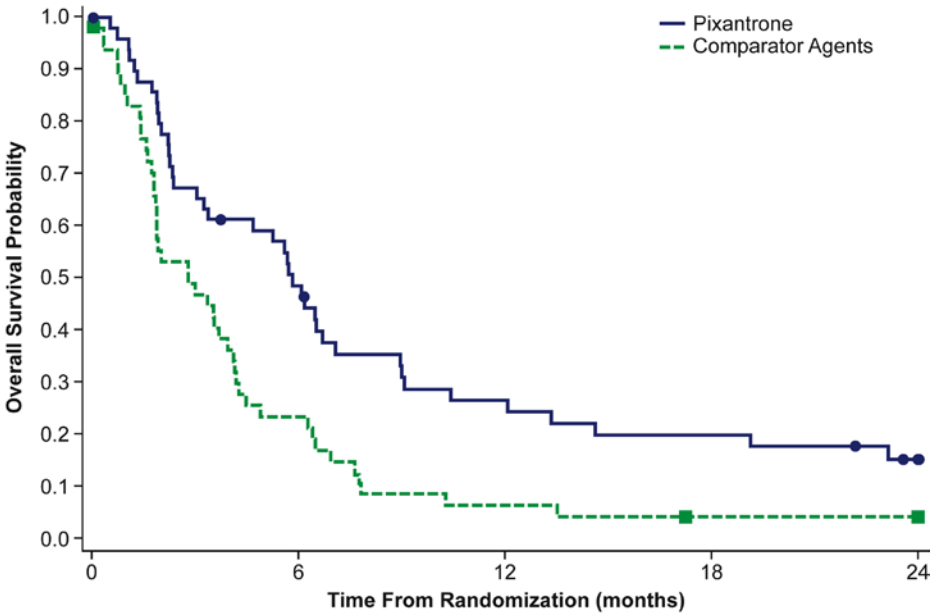
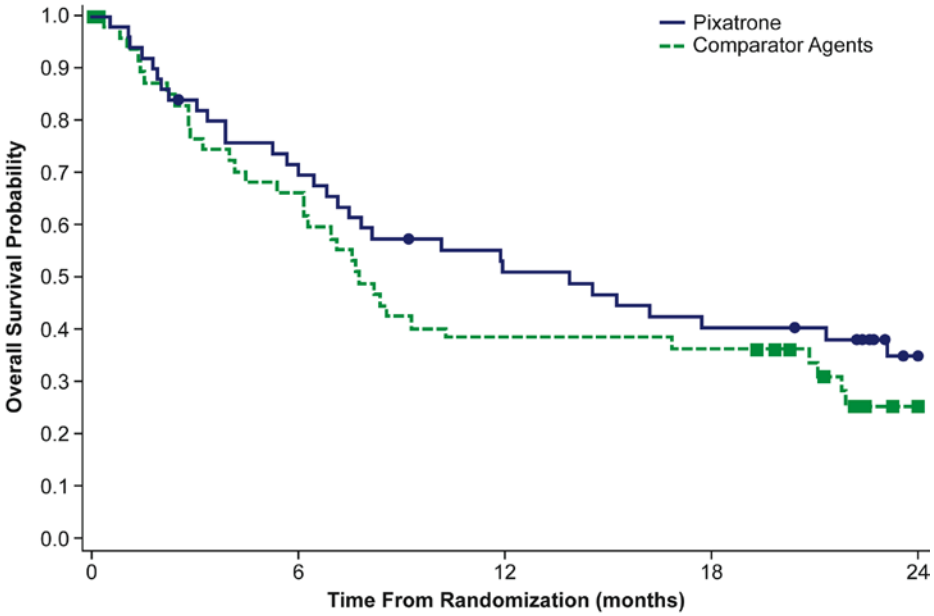



**Figure 12: Progression free survival for patients with aggressive B-cell lymphoma and 2 or 3 prior lines of therapy**



*Diffuse large B-cell lymphoma (DLBCL)*

According to baseline characteristics, 53 (75.7%) of 70 patients in the pixantrone group and 51 (72.9%) of 70 in the comparator group had DLBCL. In post-hoc analyses, the proportion of these patients with a CR/Cru and an ORR was significantly higher for those who received pixantrone than for those given a comparator agent. Median PFS was significantly longer in the pixantrone group (Table 21). Kaplan-Meier plots are shown in Figure 13.

**Table 21: Summary of efficacy in patients with aggressive DLBCL**

| | **Pixantrone (n=53)** | **Comparator (n=51)** | **P value** | **HR (95% CI)** |
|---|---|---|---|---|
| **CR/CRu** | 10 (18.9%, 9.4%-32.0%) | 2 (3.9%, 0.5%-13.5%) | 0.029 | - |
| **OR†** | 18 (34.0%, 21.5%-48.3%) | 7 (13.7%, 5.7%-26.3%) | 0.021 | - |
| **Median PFS, months‡** | 4.6 (2.3-6.5) | 2.1 (1.8-3.2) | <0.001** | 0.47 (0.30-0.71) |

Data are n (%, 95% CI) or median (95% CI) unless specified otherwise

Efficacy was determined by an independent assessment panel after 18-month follow-up

ITT=intention-to-treat. HR=hazard ratio

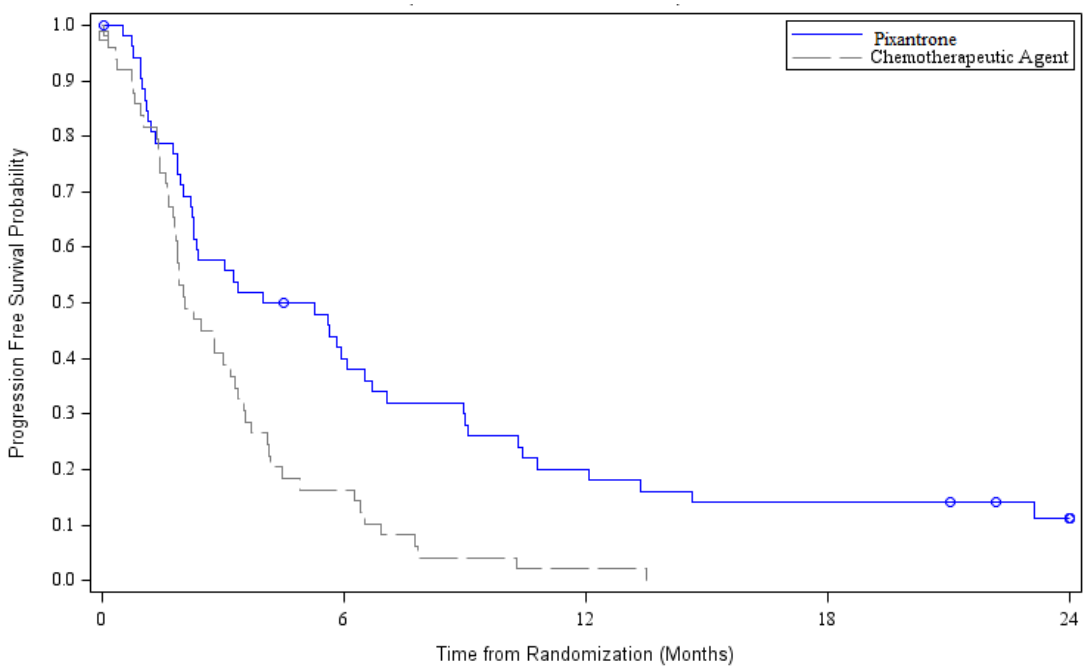
*Patients with diffuse large B-cell lymphoma, determined by on-site pathology

†Responses included patients with complete, unconfirmed complete, or partial response

‡Kaplan-Meier analysis

**Log-rank p value

Figure 13: Progression free survival for patients with DLBCL



### *Meta-analysis*

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.5.3 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individuall and combined results (such as through the use of forest plots).

No meta-analysis was conducted as only one relevant RCT was identified.

6.5.4 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

No meta-analysis was carried out as only one relevant RCT was identified.

6.5.5 If any of the relevant RCTs listed in response to Section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The

impact that each exclusion has on the overall meta-analysis should be explored.

Not applicable as no meta-analysis was conducted.

## *6.6 Indirect and mixed treatment comparisons*

| Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22. |
|---|

6.6.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

The clinical effectiveness review was designed to identify all controlled clinical trials randomised and non-randomised, on all appropriate competitor drugs as well as for pixantrone, for the study population of interest (see sections 6.1 and 6.2). Only one study was identified as a result of this process (the PIX301 trial for pixantrone). No indirect or mixed treatment comparison could therefore be carried out.

6.6.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Not applicable. Only one study was identified as a result no indirect or mixed treatment comparison could therefore be carried out.

6.6.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Not applicable. Only one study was identified as a result no indirect or mixed treatment comparison could therefore be carried out.

6.6.4 For the selected trials, provide a summary of the data used in the analysis.

Not applicable. Only one study was identified as a result no indirect or mixed treatment comparison could therefore be carried out.

6.6.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Not applicable. Only one study was identified as a result no indirect or mixed treatment comparison could therefore be carried out.

6.6.6 Please present the results of the analysis.

No applicable. Only one study was identified as a result no indirect or mixed treatment comparison could therefore be carried out.

6.6.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable. Only one study was identified as a result no indirect or mixed treatment comparison could therefore be carried out.

6.6.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable. Only one study was identified as a result no indirect or mixed treatment comparison could therefore be carried out.

6.6.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable. Only one study was identified as a result no indirect or mixed treatment comparison could therefore be carried out.

## *6.7 Non-RCT evidence*

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.7.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

Since few RCTs were expected to be found, the protocol for this review planned for the identification and inclusion of controlled but non-randomised clinical trials as well as RCTs. No non-randomised, controlled trials were identified that met the inclusion criteria. Full details of search strategy and inclusion criteria can be found in Sections 6.1 and 6.2.

## *6.8 Adverse events*

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

**Summary**

An assessment of adverse events (AEs) in the PIX301 trial demonstrates that pixantrone is well tolerated in the indicated population of heavily pre-treated NHL patients.

Pixantrone is primarily associated with myelosuppressive toxicities that may be managed with existing supportive agents.

Common AEs are similar to those expected in heavily pre-treated patient populations and predominantly affect the haematological, gastrointestinal and respiratory systems

Neutropenia is the most commonly occurring AE and may be easily managed with supportive agents. Neutropenia does not increase in severity with ongoing treatment, with recovery normally occurring by Day 28.

Although the frequency of cardiac AEs was higher in the pixantrone than comparator group, they were not dose-related and the majority of events in the pixantrone group were asymptomatic decreases in LVEF.

No patient treated with pixantrone developed congestive cardiac failure that is typical for anthracyclines, and no grade 4 declines in LVEF were observed.

6.8.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

Not applicable.

6.8.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

An assessment of adverse events (AEs) in the PIX301 trial demonstrates that pixantrone is well tolerated in the indicated population of heavily pre-treated NHL patients.

In the PIX301 pivotal trial, dose reductions were infrequent in both treatment groups (18% pixantrone vs.. 15% comparator). More patients in the pixantrone group required a dose delay (40% vs.. 22%), but the majority of delays affected only one dose. Only one patient missed a dose (pixantrone arm)[1].

The most common adverse events (seen in ≥10% of patients) and grade 3 or 4 events reported in the two groups are summarised in Table 22. Irrespective

of the relationship to treatment, similar proportions of patients had adverse events in the pixantrone (66 of 68 [97.1%]) and comparator (61 of 67 [91.0%]) groups, whereas more patients had a grade 3 or 4 event in the pixantrone group than in the comparator group (52 of 68 [76.5%] vs. 35 of 67 [52.2%]), with neutropenia as the predominant event[22].

More patients in the pixantrone group than in the comparator group reported treatment-related adverse events (55 of 68 [80.9%] vs. 38 of 67 [56.7%]), consistent with the higher incidence of neutropenia, and possibly related to more frequent blood counts. Blood counts were performed on days 1, 8, and 15 per protocol in the pixantrone patients, but only on day 1 in 52% of patients treated in the comparator arm, which may have resulted in under-reporting of hematopoietic AEs in those patients treated with a comparator[1,22].

Patients in the pixantrone group had higher rates of the common adverse events neutropenia, leucopenia, cough, and skin discolouration, whereas patients in the comparator group had higher rates of diarrhoea and renal failure. Skin discolouration disappears over a few days to weeks as the drug is cleared. The higher incidence of respiratory adverse events may have been associated with pixantrone itself, or the administration of the drug in 500 ml of saline over 1 hour. The recommended total volume of saline in the pixantrone infusion should be 250 ml administered IV over 1 hour[1,22].

The severity of neutropenia did not increase with increasing cycle number. In the pixantrone group, the highest incidence of Grade 4 neutropenia occurred in cycle 2 (eight of 54 patients [14.8%])[22]. Neutropenia reached nadir on day 15 to 20 of each cycle and recovery normally occurred by day 28[1]. More patients who received pixantrone were given an immunostimulant than were those who received a comparator agent (35 of 68 [51.5%] vs. 18 of 67 [26.9%]); however, a substantial proportion of patients who were given an immunostimulant received only a single dose[22]. Febrile neutropenia occurred in more patients given pixantrone than in those given a comparator agent; however, more patients in the comparator group had Grade 3 or 4 pyrexia (Table 22). The overall rates of grade 3 and 4 infections were similar between the study groups[1,22].

Serious adverse events were reported in 35 (51.5%) of 68 patients in the pixantrone group and 30 (44.8%) of 67 in the comparator group. Malignant neoplasm progression was reported as a serious adverse event more frequently in the comparator group. Overall for both groups, the most common serious adverse events (in ≥5% of patients) were neutropenia (nine [13.2%] of 68 patients in the pixantrone group vs. six [9.0%] of 67 patients in the comparator group), pyrexia (seven [10.3%] vs. seven [10.4%]), malignant neoplasm progression (one [1.5%] vs. nine [13.4%]), pneumonia (five [7.4%] vs. four [6.0%]), anaemia (two [2.9%] vs. five [7.5%]), and thrombocytopenia (one [1.5%] vs. six [9.0%])[22].

Ten (14.7%) of 68 patients in the pixantrone group and 12 (17.9%) of 67 in the comparator group died within 30 days of receiving their last dose of treatment. The deaths of five patients in the pixantrone group and 11 in the comparator group were thought to be caused by progressive disease; the remaining deaths were due to a range of other causes, but nearly all were from uncontrolled lymphoma[22].

**Table 22: Common Adverse Events in PIX301**

| Preferred Term | Common any-grade AE | | Grade 3 or 4 AE | |
|---|---|---|---|---|
| | **Pixantrone** (n=68) | **Comparator** (n=67) | **Pixantrone** (n=68) | **Comparator** (n=67) |
| **Any adverse event** | 66 (97.1%) | 61 (91.0%) | 52 (76.5%) | 35 (52.2%) |
| **Blood and lymphatic disorders** | | | | |
| Anemia | 21 (30.9%) | 22 (32.8%) | 4 (5.9%) | 9 (13.4%) |
| Neutropenia | 34 (50.0%) | 16 (23.9%) | 28 (41.2%) | 13 (19.4%) |
| Leukopenia | 17 (25.0%) | 7 (10.4%) | 16 (23.5%) | 5 (7.5%) |
| Thrombocytopenia | 14 (20.6%) | 13 (19.4%) | 8 (11.8%) | 7 (10.4%) |
| Febrile Neutropenia | 6 (8.8%) | 2 (3.0%) | 5 (7.4%) | 2 (3.0%) |
| Lymphopenia | 3 (4.4%) | 0 (0.0%) | 2 (2.9%) | 0 (0%) |
| **Gastrointestinal disorders** | | | | |
| Nausea | 12 (17.6%) | 11 (16.4%) | 0 (0%) | 1 (1.5%) |

| Preferred Term | Common any-grade AE | | Grade 3 or 4 AE | |
|---|---|---|---|---|
| | **Pixantrone** (n=68) | **Comparator** (n=67) | **Pixantrone** (n=68) | **Comparator** (n=67) |
| Abdominal Pain | 11 (16.2%) | 7 (10.4%) | 5 (7.4%) | 3 (4.5%) |
| Constipation | 8 (11.8%) | 3 (4.5%) | 0 (0%) | 0 (0%) |
| Vomiting | 5 (7.4%) | 10 (14.9%) | 0 (0%) | 2 (3.0%) |
| Diarrhea | 3 (4.4%) | 12 (17.9%) | 0 (0%) | 0 (0%) |
| **General disorders and administrative site conditions** | | | | |
| Asthenia | 16 (23.5%) | 9 (13.4%) | 3 (4.4%) | 3 (4.5%) |
| Pyrexia | 16 (23.5%) | 17 (25.4%) | 3 (4.4%) | 6 (9.0%) |
| Edema peripheral | 10 (14.7%) | 4 (6.0%) | 0 (0%) | 0 (0%) |
| Fatigue | 9 (13.2%) | 9 (13.4%) | 2 (2.9%) | 0 (0%) |
| Mucosal inflammation | 8 (11.8%) | 2 (3.0%) | 0 (0%) | 1 (1.5%) |
| Pain | 2 (2.9%) | 3 (4.5%) | 1 (1.5%) | 2 (3.0%) |
| **Infections and infestations** | | | | |
| Pneumonia | 5 (7.4%) | 4 (6.0%) | 4 (5.9%) | 3 (4.5%) |
| Cellulitis | 4 (5.9%) | 2 (3.0%) | 2 (2.9%) | 2 (3.0%) |
| **Investigations** | | | | |
| Ejection fraction decreased | 13 (19.1%) | 7 (10.4%) | 2 (2.9%) | 0 (0%) |
| Weight decreased | 5 (7.4%) | 5 (7.5%) | 1 (1.5%) | 2 (3.0%) |
| Platelet count decreased | 4 (5.9%) | 2 (3.0%) | 2 (2.9%) | 2 (3.0%) |
| Neutrophil count decreased | 3 (4.4%) | 0 (0%) | 3 (4.4%) | 0 (0%) |
| **Metabolism and nutrition disorders** | | | | |
| Anorexia | 8 (11.8%) | 4 (6.0%) | 2 (2.9%) | 1 (1.5%) |
| Dehydration | 5 (7.4%) | 2 (3.0%) | 3 (4.4%) | 0 (0%) |
| Hypokalaemia | 3 (4.4%) | 1 (1.5%) | 2 (2.9%) | 1 (1.5%) |
| Hyponatraemia | 2 (2.9%) | 3 (4.5%) | 1 (1.5%) | 2 (3.0%) |
| Metabolic acidosis | 2 (2.9%) | 0 (0%) | 2 (2.9%) | 0 (0%) |

| Preferred Term | Common any-grade AE | | Grade 3 or 4 AE | |
|---|---|---|---|---|
| | **Pixantrone** (n=68) | **Comparator** (n=67) | **Pixantrone** (n=68) | **Comparator** (n=67) |
| **Neoplasms, benign, malignant and unspecified** | | | | |
| Malignant neoplasm progression | 1 (1.5%) | 9 (13.4%) | 0 (0%) | 1 (1.5%) |
| **Psychiatric disorders** | | | | |
| Depression | 2 (2.9%) | 3 (4.5%) | 2 (2.9%) | 1 (1.5%) |
| **Renal and urinary disorders** | | | | |
| Renal failure | 0 (0%) | 5 (7.5%) | 0 (0%) | 3 (4.5%) |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 15 (22.1%) | 3 (4.5%) | 0 (0%) | 0 (0%) |
| Dyspnoea | 9 (13.2%) | 9 (13.4%) | 4 (5.9%) | 3 (4.5%) |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia | 9 (13.2%) | 3 (4.5%) | 0 (0%) | 0 (0%) |
| Skin discoloration | 7 (10.3%) | 0 (0%) | 0 (0%) | 0 (0%0 |
| **Vascular disorders** | | | | |
| Hypotension | 5 (7.4%) | 3 (4.5%) | 2 (2.9%) | 1 (1.5%) |

Data presented for any-grade events reported in 10% or more of patients in either group or that occurred at grade 3 or 4 in more than 2% of patients in either group. AE = adverse event.

In summary, toxicities were readily manageable in both study groups in the PIX301 trial. Although the longer duration of therapy with pixantrone led to a longer time at risk for on-study adverse events (the pixantrone treatment cycle was 28 days vs. 21 or 28 days for comparator regimens therefore median duration of therapy was 3.8 months [range 0.5 to 8.1] for pixantrone and 2.6 months [0.0 to 6.1] for comparator), the proportions of patients with adverse events were similar between the two groups and the type of events reported were consistent with what is expected in heavily pre-treated patients receiving a cytotoxic agent. Neutropenia was the most common event in the pixantrone group although it was uncomplicated and non-cumulative, febrile neutropenia

of all intensities was low in both groups, and myelosuppression did not increase with increasing cycle number in both groups[22].

### Cardiotoxicity

At baseline, consistent with prior anthracycline exposure, 55% of patients in the pixantrone arm had CTC Grade 1 LVEF decreases and 3% had Grade 2 decreases. There were no Grade 3 LVEF abnormalities.

Approximately 40% of patients of either treatment arm presented any cardiac history at inclusion in the study (Table 23); cardiac risk factors such as diabetes or hypertension were also evenly distributed between groups. However, a higher percentage of patients in the pixantrone group had a baseline history of intrinsic cardiac disorders (CHF, cardiomyopathy and valvular heart disease) than did comparator patients. Actually, no patient from the control arm presented a history of cardiomyopathy or congestive heart failure at baseline.

**Table 23: PIX301 - Pre-existing heart disease at enrolment (ITT, N=140)**

| Preferred Term | Pixantrone (n=70) | Comparator (n=70) |
|---|---|---|
| **Cardiac history** | | |
| Any cardiac history | 28 (40.0%) | 29 (41.4%) |
| Intrinsic heart disease affecting cardiac muscle | | |
| Valvular heart disease | 5 (7.1%) | 2 (2.9%) |
| Congestive heart failure | 3 (4.3%) | 0 |
| Cardiomyopathy | 2 (2.9%) | 0 |
| Coronary artery disease | 3 (4.3%) | 3 (4.3%) |
| Myocardial infarction | 1 (1.4%) | 3 (4.3%) |
| Arrhythmias | | |
| Atrial arrhythmia | 1 (1.4%) | 3 (4.3%) |
| Ventricular arrhythmia | 0 | 2 (2.9%) |
| **Other relevant history** | | |

| Preferred Term | Pixantrone (n=70) | Comparator (n=70) |
|---|---|---|
| Diabetes | 8 (11.4%) | 10 (14.3%) |
| Hypertension | 16 (22.9%) | 18 (25.7%) |
| Other | 10 (14.3%) | 8 (11.4%) |

During the study, cardiac adverse events of interest were reported for 24 patients (35.3%) in the pixantrone arm and 14 patients (20.9%) in the comparator arm. These cardiac AEs are summarized by CTCAE grade in Table 24.

Thirteen patients (19.1%) in the pixantrone group had adverse events of ejection fraction decreased (defined as a > 10% decrease regardless of absolute value). Eleven (16.2%) of these were Grade 1/2 and 2 (2.9%) events were grade 3. No Grade 4 declines in LVEF were observed. In the comparator group, adverse events of ejection fraction decreased were reported for 7 patients (10.4%); all these events were Grade 1/2.

**Table 24: PIX301 - Cardiac adverse events by toxicity grade and preferred term (safety population, N=135)**

| | Pixantrone (n=68) | | | Comparator (n=67) | | |
|---|---|---|---|---|---|---|
| | **Grade 1/2** | **Grade 3/4** | **Grade 5** | **Grade 1/2** | **Grade 3/4** | **Grade 5** |
| **Any cardiac adverse event of interest** | 17 (25.0%) | 3 (4.4%) | 4 (5.9%) | 13 (19.4%) | 0 | 1 (1.5%) |
| Ejection fraction decreased | 11 (16.2%) | 2 (2.9%) | 0 | 7 (10.4%) | 0 | 0 |
| Sinus tachycardia | 0 | 0 | 0 | 3 (4.5%) | 0 | 0 |
| Tachycardia | 3 (4.4%) | 0 | 0 | 2 (3.0%) | 0 | 0 |
| Arrhythmia | 0 | 0 | 0 | 1 (1.5%) | 0 | 0 |
| Atrioventricular block second degree | 0 | 0 | 0 | 1 (1.5%) | 0 | 0 |
| Bradycardia | 0 | 0 | 0 | 1 (1.5%) | 0 | 0 |
| Cardiac failure | 1 (1.5%) | 0 | 2 (2.9%) | 0 | 0 | 1 (1.5%) |
| Cardiac failure congestive | 1 (1.5%) | 1 (1.5%) | 1 (1.5%) | 0 | 0 | 0 |
| Left ventricular dysfunction | 2 (2.9%) | 0 | 0 | 0 | 0 | 0 |
| Bundle branch block (right) | 1 (1.5%) | 0 | 0 | 0 | 0 | 0 |
| Cardiac arrest | 0 | 0 | 1 (1.5%) | 0 | 0 | 0 |

Note: Events are not exclusive of one another

Cardiac failure (MedDRA terms cardiac failure and cardiac failure congestive) was reported in 6 pixantrone patients (8.8%) compared to 1 patient (1.5%) among comparator recipients, and one additional patient in each arm developed CHF during follow-up. Four (5.9%) out of the 6 patients had

≥Grade 3 cardiac failure. However, no patient treated with pixantrone developed congestive heart failure that was typical for anthracyclines, and no Grade 4 declines in LVEF were observed. The incidence of serious or fatal cardiac events was 7.4%.

There were no gender related differences in treatment-emergent Grade 3/4 cardiac disorders or ejection fraction decreases.

In the comparator arm, one subject (n=1/67, 1.5%) had a decline in LVEF considered related to the comparator treatment. There were no cases of CHF related to any comparator treatment.

An independent cardiology review was carried out. In the pixantrone arm, a total of 14 events in 13 patients (19.1%) were considered likely (9 events in 9 patients) or possibly (5 events in 4 patients) associated with pixantrone therapy, including two possible cases of CHF. Nine subjects experienced 9 well-defined events of asymptomatic decrease in LVEF, 2 subjects had asymptomatic and transient decrease of LVEF (that were not confirmed in follow-up), one subject presented a delayed reversible symptomatic congestive cardiomyopathy associated with elevated troponin level at baseline and in the follow-up. Finally, one subject died at home with symptoms of acute pulmonary edema (CHF).

In the 9 patients presenting with decrease in LVEF, the mean total pixantrone dose was 998.2 mg/m$^2$. Other than a greater proportion of males (89% vs.. 66%), the characteristics of this subset of patients did not differ substantially from those of the whole pixantrone cohort. In PIX301, patients enrolled in the pixantrone arm had received a mean doxorubicin dose of 285 mg/m$^2$ prior to enrollment. During the study, they received a mean pixantrone dose of 822 mg/m$^2$, which is equivalent to 242 mg/m$^2$ of doxorubicin. Hence; the mean total cumulative doxorubicin dose reached 527 mg/m$^2$ at the end of the PIX301 study.

Swain et al[3] conducted a review of doxorubicin cardiac toxicity in 630 patients from three clinical trials, of whom 32 experienced doxorubicin-related CHF. This study determined that 26% of patients experienced doxorubicin-related

CHF at a cumulative dose of 550 mg/m$^2$. In fact, cardiac events were observed in 17/66 patients exposed to 500 mg/m$^2$ (including 6 cases of CHF) and 9/36 patients exposed to 550 mg/m$^2$ (including 5 cases of CHF).

In PIX301, 34 patients had cumulative doxorubicin-equivalent doses in excess to 500 mg/m$^2$ (527 to 927 mg/m$^2$), totaling their exposure to doxorubicin and pixantrone. Of these 34 patients, 6 (17.6%) had events that met the Swain criteria for cardiac events: 5 patients (patients 39, 46, 56, 85, 111, 118) had asymptomatic decreases in LVEF, which on review were judged likely associated with pixantrone; one additional patient (number 125) had an asymptomatic LVEF decline considered possibly related to pixantrone. This supports the preclinical observations that pixantrone may have a lower cardiotoxic potential than equipotent doses of doxorubicin.

### 6.8.3 Give a brief overview of the safety of the technology in relation to the decision problem.

There is currently no treatment available with reliable, durable efficacy for patients with aggressive NHL who relapse following two or more lines of therapy. Many patients, by the time they reach this stage, are no longer eligible for anthracycline-based therapy due to cardiotoxicity concerns. Pixantrone has been specifically developed to address this unmet medical need. Unlike other anthracycline and anthracycline-like agents, pixantrone is not associated with the alcohol metabolite production that can lead to long-term cardiotoxicity.

The pivotal phase III trial PIX301 assessed pixantrone in this difficult to treat patient population. Data from the trial demonstrated the AE profile of pixantrone to be consistent with what is expected in heavily pre-treated patients receiving a cytotoxic agent. Haematological toxicity is the primary adverse event resulting from pixantrone treatment; however, it is reversible.

Pixantrone also has an acceptable cardiac safety profile. Cardiac toxicity was seen at lower frequency and with apparent less severity than that reported

with other anthracyclines[1,3,16]. Data suggest that pixantrone can be administered to patients who have received their maximum lifetime dose of anthracyclines, without an apparent increase in clinically significant cardiac toxicity. Pixantrone therefore offers physicians an efficacious and tolerated option for a difficult-to-treat patient group.

In addition to PIX301, 12 additional clinical trials have been performed with pixantrone. These provide additional safety data and are supplied for review. A summary of the studies is contained in Table 25. It should be noted that none of these studies met the inclusion criteria outlined in section 6.2.

**Table 25: Summary of completed clinical trials**

| Study group | Study | Patient population | Treatment | Number of patients |
|---|---|---|---|---|
| Single-agent therapy, uncontrolled studies | AZA I-03<br>AZA II-01 | NHL | Pixantrone | 59 |
| | AZA I-01<br>AZA I-02<br>AZA I-04<br>PIX 109 | Other malignancies | Pixantrone | 70 |
| Combination therapy, all studies | AZA I-05<br>AZA I-06<br>AZA I-07<br>AZA II-02<br>AZA III-02* | NHL | Variety of pixantrone combination regimens | 151 |
| Controlled combination therapy | PIX203 | NHL | CPOP-R<br>CHOP-R | 61<br>63 |

CHOP-R = cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab; CPOP-R = cyclophosphamide, pixantrone, vincristine, prednisone, and rituximab; NHL = non-Hodgkin lymphoma
*AZA III-02 was the only controlled study utilizing a combination regimen and had 18 patients in the control group.

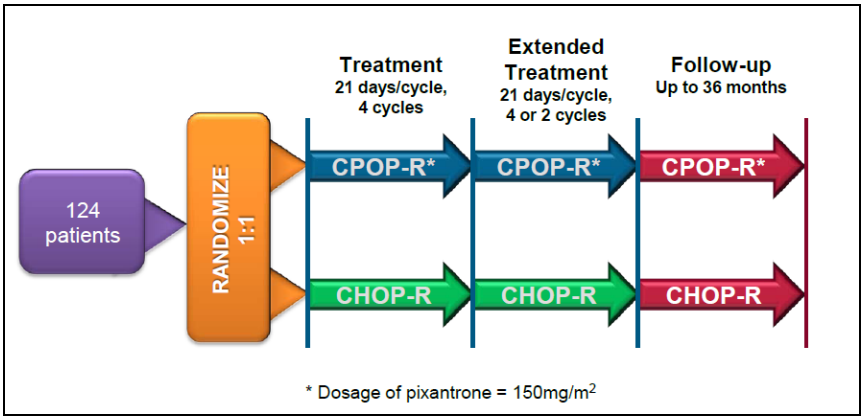
These patients are not included in the integrated analysis of the combination therapy studies.

The cardiotoxicity results reported in section 6.8.2 are supported by a Phase II Trial, PIX203, summarised below:

*Cardiac toxicity in PIX203*

PIX203 was a Phase II, randomized, open-label, multicenter trial designed to establish the non-inferiority (based on CR/CRu rates) of CPOP-R (cyclophosphamide, pixantrone, vincristine, prednisone, rituximab) compared to the standard of care CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) as first-line treatment in patients with DLBCL (according to REAL/WHO classification). Patients were randomized 1:1 to either the R-CPOP arm (n=61) or R-CHOP arm (n=63). Pixantrone was administered at the dose of 150 mg/m$^2$ on Day 1 of a 21-day cycle.

**Figure 14: PIX203 Study design**




Patients were followed up for 36 months after end of treatment. Follow-up therapies and cardiac history were monitored during follow up. Cardiac function was assessed by multigated acquisition (MUGA) scan or echocardiogram (ECHO) at baseline, after Cycles 2, 4, and 6, at EOT, and 6, 12, 24, 30, and 36 months after EOT.

The required total sample size was 276 patients to achieve at least 80% power (assuming a 15% non-inferiority margin in the CR rates between the treatment groups and a 5% dropout rate). Because of budgetary constraints, enrolment ended (after accrual of 124 patients) before the study reached a sample size sufficient to detect a statistically significant difference between the study groups and establish non-inferiority.

Demographic and baseline disease characteristics were well balanced between the study groups. The number of patients who completed the study was similar between the study arms: 45 (73.8%) completed the R-CPOP treatments and 44 (69.8%) completed the R-CHOP treatments. Patients assigned to the CPOP-R group received a median number of 8 cycles, versus 6 cycles for CHOP-R (mean number of cycles were 7.0 and 6.6 respectively).

At baseline, 8 patients on the CPOP-R arm and 3 patients on the CHOP-R arm had prior histories of diseases associated with impaired myocardial function including CHF, myocardial infarction, cardiomyopathy, or coronary artery disease (CAD). Similar proportions of patients in both arms had hypertension (CPOP-R 55.7%, versus CHOP-R 52.4%).

Careful serial monitoring of cardiac function was performed for the 3 year study duration including serial troponin T assays in a central laboratory, LVEF by either MUGA or ECHO, and clinical assessments. The results of these studies are summarized in Table 26 and include all events occurring during the treatment period and those events reported to pharmacovigilance during the follow-up period.

**Table 26: PIX203 Adverse events of particular interest (Safety population)**

| **System Organ Class/** ***Preferred Term*** | **CPOP-R** (N=59) | **CHOP-R** (N=63) |
|---|---|---|
| **Patients with any Adverse Event of Interest** | 24 (40.7%) | 24 (38.1%) |
| Cardiac Disorders | 6 (10.2%) | 8 (12.7%) |
| Arrhythmia | 1 (1.7%) | 2 (3.2%) |
| Atrial fibrillation | 1 (1.7%) | 2 (3.2%) |
| Tachycardia | 1 (1.7%) | 2 (3.2%) |
| Sinus tachycardia | 1 (1.7%) | 1 (1.6%) |
| Cardiac arrest | 1 (1.7%) | 0 |
| Cardiac failure congestive | 0 | 1 (1.6%) |
| Left ventricular dysfunction | 0 | 1 (1.6%) |
| Sinus bradycardia | 1 (1.7%) | 0 |
| Supraventricular tachycardia | 0 | 1 (1.6%) |
| Respiratory, Thoracic & Mediastinal Disorders | 2 (3.4%) | 0 |
| Pulmonary congestion | 1 (1.7%) | 0 |
| Pulmonary edema | 1 (1.7%) | 0 |
| Investigations | 20 (33.9%) | 20 (31.7%) |
| Ejection fraction decreased | 19 (32.2%) | 20 (31.7%) |
| Ejection fraction abnormal | 1 (1.7%) | 0 |

Source: PIX203 CSR Appendix 14.3.2, Table 3.1.7

Note: Events are not exclusive of one another

Twenty-four patients in each group experienced a cardiac adverse event during the study period. The most common cardiac AE was decrease of LVEF, which was observed in 19 (32.2%) patients receiving CPOP-R and 20 (31.7%) patients receiving CHOP-R. Eighteen of the 19 AEs of ejection fraction decrease on the CPOP-R arm were grade 1/2 and one was grade 3/4; on the CHOP-R arm, 16 of 20 AEs of ejection fraction decrease were grade

1/2 and four were grade 3/4. Arrhythmia, atrial fibrillation, and tachycardia were each reported for 1.7% of the patients in the CPOP-R arm and 3.2% in the CHOP-R arm.

More CHOP-R than CPOP-R patients had congestive heart failure (CHF), > 20% declines in LVEF, and increases in troponin T levels.

Four events of cardiac failure were reported, all on the CHOP-R arm. Two patients in the CHOP-R arm experienced Grade 3 cardiac failure congestive during the study; one event was included in the clinical database and is presented in the tables and one event was reported through safety surveillance and was not included in the clinical database. Continued safety reporting past database cut-off revealed two additional patients in the CHOP-R arm who experienced Grade 3 events of cardiac failure congestive; these events occurred 1000 days and 245 days following randomization.

One patient in the CPOP-R arm, who had significant cardiac comorbidities including COPD and peripheral vascular disease, experienced a Grade 5 cardiac arrest 18 days after the first and only cycle of CPOP-R.

Patients' cardiac symptoms were updated at EOT and follow-up months 3, 6, 9, 12, 15, 18, 21, 24, 30, and 36. In the CPOP-R group, 1 patient developed new cardiomyopathy, which resolved during follow-up. No patient in the CPOP-R group developed new congestive heart failure or coronary artery disease at any follow-up timepoint. In the CHOP-R group, 4 patients reported new CAD (1 of which resolved during follow-up), 6 reported new CHF (2 resolved), and 1 reported new cardiomyopathy during follow-up.

From baseline to EOT, the mean LVEF values decreased by 4.0 points in the CPOP-R group, and by 6.3 points in the CHOP-R group. Approximately 17% of patients in the CPOP-R arm and 27% of patients in the CHOP-R arm had a decline in LVEF of at least 15% from baseline as determined by MUGA. Significantly more patients in the CHOP-R group had an LVEF decline of ≥ 20% from baseline (CPOP-R 1.7% versus CHOP-R 14.3%) or a LVEF decline from baseline of at least 10% to a value of < 50% (CPOP-R 15.3%

versus CHOP-R 25.4%). At EOS, new events of LVEF decrease had been reported in the CHOP-R arm (Table 27).

**Table 27: PIX203 - Frequency of maximum LVEF reduction from baseline (safety population)**

| | CPOP-R (N=59) | CHOP-R (N=63) | P-value |
|---|---|---|---|
| **At EOT** | | | |
| Patients with at least a 15% point drop in LVEF compared to baseline | 10 (16.9%) | 17 (27.0%) | 0.198 |
| Patients with at least a 20% point drop in LVEF compared to baseline | 1 (1.7%) | 9 (14.3%) | 0.017 |
| Patients with at least a 10% point drop in LVEF compared to baseline and to less than 50% | 9 (15.3%) | 16 (25.4%) | 0.185 |
| **At EOS*** | | | |
| Patients with at least a 15% point drop in LVEF compared to baseline | 10 (16.9%) | 20 (31.7%) | - |
| Patients with at least a 20% point drop in LVEF compared to baseline | 1 (1.7%) | 11 (17.5%) | - |
| Patients with at least a 10% point drop in LVEF compared to baseline and to less than 50% | 9 (15.3%) | 17 (27.0%) | - |
| *: Includes data from the study database and pharmacovigilance database (follow-up period) | | | |

Evaluation of all cardiac data reported to the clinical and safety databases demonstrates less clinically significant cardiotoxicity in the CPOP-R arm than in the CHOP-R arm of this study. Despite more patients in the CPOP-R treatment group having preexisting coronary artery disease, history of myocardial infarction, or CHF (13% versus 3%), four patients on the CHOP-R arm developed Grade 3 cardiac congestive failure compared with no patients on the CPOP-R arm.

Overall, patients receiving CHOP-R had cumulative decreases in median LVEF values with increasing numbers of cycles that persisted during the follow-up period. Such cumulative decreases were not observed in the CPOP-R arm.

## *6.9 Interpretation of clinical evidence*

6.9.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Aggressive B-cell non-Hodgkin lymphoma is curable, but relapse occurs in over a third of patients. After first relapse, only a small proportion of patients will receive a potentially curative ASCT. There is no approved treatment or established standard of care for individuals who fail first- and second-line treatment. Existing treatment options for multiply relapsed or refractory disease do not adequately address the key aims of extending life while maintaining quality of life.

Pixantrone is the first regulatory approved product for the treatment of multiply relapsed or refractory aggressive B-cell NHL. Pixantrone was evaluated in the first and largest randomized study with an active control conducted in this patient population. This trial population is representative of the target population.

The Phase III trial PIX301 is the main evidence base for this submission and is the pivotal licensing registrational trial. The main findings from this study showed that pixantrone demonstrated significantly higher rates of confirmed and unconfirmed complete responses compared to other single agent therapies in patients with multiply-relapsed or refractory aggressive NHL. At the end of treatment, CR/CRu rates were 20.0% in the pixantrone group and 5.7% in the comparator arm (p=0.021), which rose to 24.5% for pixantrone and 7.1% for comparator at the end of the study. Pixantrone also improved progression-free survival, 5.3 months for pixantrone and 2.3 months for comparator agents (p=0.005).

Results from the pivotal Phase III PIX301 study show that when pixantrone is given as a single agent salvage therapy to patients with relapsed or refractory

aggressive NHL, patients can achieve a better and more durable response than if given a comparator agent, with manageable toxicities. To put these findings in context, the response rates demonstrated by pixantrone in the PIX301 study are clinically meaningful given the poor prognosis of heavily pre-treated patients with multiply-relapsed or refractory aggressive NHL. In the CORAL study, progression or relapse was experienced by 104 patients in the R-ICE arm and 97 patients in the R-DHAP arm. Various multi-agent salvage treatments were administered, including radiotherapy and chemotherapy, with or without transplantation. A second CR was experienced by 32 of 176 patients (18%)[10]. In a comparable group of heavily pre-treated patients, the response rate achieved in PIX301 with pixantrone as a monotherapy was 24.3%. Pixantrone will address a significant unmet need being the first regulatory approved product for the treatment of multiply-relapsed or refractory aggressive B-cell NHL.

6.9.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

**Strengths**

*Study design*

The Phase III clinical trial PIX301 is the only randomised study with an active control conducted in patients 18 years or older with aggressive NHL who had relapsed after two or more previous regimens of chemotherapy, and is the main evidence base for this submission. PIX301 was a global study, taking place at 189 sites in academic and community based hospitals in the US, India, Russia, South America and across the EU, including three sites in the UK. It was performed in compliance with good clinical practice and the principles of the Declaration of Helsinki[22].

In contrast to many trials conducted in late stage cancer, this study was an active comparator trial where the choice of comparator was decided by the treating physician. The treatments used at this stage of disease are unlicensed for the population in question and there is no consensus as to the most effective regimen in this difficult to treat patient group. The PIX301 trial is

therefore highly reflective of current clinical practice in England and the outcomes therefore highly significant.

*Patient demographics*

Demographic and disease characteristics of patients at baseline were well-balanced in both treatment arms, with the exception of cardiac history. Both groups had an International Prognostic Index score of 2, both had received the same median number of previous chemotherapy regimens, and the median dose of doxorubicin dose-equivalent exposure was only slightly lower in the pixantrone group than in the comparator group. A similar number of patients in each group had previously received rituximab and the same number of patients in each group were refractory to their previous therapy[22].

*Study outcomes*

The primary endpoint of the study was an analysis of the ITT population at the end of treatment comparing the CR and CRu rates of pixantrone to a single comparator agent preferred by the physician. The trial was considered sufficiently powered (about 80%) to detect a 15% difference in the CR/CRu rate, assuming a ≥18% CR/CRu rate in the pixantrone arm. The study also observed PFS as a secondary endpoint, which is particularly relevant measure of clinical activity[22]. Clinical outcomes were assessed by an independent panel of three experts – a radiologist, and oncologist and a pathologist. An independent radiological review panel also reviewed CT imaging of tumor response. Although the trial was open-label, the independent assessment panel was masked to the treatment assignment and to the tumor response assessments made by the investigators. The success of the masking was confirmed by an external audit[22].

**Limitations**

*Sample size*

The PIX301 study was unable to enrol the desired patient number. The trial was initially designed with a sample size in each group of 160 patients.

Despite expansion of the study to include 189 sites in 24 countries, enrolment was slow, and it was decided in September 2007 to close the study to enrolment once 100 patients with confirmed pathology had been randomly assigned. Thus, the study was underpowered according to the original sample size assumptions. Despite this change, the study still attained 80% power to test the primary endpoint in the ITT population.

The small population size may present difficulties extrapolating results to patients with previous stem cell transplantation and those who have received rituxumab, which is now a standard component of first-line therapy, but at the time of trial design was not available in all regions[22].

*Patient demographics*

The cardiac history of patients in PIX301 was not balanced at baseline. Two patients in the pixantrone group had a history of congestive heart failure and two had continuing cardiomyopathy, compared with no patients with either disorder in the comparator group.

*Inclusion criteria*

The study was initiated in 2004, before the adoption of the 2007 International Working Group (IWG) response criteria for non-Hodgkin lymphoma; therefore, assessments were based on the 1999 IWG criteria[43]. In 2007, the IWG criteria introduced the use of PET and removed the outcome of unconfirmed complete response. The PIX301 study investigators made minor modifications to the study to provide clarification to the radiology reviewers, which was routine for lymphoma trials before 2007, because criteria for target and non-target nodal disease were not clearly defined in the 1999 IWG document. In PIX301 target lesions needed to be 1.5 cm or larger in both perpendicular directions. The 1999 IWG criteria regarded lesions of 1.1–1.5 cm to be non-target lesions, as did the PIX301 study. To identify a new lesion as a sign of progressive disease, the new lesion needed to be 1.5 cm or larger. This minimum requirement is consistent with the 2007 IWG criteria[22].

A central analysis of patient histology was not performed in addition to a histology assessment from each trial site's pathology laboratory to determine eligibility for the study. This was deemed to be unfeasible due to the urgent need for therapy, coupled with the many geographical study sites. However, a retrospective analysis of histology took place at a central laboratory to verify aggressive NHL. Although the central histological review was retrospective, analysis of those patients with histologically confirmed NHL was consistent with the overall study results[22].

*Comparator agents*

No standard single-agent salvage therapy exists for patients with aggressive NHL; therefore, to determine comparator doses, the PIX301 trial investigators relied on published reports and the advice of clinical experts to establish the doses and treatment schedules for the agents tested in the comparator group. Of all the agents in the group, vinorelbine was the only agent that required substantial adjustment and delay of dose during the study[22].

*Study outcomes*

Complete response was the primary endpoint of trial PIX301, not progression-free survival and overall survival, which are generally considered more appropriate primary outcomes for this type of study. However, this point is not of major concern due to the positive results of pixantrone in this heavily pretreated population and the finding that PFS, which was a secondary endpoint, showed consistent improvement of statistical significance with pixantrone treatment across all analysis.

6.9.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The evidence provided is relevant to the decision problem which is the clinical efficacy of pixantrone as a monotherapy within its licensed indication for the treatment of relapsed or refractory aggressive non-Hodgkin lymphoma in people who have had at least two prior therapies. The evidence considers relevant patient outcomes including overall survival, progression-free survival, response rate, and adverse effects of treatment. The evidence does not, however, explore health-related quality of life (HRQL).

The population enrolled in PIX301 is representative of the aggressive NHL population in the EU for which pixantrone treatment is intended. The population defined by the inclusion and exclusion criteria was aggressive NHL by the REAL/WHO classification having received at least 2 prior chemotherapeutic regimens including an anthracycline-containing regimen such as CHOP or CHOP-equivalent, as well as rituximab where it was considered to be the standard of care. The enrolled population was a high-risk multiply relapsed population consistent with these criteria. Overall, the histologic subtype distribution was consistent with that of aggressive histologic subtypes observed worldwide, with DLBCL being the most common aggressive histologic subtype, and anaplastic large cell and peripheral T cell lymphoma among the least common (Anderson 1998). The predominant histologies in PIX301 were DLBCL and transformed indolent NHL, while follicular lymphoma grade III comprised a minority of the population which is consistent with DLBCL comprising 30-58% of NHL overall in Europe[44].

6.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

**Patient demographics and eligibility**

Results from the PIX301 study are expected to be directly relevant in clinical practice for clinicians who treat patients with multiply-relapsed or refractory NHL. Patient demographics in the study were typical of those in the target patient population[1]. The study took place at academic and community based hospitals across the globe, including three centres in the UK, with seven UK patients, thus data from the trial are expected to be applicable to UK clinical practice[22].

As with the PIX301 trial, it is anticipated that eligible patients for pixantrone monotherapy would be patients 18 years or older with aggressive de novo or transformed NHL (according to the Revised European-American Lymphoma and WHO classification) who have relapsed after two or more previous therapies, including at least one standard anthracycline-containing regimen, with a response that had lasted at least 24 weeks. The study did not evaluate paediatric patients, elderly patients or patients with renal or hepatic failure or poor performance status. It is anticipated that no specific dose adjustment would be required in elderly patients, but pixantrone should be used with caution in patients with poor performance status, impaired renal function and mild or moderate liver impairment.

**Application of pixantrone in clinical practice**

There is no current consensus for the best clinical practice in treating aggressive NHL beyond first relapse in patients not eligible for stem cell transplant or in refractory disease, and no single agent or regimen is currently approved or considered a standard of care for these patients. PIX301 is the only randomised study with an active control conducted in this patient population. Primary and secondary endpoints of the trial were validated by the CHMP and the trial complied with its advice. Although the trial was open-label, masking was deemed successful by independent audit. These factors suggest the strong efficacy results and safety data from the study would be directly transferable to clinical practice. Pixantrone monotherapy resulted in higher

complete response rates and progression-free survival than existing single therapy options, which are both statistically significant and clinically relevant.

**Dosing**

In clinical practice, as in the PIX301 trial, the dose of pixantrone must be adjusted before the start of each cycle based on nadir haematological counts or maximum toxicity from the preceding cycle of therapy. Cardiac function also requires monitoring.

**Identification of patients**

A pathway for the identification of patients suitable for treatment is shown in Figures 1& 2[12], (see section 2.5).

# 7 Cost effectiveness

## *7.1 Published cost-effectiveness evaluations*

**Identification of studies**

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A combined search was conducted for full economic evaluations and resource use and cost studies in patients with relapsed or refractory aggressive non-Hodgkin lymphoma who have had at least two therapies. The following electronic bibliographic databases were searched for studies.

- MEDLINE
- EMBASE
- EconLit
- NHS EED

Other sources that were hand-searched for relevant articles were identical to those listed in Section 6.1.1.

A full list of databases and other sources searched is also provided in Section 10.10, Appendix 10.

To ensure identification of all relevant studies for the population of interest (aggressive B-cell non-Hodgkin lymphoma), search terms that related to any type of non-Hodgkin lymphoma were used (for example, lymphoma; lymphoma, high-grade; lymphoma, non-Hodgkin; and lymphoma, large-cell).

These terms were combined with search terms relevant to economic evaluations (for example, cost utility or cost effectiveness) or terms for costs and resource utilisation (for example, cost* or resource utiliz*). The full search strategy and search restrictions are provided in Section 10.10, Appendix 10.

The inclusion criteria used to screen studies is provided in Table 28. In summary, studies were selected for inclusion because they were relevant to the subpopulation of interest, namely patients undergoing third-line therapy for relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Interventions were selected as being licensed or widely used for treatment of non-Hodgkin lymphoma.

In order to select those studies relevant to the decision problem and the current clinical practice in the UK, studies were included if they were published in 2000 onwards, and in English. However, because few publications were expected to be identified, studies from any country were included in the review if they met the other inclusion criteria (Table 28).

**Table 28: Eligibility criteria used in search strategy**

| | Inclusion criteria | Rationale | Comparison with the decision problem and license |
|---|---|---|---|
| Population | Adults with relapsed or refractory aggressive non-Hodgkin lymphoma who have had at least two therapies. | This is consistent with the licensed population for pixantrone. | In line with PIX301 trial population. However it is wider than license, which incorporates only patients with B-cell lymphomas up to, but not including patients on fifth-line treatment. |
| Intervention | • Pixantrone<br>• Etoposide<br>• Gemcitabine<br>• Ifosfamide<br>• Mitoxantrone<br>• Oxaliplatin<br>• Vinorelbine<br>• Rituximab<br>• Bendamustine<br>• Bortezomide<br>• Lenalidomide | These are pharmacological interventions that can be used to treat this population or for which clinical trials are still ongoing. | In line with the decision problem, however extended since model structures and assumptions used in this patient population could be informative.<br>Although not relevant in the UK patient population as per decision problem, for completeness rituximab, lenalidomide, bortezomib and bendamustine were incorporated in the search. |
| Comparison | • Head-to-head<br>• Placebo<br>• Combination therapy including the intervention compared with combination therapy without the intervention. | One of the requirements of full economic evaluations is that these drugs are compared with each other and/or placebo. | In line with the decision problem. |

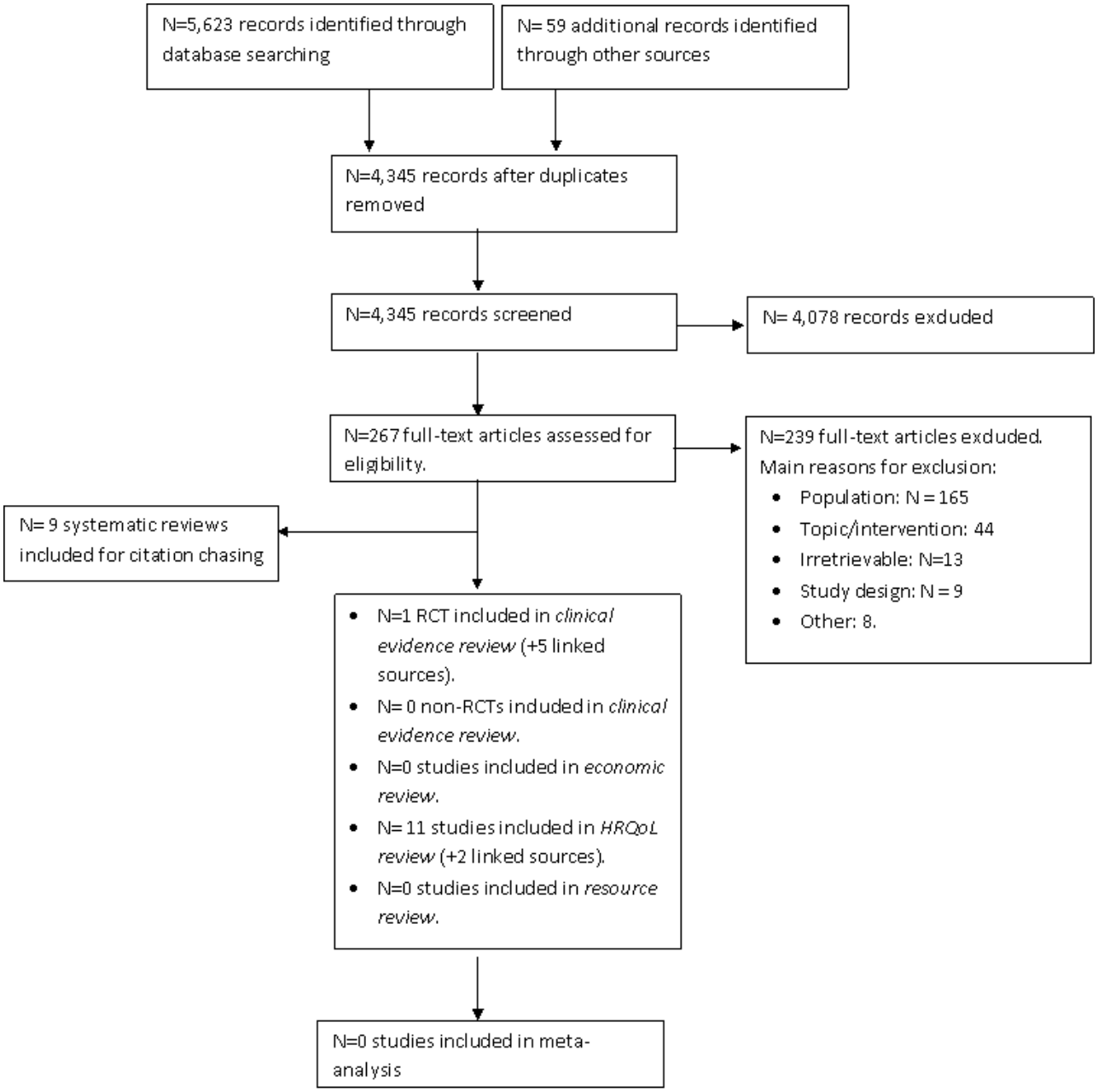
| | Inclusion criteria | Rationale | Comparison with the decision problem and license |
|---|---|---|---|
| Outcomes | Any relevant economic outcomes<br>including:<br>• Costs<br>• Quality Adjusted Life Years (QALY)<br>• Disability Adjusted Life Years (DALY)<br>• Years of Life Lost (YLL)<br>• Years Lived with Disability (YLD)<br>• Life years gained (LYG)<br>• Death years averted<br>• Net benefits gained or lost<br>• Incremental cost effectiveness ratio (ICER)<br>• Average cost effectiveness ratio (ACER). | These outcomes are the most relevant to understand the cost-effectiveness of the pharmacological interventions and also the costs. | In line with the decision problem |
| Study design | Full economic evaluations. | Encompasses relevant economic analyses. | NA |
| Country | Any | Studies carried out in any country are relevant to the review. | In line with the decision problem, however extended. |
| Language | English | Limiting the review to English language articles means the content is most relevant to the UK context. | In line with the decision problem. |
| Publication year | 2000 to present | Economic evaluations and costs from 2000 will be included to maximise relevance to the costs of current practice. | NA |

**Description of identified studies**

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

The CONSORT diagram for the identification of studies for the cost-effectiveness review is provided below in Figure 15. No economic evaluations that met the inclusion criteria were identified.

**Figure 15: Study identification CONSORT diagram**




7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated

instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

No studies were identified.

## *7.2 De novo analysis*

**Patients**

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The economic evaluation focused on patients with relapsed or refractory aggressive B-cell lymphoma who had received two or three prior therapies and were sensitive to treatment with anthracyclines. This population is consistent with the licensed indication of pixantrone as a monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive NHL

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

up to and excluding fifth-line treatment in patients who are refractory to the last therapy[14]. This patient population is almost identical to that of the PIX301 trial[2]. Clinical data for this population was derived from the PIX301 trial[2].

The PIX301 trial incorporates patients with peripheral T-cell lymphoma (10 patients, 7.1% of the patient population) and anaplastic large cell lymphoma/null cell/primary (4 patients, 2.9% of the patient population); however, these constitute a low percentage of the overall study population. It should be noted that these disease states are very similar to B-cell lymphomas in terms of treatment and disease progression. Similarly the patient population starting on fifth or further lines of treatment is small.

**Model structure**

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

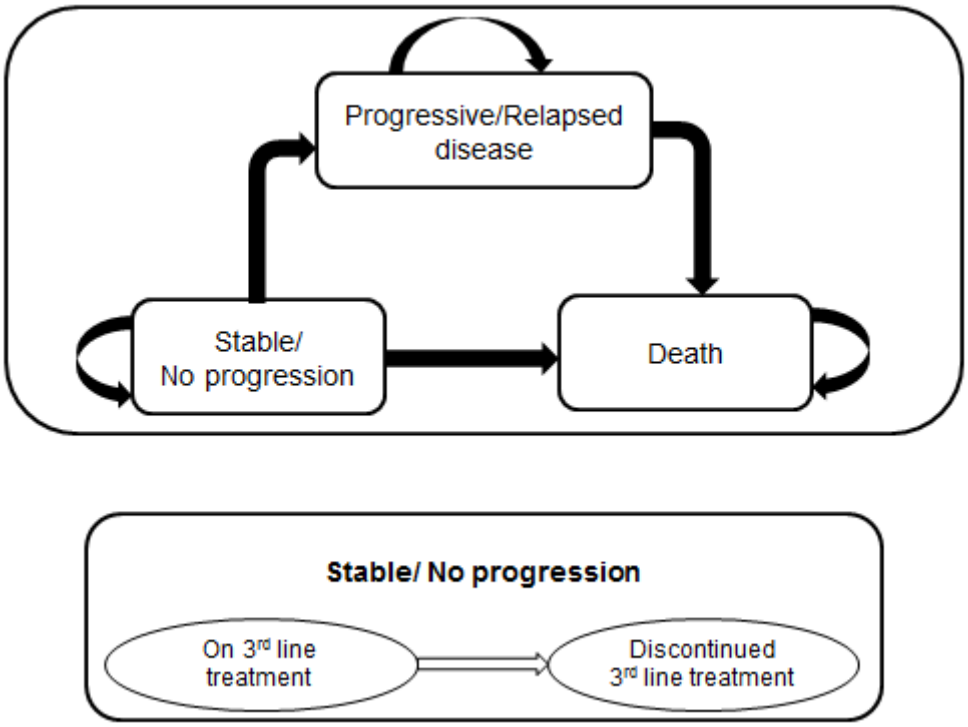
A diagrammatical representation of the semi-Markov model developed for this submission is provided in Figure 16. The model tracks patients through three main health states, including:

- Stable / no progression
- Progressive / relapsed disease
- Death

Patients in the stable / no progression health state incorporate those who had response (complete response (CR), unconfirmed complete response (CRu) and partial response (PR)) or have not progressed (CR, CRu, PR and stable disease (SD)). In this health state two subpopulations are distinguished:

- Patients on initial third- or fourth-line treatment
- Patients who discontinued third- or fourth-line treatment due to CR, adverse event (AE), completion of six months treatment duration, or non-clinical reason

**Figure 16: Model Design**




7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model structure (see Section 7.2.2) represents an appropriate way of modelling when patients with aggressive NHL pass through a series of clearly defined and mutually exclusive health states based on disease progression. The Markov approach has also been extensively used in oncology because it is particularly suited to conditions in which time-varying ongoing risks exist.

The structures of previously published NHL models vary[45-54]. However, most published economic evaluations in different patient populations with NHL follow the commonly used three health state (stable, progressive, death) structure[48,49,50,51], or split the stable health state according to line of treatment[51,54].

The model approach that most reflects the natural history of NHL would include the differentiation of the patients with CR from the patients with PR and SD, and the incorporation of stem cell transplantation as a potential

intervention for patient with CR. However due to small number of patients in each of these categories, some simplifying assumptions were required.

For example, in the model structure, CR, PR, and SD are considered a single state to enable use of the PIX301 trial composite outcome data to facilitate the modelling. Patients with PR and SD are treated similarly in clinical practice and can be assumed to have the same utility. Although patients with CR can be assumed to have the same utility based on English expert opinion, they have the potential to receive stem cell transplantation and would discontinue initial treatment upon the determination of CR. Stem cell transplant would have additional costs, but at the same time could increase OS significantly.

However in spite of the simplifications, the effect of CR is taken into account in terms of treatment discontinuations, since it was taken from the trial across patients with CR, PR, and SD, and there is no reason to assume the proportion of these would differ in the UK patient population. In addition, due to the significantly fewer patient achieving complete response or unconfirmed complete response in the chemotherapeutic agents arm compared to the pixantrone arm (24.3% vs.. 7.1%, p=0.009 in the pixantrone and comparator arms respectively),[2] not taking the potential stem cell transplant into account was a conservative assumption.

The different lines of treatments were modelled in some published studies as separate health states only in earlier stages on the disease for patients starting on first-line treatment. In the current pretreated patient population, based on expert opinion from English clinicians, the impact of subsequent treatments on OS and health related quality of life (HRQL) is negligible[24,55,56]. The main impact of subsequent lines of treatment is on cost. Therefore, these treatments are accounted for within the health states (both stable/no-progression and progressed/relapsed), but not modelled as separate health states. Their effect on OS is incorporated in the OS from the PIX301 trial, and their effect on QoL and AE are not taken into account. Since the same subsequent treatments are assumed for both treatment arms, the effect of this is negligible.

AEs are taken into account as events, not as health states for the initial treatment options, with both QoL and cost consequences estimated.

The model is based on weekly cycles to capture the 4-week treatment cycles of pixantrone and 3-week treatment cycles of some of the comparator treatments (oxaliplatin and mitoxantrone). It can also capture the frequency of regular disease monitoring described in Section 1.13 and 2.9. Both median OS (13.8 months vs.. 7.6 months for the pixantrone and the comparator arm, respectively) and PFS (6.4 months vs.. 3.5 months for the pixantrone and the comparator arm, respectively) are relatively short; thus, in order to be able to map the patients' progress, short cycle lengths are needed.

The model structure described above was reviewed with five clinical experts based in England, who validated the proposed model structure (Section 7.2.2) and model assumptions (Section 7.3.8) as being consistent with current clinical practice in England, with the simplifications and caveats mentioned above.

As a last step in the model validation process, the model was reviewed by an independent health economics consultancy, BresMed Health Solutions Limited (BresMed), who were not previously involved with the project, using the Drummond checklist and Glasgow checklist, as well as a proprietary internal checklist. Following this review discussions were held and changes made to the model and documentation accordingly.

7.2.4 Please define what the health states in the model are meant to capture.

For transparency and interpretability, the model follows a simple structure with three health states (see Section 7.2.2): (1) 'stable/no progression', (2) 'progressive/relapsed disease', (3) 'death'. Patients start in the 'stable/no progression' health state. Within each weekly model cycle, patients can either remain in the 'stable/no progression' health state, progress or relapse (progressive/relapsed disease) or die (death). When a patient in the model

has moved to the ‘progressive/relapsed disease’ state, in each subsequent model cycle that patient either remains in the ‘progressive/relapsed disease’ state or enters the ‘death’ state. At any point in the model, patients may die due to all cause (general) mortality. Given a lifetime model time horizon, all patients will eventually move to the ‘death’ state.

These health states seek to represent the main stages of the disease while providing the necessary flexibility to model the different treatment strategies, best utilise the available data, and perform sensitivity analyses. AEs are treated as events and not health states in the model. Patients are only allowed to progress in the direction of the arrows showed in Figure 16. The model assumes that following disease progression, patients stop the initial active treatment and receive best supportive care (BSC) or further lines of treatment while in the ‘progressive/relapsed’ state.

The ‘stable/no progression’ health state incorporates patients who achieve CR, PR, and SD (please see Section 7.2.3 for more detail). It is divided into two patient populations: those on the initial line of treatment, and those who have discontinued it, but have not yet progressed. According to the PIX301 trial, 31.4% (22 out of 70) of the patients in the pixantrone arm and 21.4% (15 out of 70) of the patients in the comparator arm stopped initial line of treatment either due to AE, patient request, or were lost to follow-up[2].

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model structure captures the important aspects of treatment of relapsed or refractory aggressive NHL, including stable/non-progressive disease incorporating CR, PR, and SD, disease progression, death, and treatment discontinuation. The costs and disutilities of adverse events associated with

clinical treatment are also captured. The effect of subsequent lines of treatments is incorporated in terms of OS and costs (see section 7.2.3 for more detail). Therefore, these treatments are accounted for within the health states (both stable/no-progression and progressed/relapsed), but not modelled as separate health states.

As the comparator arm of the PIX301 trial reflects the current treatment pattern of the patient population in England, this arm was assumed to reflect the underlying disease progression without pixantrone. The use of clinical data to inform these areas is discussed in greater detail in Section 7.3.1.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

**Figure 17: Key features of analysis**

| Factor | Chosen values | Justification | Reference |
|---|---|---|---|
| Time horizon | Lifetime | The reference case stipulates that the time should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. | National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. 2008[57] |
| Cycle length | Weekly cycles to capture the four week treatment cycles of pixantrone and three week treatment cycles of some comparator treatments. | Greatest common divisor to capture the four week treatment cycles of pixantrone and three week treatment cycles of comparator, the disease monitoring schedule within the NHS and to be sensitive to changes in the relatively short PFS and OS | Section 7.2.3 |
| Half-cycle correction | Yes | NICE reference case | Sonnenberg & Beck 1993 |
| Were health effects measured in QALYs; if not, what | Yes | NICE reference case | National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. |

| | | | |
|---|---|---|---|
| was used? | | | 2008[57] |
| Discount of 3.5% for utilities and costs | Yes | NICE reference case | |
| Perspective (NHS/PSS) | NHS/PSS | NICE reference case | |
| NHS, National Health Service<br>PSS, Personal Social Services<br>QALYs, quality-adjusted life years | | | |

**Technology**

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The economic model compares pixantrone (dose of 85 mg/m$^2$ IV on Days 1, 8, and 15 of each 4-week cycle for up to six cycles) with the standard practice (i.e., chemotherapy agents) according to the PIX301 trial[2]. This is in line with the SPC where "50 mg/m$^2$ of pixantrone base on Days 1, 8, and 15 of each 28-day cycle for up to 6 cycles" is recommended. 50 mg/m$^2$ of pixantrone base is equivalent to pixantrone dimaleate 85 mg/m$^2$.[14] The Markov model is based on weekly cycles to capture the 4-week treatment cycles of pixantrone, vinorelbine, ifosfamide, etoposide and gemcitabine and 3-week cycles of oxaliplatin and mitoxantrone[2]. The comparators are detailed in Table 13 (section 6.3.2).

The dosing schedules for all drugs in the trial are those detailed in Table 13 (section 6.3.2) and are consistent with the respective Summary of Product Characteristics (SPCs). However it should be noted that many of the comparators are not licensed for use in the patient population contained in this submission.

The monotherapies included in the PIX301 trial comparator arm are applicable for the England, and have been validated by discussion with clinical experts[23-25]. In real world practice, the utilisation of chemotherapy agents varies from one clinical centre to another[24,55,56]. Whether or not a chemotherapy agent will be used in third-line or subsequent line of treatment depends on the previous treatment regimen, i.e., only chemotherapy agents that were not previously used will be employed in subsequent line(s) of treatment.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

All comparators can be administered for up to six cycles in the PIX301 trial, which is consistent with clinical practice in England. Patients can also discontinue due to disease progression, adverse events (AEs), withdrawal of consent, loss to follow-up, or non-compliance with therapy. Assessment of response was based on the IWG criteria.

No additional treatment continuation rule was assumed.

## *7.3 Clinical parameters and variables*

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Statistical analysis of patient level data from the aggressive B-cell population of the PIX301 trial (see Section 6.3) was used to derive the following inputs for the model:

1. Predictive equations for progression-free survival (PFS)
2. Predictive equation for overall survival (OS)
3. Cycle probability of treatment discontinuation (TTD)
4. Frequency and duration of occurrence of Grade 2, 3, and 4 AEs
5. Mean dose for the comparator treatments
6. Gender, BSA, mean time on treatment

For every cycle, the economic model assigned the proportion of patients in each health state and the probability of patients experiencing an AE based on the treatments received.

***Overall Survival and Progression Free Survival***

The OS and PFS for both the pixantrone arm and comparator arm were calculated from patient level data from the PIX301 trial. An appropriate statistical distribution was selected to fit the patient-level data. The fitting was extrapolated beyond the two year endpoint of the PIX301 trial for OS and PFS (see Section 6.3.7) and was used to reduce the effect of the assessment schedule in the trial (i.e. smooth out the curve) for PFS. A log-normal distribution was employed in the model base case for both PFS and OS following evaluation of the hazards for proportionality and monotonicity. Goodness-of-fit of various functional forms was assessed graphically and with the help of statistical criteria.

The predicted OS and PFS were also assessed by clinical experts for external validation by comparing them to survival pattern seen in clinical practice and determining if they make sense clinically and biologically[58,59]The functional forms assessed included Weibull, log-normal, log logistic, and generalised gamma. Weibull-based fittings demonstrated a poor visual goodness-of-fit (see Section 7.3.7) and higher Akaike and Bayesian Information Criteria (AIC and BIC) scores than log-normal, generalised gamma, or log logistic distribution (see Appendix C). Alternate parametric fittings for OS and PFS were reserved for sensitivity analyses (see Section 7.6).

PFS reported in the primary analysis of the PIX301 trial incorporates treatment switching as an event in addition to progression and death. The inclusion of treatment switching in the PFS definition is not common in most oncology clinical trials. In the economic model, treatment discontinuation and switching are handled separately from PFS. Therefore, for the purposes of the base case of the economic model, parametric fitting was performed for PFS defined as progression or death, but not including treatment switching. Predictive equations were also developed for PFS as defined in the primary definition of the PIX301 trial for use in sensitivity analysis (see Section 7.6)

### *Treatment Discontinuation*

Discontinuation of the initial line of treatment occurred in the PIX301 trial due to progression, AEs, withdrawal of consent, loss to follow-up, or non-compliance. A significant number of patients (71.4% and 77.1% in the pixantrone and comparator arm, respectively)[2] discontinued treatment before progression. In addition patients on active treatment and those on palliative care receive different follow-up care and as a consequence have different costs. Potentially, patients stopping the initial treatment could also have different HRQL compared to those continuing treatment, although no such data are currently available. Thus, patients remaining on initial treatment and those who discontinued while stable were distinguished.

### *Adverse Events (AEs)*

The model accounts for both the costs of management of AEs and their effect on utilities. The AE profile per treatment arm for the initial of treatments pre-progression was determined via statistical analysis of the PIX301 trial[2]. Treatment emergent grade 3 and 4 AEs occurring in at least 5% of the total patient population of the PIX301 trial were considered to have cost and utility consequences. In addition, some rarer Grade 3 and 4 and some Grade 2 AEs were considered important by clinical experts in England[23-25], and were also included in the analysis (Tables 27 & 28).

The duration of AEs were estimated from the PIX301 trial to calculate the length of time the AE affects the quality of life of the patients in terms of disutilities.

**Table 29: List of Grade 2 AEs that were considered important by clinical experts**

| Grade 2 Event | Number of Events Observed | |
|---|---|---|
| | Pixantrone | Comparator |
| Neuropathy (Grade 2) | - | - |
| Abdominal pain (Grade 2) | 3 | 3 |
| Vomiting (Grade 2) | 2 | 4 |

| | | |
|---|---|---|
| Asthenia (Grade 2) | 6 | 3 |
| Pain in extremity (Grade 2) | - | - |
| Fatigue (Grade 2) | 2 | 6 |

**Table 30: List of Grade 3/4 AEs that occurred in at least 5% of the PIX301 trial patient population or were considered important by clinical experts**

| Grade 3 or 4 Event | Number of Events Observed | |
|---|---|---|
| | Pixantrone | Comparator |
| Abdominal Pain | 3 | 1 |
| Anaemia | 2 | 8 |
| Anorexia | 3 | 1 |
| Asthenia | 3 | 2 |
| Back Pain | - | - |
| Bronchitis | 1 | - |
| Cellulitis | 1 | 4 |
| Dehydration | 2 | - |
| Dyspnoea | 2 | 2 |
| Ejection Fraction Decreased | 2 | - |
| Fatigue | 1 | - |
| Febrile Neutropenia | 4 | 2 |
| Hypotension | 2 | 1 |
| Leukopenia | 19 | 3 |
| Lymphopenia | 2 | - |
| Malignant Neoplasm Progression | - | - |
| Mucosal Inflammation | - | 1 |
| Nausea | - | - |
| Neutropenia | 52 | 16 |
| Pain In Extremity | - | 1 |
| Platelet Count Decreased | 1 | 1 |
| Pleural Effusion | 1 | - |
| Pneumonia | 1 | 1 |
| Pyrexia | 3 | 6 |
| Renal Failure | - | 4 |

| | | |
|---|---|---|
| Thrombocytopenia | 7 | 5 |
| Vomiting | - | 3 |
| Weight Decreased | - | 1 |

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The transition between health states does not necessarily need to be characterised by transition probabilities from one health state to another, as semi-Markov models allow the use of a partition approach. By calculating the area under the survival curves at each cycle, the distribution of the patient cohort between the different health states defined by these curves are estimated. The partition model approach has been used extensively in oncology since it is particularly suited to conditions in which ongoing risks exist, although the size of these risks may vary over time. OS and PFS curves for each comparator were derived from patient-level clinical trial data for each comparator (discussed in Section 7.3.1). The PFS curve defines the stable/no progression state, while the progressed state is defined by all patients surviving (OS) less those who remain progression free (PFS); thus, the calculation to determine the patients in the progressed state is OS-PFS. The death state is defined as 1-OS. A half cycle correction is used to adjust the number of patients in each health state. For further details see Appendix K.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Aggressive B-cell lymphoma is a progressive disease; therefore both PFS and OS vary over time. This time dependency was taken into account with log-normal parametric fittings for PFS and OS in the model base case (see Section 7.3.2).

AEs in the model are assumed to be time-independent. In clinical practice, AEs are likely to be experienced at different stages of treatment, particularly on initiation and then tachyphylaxis develops to the AE or they resolve following dose reduction. Hence, the assumption of time-independence is likely to overestimate the occurrence of AEs following pixantrone treatment due to the extrapolation.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Surrogate outcome measures were not linked to final clinical outcomes.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts did not provide data used for model inputs that were related to clinical efficacy of pixantrone or comparators. All such information was derived from statistical analysis of the PIX301 clinical trial data.

**Summary of selected values**

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 31: Summary of variables applied in the economic model

| Variable | Value | CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Time horizon | Lifetime | | Section 7.2.6. |
| Percentage male | 61.4% | Standard error 4.1% (Beta) | Section 6.3.4 |
| Cycle length | Weekly cycles to capture the four week treatment cycles of pixantrone and three week treatment cycles of comparator treatments. | -- | Section 7.2.3 |
| Overall survival | Lognormal parameters for pixantrone:<br>Intercept 4.0486, scale 1.4910<br>Lognormal parameters for standard care:<br>Intercept 3.6986, scale 1.4051 | Variance-covariance tables for the lognormal parametric fitting (using Cholesky decomposition) | Appendices B, C, N and P |
| Progression free survival | Lognormal parameters for pixantrone:<br>Intercept 3.2826, scale 1.3184<br>Lognormal parameters for standard care:<br>Intercept 2.4763, scale 0.9964 | Variance-covariance tables for the lognormal parametric fitting (using Cholesky decomposition) | Appendices B, C, N and P |

| Variable | Value | CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Utilities | Stable, No progression 0.81<br>Progressive/Relapsed Disease 0.60 | Standard error:<br>Stable, No progression 0.08<br>Progressive/Relapsed Disease 0.06<br>(Beta) | Section 7.4.9 Appendix N and P |
| Adverse events | Pixantrone Arm: Grade 3 and 4 AE weekly rate 0.136<br>Grade 2 AE weekly rate 0.0003<br>Comparator Arm: Grade 3 and 4 AE weekly rate 0.108<br>Grade 2 AE weekly rate 0.0006 | The number of individual AEs were varied instead of the overall rate using standard gamma distribution | Section 7.3.1 Appendix N and P |
| Time to treatment discontinuation (TTD) | TTD was incorporated using the Kaplan-Meier estimates for each cycle | A multiplication factor of 1 was varied | Section 7.6.2 Appendix C |
| Drug costs | | | Appendix F, N and P |
| Unit costs for resource use | | | Appendix F, N and P |
| Resource use | | | Appendix G,H,I, M, N and P |
| CI, confidence interval | | | |

For the detailed list of parameters see appendices F-I. For ranges used in the deterministic sensitivity analysis see Appendix N and for standard errors, distributions and the parameters, Appendix O.

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Because a proportion of patients were alive at the end of the trial follow-up period, an approach to extrapolating survival data beyond the trial period was required to attain an estimate of total mean survival and model costs and health effects through the lifetime model time horizon[57]. Therefore, PFS and OS were extrapolated beyond the two-year trial period.

A natural choice for maximizing the internal validity of an economic evaluation is to extrapolate survival patterns observed in clinical trials using various statistical techniques. In particular, parametric methods have commonly been used to extrapolate survival times beyond the duration of clinical trials[58]. These methods assume that survival times for patients follow a given theoretical distribution.

Accordingly, parametric survival analysis was used to derive OS and PFS. They were derived by applying the following:

1) The smoothed hazard curves were checked for proportionality and monotonicity. Lack of proportionality implies the use of separately fitted distributions as opposed to distributions fitted with a treatment covariate. Non-monotonicity implies the inappropriateness of the use of monotonic distributions, such as the Weibull distribution.

2) For each treatment arm, commonly used distributions such as exponential, Weibull, log-normal, log-logistic and generalized gamma were tested for fit using statistical criteria (AIC and BIC).

3) If the analysis showed that the shape of the hazard was coming from the same distribution in both treatment arms, then the two arms were

modelled together and a treatment indicator was included as a predictor in the model; otherwise, each treatment arm was modelled separately.

4) Observed curves were graphically compared to the predicted distributions by treatment group. If deviations were noted, alternate methods that allowed greater flexibility (e.g. with piecemeal-linked distributions) were applied. A piecemeal linear approach required separating the time axis into smaller intervals and fitting exponential or Weibull distributions into each of these.

5) The final model was then tested by comparing observed and predicted distributions.

6) The model has undergone external validation, where the predictions from the distributions have been assessed by clinicians in England to assess whether it matches their experience in clinical practice.

Because long-term model predictions were influenced by the choice of the survival distribution, parametric fits for other distributions were also incorporated in the model as sensitivity analyses.

In addition, sensitivity analyses were conducted using Kaplan-Meier curves from the trial for the duration of study follow-up, instead of fitted distributions. After the trial period the distributions selected in the base case were used.

*OS*

Since the hazard curves crossed each other multiple times and the shape of the hazard functions was different in the two treatment arms, analysing both arms together and using treatment as predictor was not appropriate. Therefore, separately fitted distributions were chosen (see Appendix B and C). As the hazard curves were not monotonic, the Weibull distribution was not appropriate as indicated by the parametric fits. Based on visual goodness-of-fit estimations during the two-year trial period and AIC/BIC criteria comparisons (see Appendix B), generalised gamma, log-normal and log-logistic distributions provided the best fit for OS in the aggressive B-cell

population (Figures 17 & 19, below). As the fits were good, piecemeal fittings were not considered.

These distributions have a longer tail compared to the commonly used Weibull distribution, indicating that a small percentage of patients would have a relatively long survival. This finding is not unique and has been seen in multiple oncology diseases[60]. However, an excessively long tail can overestimate long-term survival. Thus clinical validation was sought for the long-term predictions. Clinical experts from England suggested that the generalised gamma distribution overestimated long-term survival, and the log-normal distribution provided a realistic estimation consistent with observations in clinical practice. Thus separately fitted lognormal distribution was selected as the base case for OS.

Generalised gamma and log-logistic distributions fitted separately were also incorporated into the model as sensitivity analyses. In addition, the Kaplan-Meier curves from the PIX301 trial were added in the sensitivity analyses for the duration of the trial follow-up (with the base case distributions incorporated after the trial period).

*PFS*

PFS was defined as time to progression or death in the base case. Treatment switches were incorporated in its definition in the sensitivity analyses (see Section 7.3.1). Similarly to OS, the shape of the hazard functions for PFS was different in the two treatment arms, so separately fitted distributions were chosen (please see Appendix C). As the hazard curves were not monotonic, the Weibull distribution was not appropriate as indicated by the parametric fits. Based on visual goodness-of-fit estimations during the two-year trial period and AIC/BIC criteria comparisons (see Appendix B), generalised gamma, log-normal and log-logistic distributions provided the best fit for PFS according to both definitions. As the fits were good, piecemeal fittings were not considered. For the same reasons as for OS, lognormal distribution was chosen as the base case.

Generalised gamma and log-logistic distributions fitted separately were also incorporated into the model as sensitivity analyses. In addition, the Kaplan–Meier curves from the PIX301 trial were added in the sensitivity analyses for the duration of the trial follow-up (with the base case distributions incorporated after the trial period).

**Figure 18: Parametric fitting of overall survival – pixantrone arm (trial time horizon)**

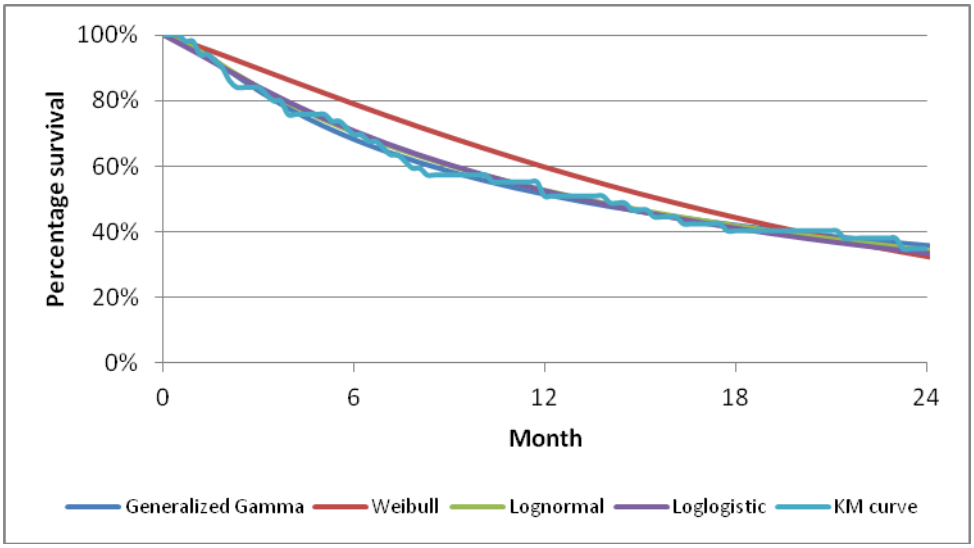



**Figure 19: Parametric fitting of overall survival – pixantrone arm (long time projection)**

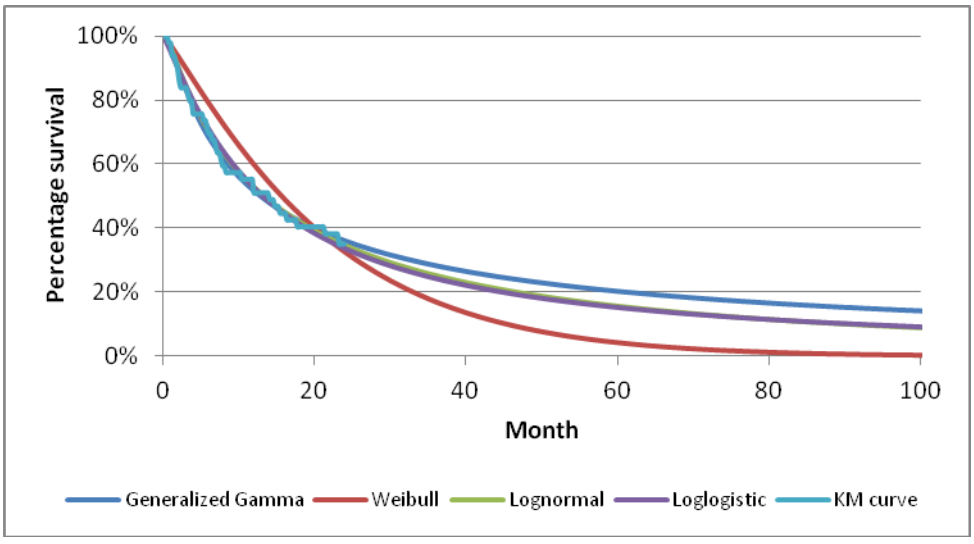


**Figure 20: Parametric fitting of overall survival – comparator arm (trial time horizon)**

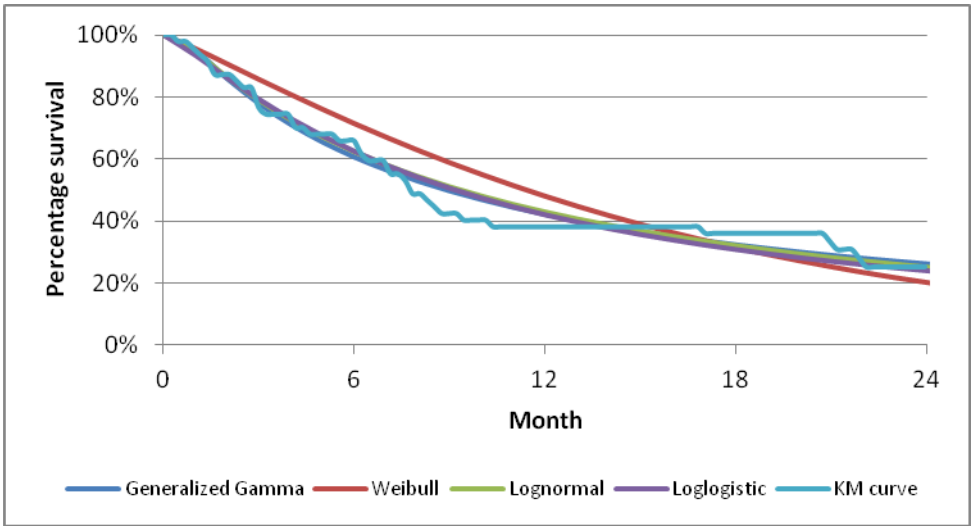



**Figure 21: Parametric fitting of overall survival – comparator arm (long time projection)**

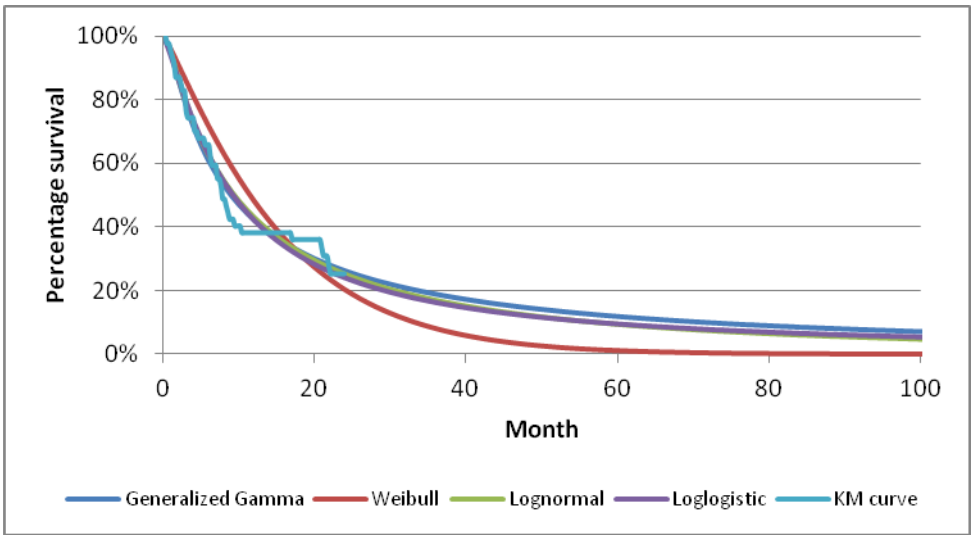


**Figure 22: Parametric fitting of progression free survival – pixantrone arm (trial time horizon)**

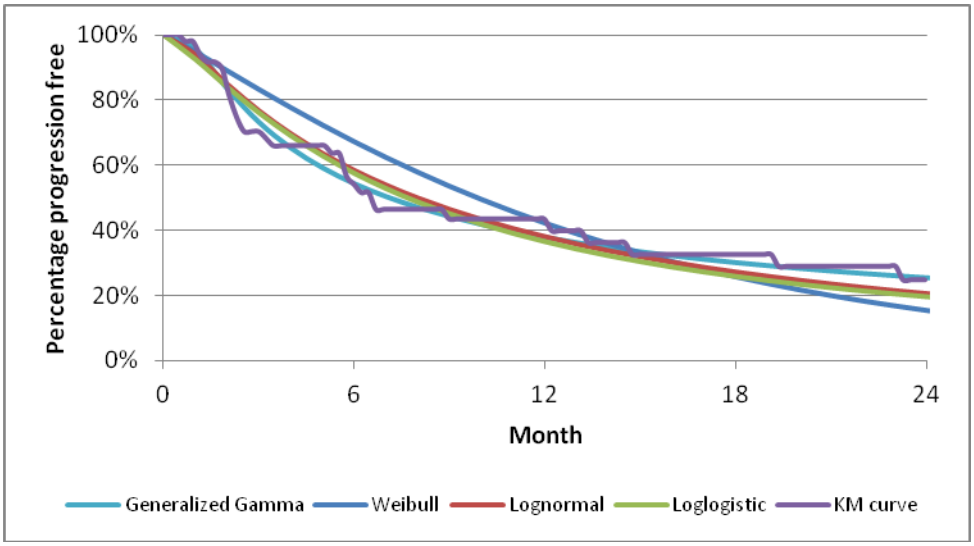



**Figure 23: Parametric fitting of progression free survival – pixantrone arm (long time projection)**

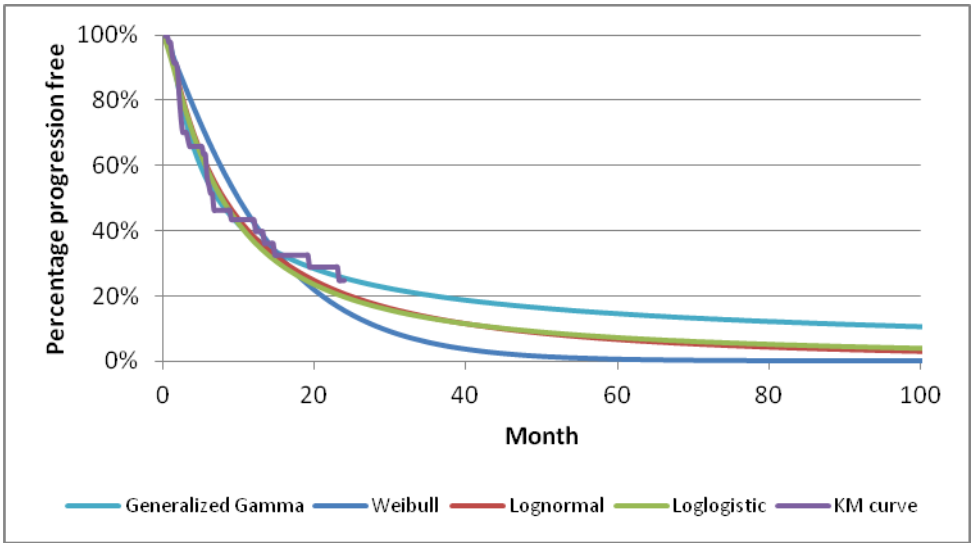


**Figure 24: Parametric fitting of progression free survival – comparator arm (trial time horizon)**

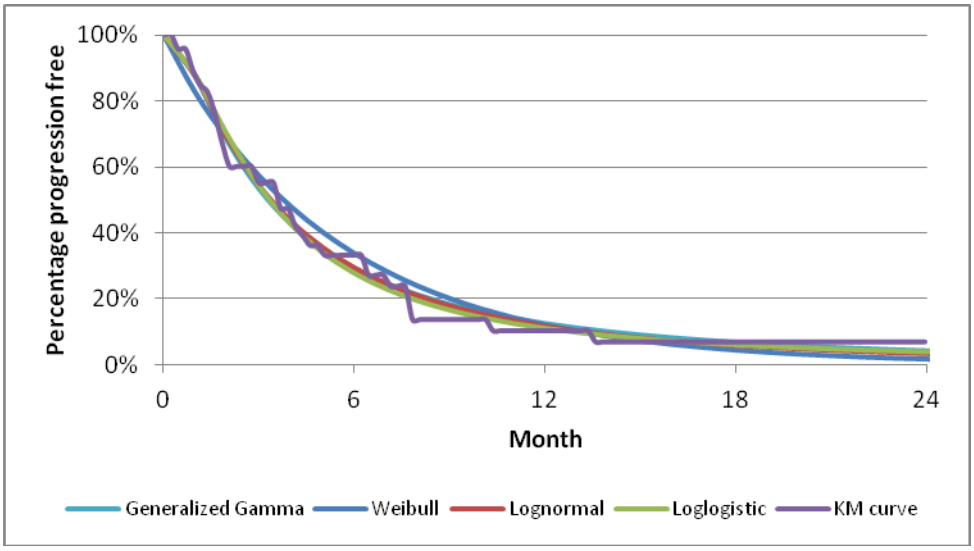
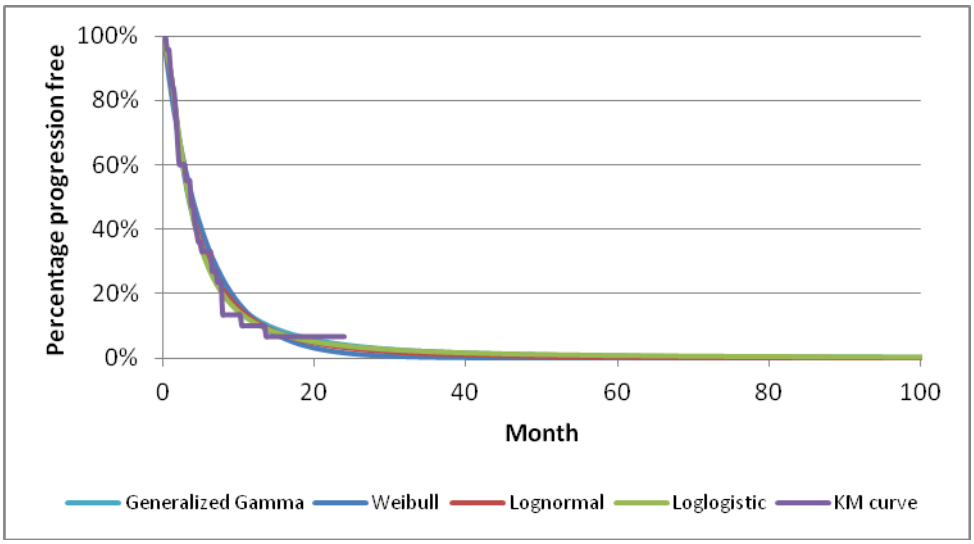



**Figure 25: Parametric fitting of progression free survival – comparator arm (long time projection)**




7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The following assumptions were made in the model:

1. The assumption of the PIX301 trial representing the actual patient population in England was justified by clinical experts.

2. The PIX301 trial represents actual treatment practice in England. The comparators and the treatment patterns are consistent with the actual clinical practice, the lead investigator is a clinician practising in England. While the protocol had the option to include treatment with rituximab (which is not used in England and Wales) no patients received it as an initial treatment (see Section 6.3)

3. In the absence of data, the maximum duration of survival was assumed to be the mean life expectancy of the general population with the mean age of the patients participating in the PIX301 trial.

   Since the mean life expectancy in the UK for the general population is 78 years for males and 82 for females[61], using the gender split in the PIX301 trial, the overall mean life expectancy would be 79.78. The mean age of the trial population is 57 (PIX301 CSR 2010), the patients in the general population would be expected to live a further 22.58 years. Thus 23 years was assumed as the maximum life expectancy for these patients.

4. All stable/no progression patients have similar quality of life, including SD, CR, and PR. Similarly all stable/no progression patients have similar follow-up costs per week if on active treatment, including SD, CR, and PR. The only difference is how long they are in that health state, accounting for the difference in total costs and QALYs between the comparators.

   This was a reasonable assumption based on expert opinion from clinicians based in England. Although the eligibility of stem cell transplant could be potentially offered to some patients with CR, this would be a very small patient population. For more details please see Section 7.2.3.

5. The rate of AEs will remain the same throughout the treatment duration. For more details please see Section 7.3.3.

6. The distributions of prior and subsequent therapies are assumed to be the same between comparators, based on expert opinion from clinicians based in England.

7. End of life care is excluded from the calculations since it affects only the last few weeks of life and as most patients will require end of life care, the estimates would be the same for pixantrone and the comparators. After discounting, cost of end of life care in the pixantrone arm would be slightly less than in the comparator arm due to the survival benefit. Thus excluding end of life care is a conservative scenario overestimating the additional costs with pixantrone slightly.

8. Fourth-line or later treatment is assumed to have no impact on patients' quality of life in the absence of data. (The costs of subsequent lines of treatments have been taken into account.)

9. AEs Grades 1-4 which occur in fewer than 5% of the trial population are assumed to have no impact on quality of life and cost. This was confirmed by the expert opinion of clinicians practicing in England.

10. The rate of future events was assumed to be independent of the events that occurred during previous cycles according to the limitations of Markov models.

11. A patient's history was not taken into account – those in the progressed health state were treated irrespective of their prior treatment options according to the limitations of Markov models.

12. In the absence of further data, disutilities for the specific AEs were assumed not to differ among different types of cancers, except in the duration over which they were experienced.

13. As the PIX301 trial did not report resource use or costs, and no costs for treating multiply relapsed/progressed aggressive NHL in the UK had been reported in the published literature, these were collected separately outside of the clinical trial using a resource use survey.

Resource use based on the English physician survey was assumed to be representative of clinical practice in the UK.

14. Utility values were assumed to depend only on the health state a given patient was in and on the patient experiencing an AE (disutilities), but not the treatment arm.

15. In the absence of further data, utility values based on self-reported quality of life during chemotherapy (CHOP) in elderly patients with aggressive non-Hodgkin lymphoma were decided to be used as base case inputs[62,63]. However to assess the effect of the uncertainty around these utilities (elicited for previous lines of treatment) a list of utility values in similar patient populations, in indications with similar expected outcome, severity of disease, and quality of the life were incorporated in sensitivity analyses.

16. OS and PFS are assumed to follow separately fitted lognormal distributions. Alternative distributions were explored in sensitivity analysis.

17. A half-cycle correction was applied by taking the average number of patients in the previous and the current cycles in the different health states.

18. All patients progressed/relapsed for a minimum of one week before they died (to estimate newly progressed/relapsed patients).

    Since the area under the curve/partition model approach was employed, only the proportion of patients in each health state was estimated for each cycle; how the patients got to that health state was not taken into account. This was particularly important for the 'Progressed/relapsed' health state, since there was no information on the proportion of the population that had just progressed and the proportion that stayed in this health state from the previous cycle.

    At the same time, in order to estimate the proportion of patients receiving subsequent regimens and the one-off cost of progression, the

newly progressed patient population needed to be determined. This could be done by two methods. The first assumed that there was no difference between the mortality rate pre- and post-progression. In this case with the overall mortality rate, the proportion of patients that died in the previous cycle while in progression could be estimated, and as a result the proportion of patients who stayed in the 'Progressed/relapsed' health state could be determined. In the next cycle, taking the patients who stayed in this health state from the total progressed patients would give the proportion of newly progressed patients.

The second method assumed that patients progressed/relapsed for at least a week (one cycle) before they died. This allowed for estimating the newly progressed patients as 'Progressed' patients in the current cycle minus progressed patients in the previous cycle adjusting for incident deaths. Since the first assumption is not known to be appropriate, the second assumption was chosen.

## *7.4 Measurement and valuation of health effects*

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

**Patient experience**

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

The majority of patients with aggressive NHL are of advanced age (>60), and suffer from both disease and treatment-related symptoms that impact their

quality of life. Disease-related symptoms can include fatigue, weight loss, fever and night sweats, as well as reduced mobility, disfigurement, and pain resulting from enlarged lymph nodes [64-65]. Chemotherapy regimens for NHL may have an important negative impact on HRQL than the disease itself, as chemotherapy patients suffer from treatment-related AEs events, including nausea, vomiting, hair loss, skin irritation, and depression, among others [62].

These issues are likely to be exacerbated in older patients and those who have failed one or more lines of treatment. A survey of English clinical experts determined that with currently available treatment options, 20-50% of patients with stable disease after two lines of chemotherapy would be referred to palliative care rather than subjected to further active treatment, while 30-100% of patients with progressive or relapsed disease would be referred to palliative care, depending upon the specific practice[23-25]. The high degree of referrals to palliative care in real world practice likely reflects the subjective decision of physicians to avoid further compromising patient quality of life with additional active treatment regimens given the advanced age of most NHL patients, as well as the absence of treatment option designed for this particular population.

### 7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Aggressive NHL is a progressive disease where HRQL decreases with time as the disease progresses. Potentially curative treatment, such as stem cell transplant, for multiply relapsed patients is rare, and is reserved mainly for younger patients with good performance status and CR[55] .

HRQL data for a broad spectrum of aggressive NHL patients, particularly for those who have failed first or second line treatment, are not available, However, HRQL surveys of patients with follicular lymphoma who have undergone first or second line treatment suggest that as disease progresses, patient HRQL declines both due to increasing severity of disease symptoms and AEs associated with chemotherapy treatments. Patients with progressive

or relapsed disease typically report worse HRQL than patients with stable disease or partial or complete remission[62,64].

**HRQL data derived from clinical trials**

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

No HRQL data were collected in the PIX301 clinical trial.

**Mapping**

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No HRQL data were collected and therefore mapping was not used.

**HRQL studies**

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale

for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A specific HRQL search was carried out using the MEDLINE and EMBASE electronic databases. Search terms were relevant to the population of interest, aggressive non-Hodgkin lymphoma (for example, lymphoma; lymphoma, high-grade; lymphoma, non-Hodgkin; and lymphoma, large-cell). These terms were combined with terms for quality of life (for example, quality of life, health status, well-being or utilities). The search was restricted to English language papers. The same search strategy that was used to identify full economic evaluations in NHS EED, EconLIT, and HEED was used to identify HRQL studies in these databases. These searches only included terms for the population and therefore could be used across multiple reviews.

In contrast to the literature reviews on the clinical effectiveness and cost-effectiveness, which only included studies that were of relevance to third-line treatment of relapsed or refractory aggressive non-Hodgkin lymphoma, the HRQL review had broader inclusion criteria. Studies were included if they reported HRQL outcomes for patients with either aggressive NHL, regardless of the number of prior therapeutic regimens received, or with indolent or aggressive NHL who had already received two or more chemotherapeutic regimens. The rationale for this was to increase the quantity of HRQL outcome data to inform the economic model. It was considered that HRQL data was likely to be applicable across this wider population of patients with NHL and would still be of relevance to the specific population of interest. The full search strategy and search restrictions are provided in Appendix 12. The inclusion criteria used are provided in Table 32.

**Table 32: Eligibility criteria used in search strategy**

| | **Inclusion criteria** | **Rationale** |
|---|---|---|
| Population | Two populations were considered: (1) Adults with aggressive non-Hodgkin lymphoma, without a requirement for the number of prior therapies; and (2) adults with indolent NHL who have had | The inclusion criteria were widened to identify relevant data for HRQL. |

| | | |
|---|---|---|
| | at least two prior therapies. | |
| Intervention | N/A | N/A |
| Comparison | N/A | N/A |
| Outcomes | Health related quality of life collected with the help of a validated instrument. | Outcomes relevant to HRQL. |
| Study design | N/A | N/A |
| Country | Any | Studies carried out in any country were relevant to the review. |
| Language | English | English language reports were considered to be most relevant to the UK context. |
| Publication year | 1995 to present | Rapid changes in cancer research may mean studies published before 1995 are of little relevance to current practice. |

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

- Appropriateness of the study for cost-effectiveness analysis.

The full data extraction of the studies in which HRQL is measured is provided in Appendix 12.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No HRQL value was identified from the literature search for the relevant patient population. Only one identified study reported utilities[62] but the reported values were not useful for the present evaluation as they focused on HRQL during first-line treatment with CHOP and during the follow-up period, and did not provide any further HRQL estimates.

None of the clinical trials that were identified in the clinical effectiveness section reported on HRQL.

**Adverse events**

7.4.8 Please describe how adverse events have an impact on HRQL.

The studies included in the systematic review did not provide data on whether or how adverse events had an impact on HRQL. However, it is known that each adverse event (AE) negatively impacts HRQL. Disutilities associated with each AE in the model were determined from a targeted review of relevant literature from other oncology indications for which similar AEs occur (see Section 7.4.9 for details).

**Quality-of-life data used in cost-effectiveness analysis**

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Utility data were not captured in the PIX301 trial, and no utility data were identified by the systematic literature review for any line of treatment in

aggressive NHL. Utilties data were identified from published sources for similar patient populations, and for disease area with similar expected survival, disease progression, nature of the disease and quality of life. The identified utilities included those for patients with diffuse large B-cell lymphoma, chronic myelogeneous leukemia, chronic lymphocytic leukemia, follicular lymphoma, renal cell carcinoma and melanoma. Among all studies, the utility values from Doorduijn et al[62] based on self-reported quality of life in elderly patients with aggressive diffuse large B-cell lymphoma provided the estimation which is most close to the PIX301 trial population. Thus these values were used for the base case analysis (see Table 33). Utility values from other sources were tested in sensitivity analysis. Separate utilities were applied for patients in the 'Stable/No disease' state and for patients in the 'Progressive/relapsed' state. Utility decrements were applied on the occurrence of AEs for the full duration of each AE, as determined from analysis of the PIX301 trial data. Disutilities associated with each AE included the model were determined from relevant literature from other oncology indications for which similar AEs occur (see Table 34)[66-73]. Where no utility decrements were available, the maximum value of the range identified was assumed to keep the calculations conservative.

Since no disutility values were available for Grade 2 and Grade 3/4 AEs, they were assumed to be the same.

**Table 33: Summary of utility values for cost-effectiveness analysis – health state**

| Description of data sources | Pre-progression Utility | Post-progression utility | Reference in submission | Justification and analysis |
|---|---|---|---|---|
| Self-reported quality of life during chemotherapy in elderly patients with aggressive non-Hodgkin lymphoma | 0.81 | 0.60 | Doorduijn et al., 2005 in Groot et al., 2005;[62-63] | The study population was most relevant to the EXTEND trial population with elderly patients with diffuse large B-cell lymphoma<br>Base Case |
| 2nd line treatment in patients with chronic myelogenous leukaemia, | 0.85 | 0.73 | NICE 2011 (FAD from TA 241)[79] | Similar indication, used for sensitivity analysis |
| 3rd line treatment in patients with chronic lymphocytic leukemia | 0.65 | 0.47 | Ferguson et al., 2008[80] | Similar indication, used for sensitivity analysis |
| 1st line maintenance treatment in patients with follicular lymphoma | 0.78 | 0.62 | Wild et al.,2006; Pettengell et al., 2008; NICE TA226, 2011[81,64,45] | Similar indication, used for sensitivity analysis |
| 1st line treatment in patients with metastatic renal cell carcinoma | 0.7 | 0.59 | Kilonzo et al 2010 (NICE TA215)[82] | Similar indication, used for sensitivity analysis |
| 2nd line treatment in patients with renal cell carcinoma | 0.76 | 0.68 | NICE 2009 (FAD from NICE TA178)[83] | Similar indication, used for sensitivity analysis |
| 2nd line treatment in patients with malignant melanoma | 0.80 | 0.76 | Bagust 2011 (NICE ERG report ID73)[84] | Similar indication, used for sensitivity analysis |

**Table 34: Summary of disutility values for cost-effectiveness analysis – adverse events**

| Adverse Events | Duration of Adverse Events* | Utility Decrement | Reference | Justification |
|---|---|---|---|---|
| **Grade 2** | | | | |
| Neuropathy | 35.3 | -0.115 | - | Assumed to be the same as for fatigue and asthenia, assumed to be the same as for grade 3/4 |
| Abdominal pain | 17.0 | -0.069 | Doyle et al., 2008 374 – 380. Table 2[67] | Assumed to be the maximum disutility of all the other grade 2 AEs, assumed to be the same as for grade 3/4 |
| Vomiting | 2.3 | -0.103 | Lloyd et al 2006, 683 – 690. Table 3[68] | Assumed to be the same as for grade 3/4 |
| Asthenia | 35.3 | -0.115 | Lloyd et al 2006, 683 – 690. Table 3[68] | Assumed to be the same as for grade 3/4 |
| Pain in extremity | 3.0 | -0.069 | Doyle et al., 2008 374 – 380. Table 2[67] | Assumed to be the same as for grade 3/4 |
| Fatigue | 31.5 | -0.115 | Lloyd et al 2006, 683 – 690. Table 3[68] | Assumed to be the same as for grade 3/4 |
| **Grade 3/4** | | | | |
| Abdominal Pain | 17.0 | 0.07 | Doyle et al., 2008 374 – 380. Table 2[67] | |
| Anaemia | 16.1 | -0.069 | Doyle et al., 2008 374 – 380. Table 2[67] | |
| Anorexia | 35.0 | -0.254 | Swinburn et al, 2010, 1091–1096 Table 1[72] | |
| Asthenia | 35.3 | -0.371 | - | Assumed to be the maximum disutility of all the other grade 3/4 AEs |
| Back Pain | 18.0 | -0.115 | Lloyd et al 2006, 683 – | |

| Adverse Events | Duration of Adverse Events* | Utility Decrement | Reference | Justification |
|---|---|---|---|---|
| | | | 690. Table 3[68] | |
| Bronchitis | 24.0 | -0.069 | Doyle et al., 2008 374 – 380. Table 2[67] | |
| Cellulitis | 12.5 | -0.371 | - | Assumed to be the maximum disutility of all the other grade 3/4 AEs |
| Dehydration | 8.0 | -0.371 | - | Assumed to be the maximum disutility of all the other grade 3/4 AEs |
| Dyspnoea | 12.7 | -0.103 | Lloyd et al 2006, 683 – 690. Table 3[68] | |
| Ejection Fraction Decreased | 11.5 | -0.050 | Doyle et al., 2008 374 – 380. Table 2[67] | |
| Fatigue | 31.5 | -0.371 | - | Assumed to be the maximum disutility of all the other grade 3/4 AEs |
| Febrile Neutropenia | 7.1 | -0.115 | Lloyd et al 2006, 683 – 690. Table 3[68] | |
| Hypotension | 8.0 | -0.150 | Lloyd et al 2006, 683 – 690. Table 3[68] | |
| Leukopenia | 14.0 | -0.371 | - | Assumed to be the maximum disutility of all the other grade 3/4 AEs |
| Lymphopenia | 34.0 | -0.371 | - | Assumed to be the maximum disutility of all the other grade 3/4 AEs |
| Malignant Neoplasm Progression | 11.0 | -0.371 | - | Assumed to be the maximum disutility of all the other grade 3/4 AEs |
| Mucosal Inflammation | 4.0 | -0.371 | - | Assumed to be the maximum disutility of all the other grade 3/4 AEs |
| Nausea | 6.0 | -0.371 | Swinburn et al, 2010, 1091–1096 Table 1[72] | |

| Adverse Events | Duration of Adverse Events* | Utility Decrement | Reference | Justification |
|---|---|---|---|---|
| Neutropenia | 15.1 | -0.048 | Nafees B, et al, 2008. 84 Table 2[69] | |
| Pain In Extremity | 3.0 | -0.090 | Nafees B, et al, 2008. 84 Table 2[69] | |
| Platelet Count Decreased | 16.5 | -0.069 | Doyle et al., 2008 374 – 380. Table 2[67] | |
| Pleural Effusion | 3.0 | -0.108 | Tolley K, 2010 (A273-A274)[73] | |
| Pneumonia | 14.9 | -0.371 | Swinburn et al, 2010, 1091–1096 Table 1[72] | |
| Pyrexia | 12.3 | -0.200 | Beusterien 2010 p50. Table 1[66] | |
| Renal Failure | 29.8 | -0.110 | Beusterien 2010 p50. Table 1[66] | |
| Thrombocytopenia | 23.2 | -0.273 | Poole et al 2009 (A203)[70] | |
| Vomiting | 2.3 | -0.108 | Tolley K, 2010 (A273-A274)[73] | |
| Weight Decreased | 55.3 | -0.048 | Nafees B, et al, 2008. 84 Table 2[69] | |
| * Duration of AE taken from PIX301 trial CSR PIX301 CSR 2010 | | | | |

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts did not provide information on parameter values associated with HRQL assessments (see Section 7.4.9)

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Within the stable/no progression health state, patients are likely to experience the same HRQL irrespective of whether they achieve CR, PR or SD (see

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Section 7.2.1). Patients could potentially experience minor differences in HRQL depending on whether they are on active treatment or palliative care. However these differences are likely to be due to the AEs associated with active treatment, which are taken into account with the help of utility decrements (Section 7.4.9; Table 34).

In the progressive health state, patients are likely to experience an important drop in HRQL during the end of life care in the final few weeks of life, though there is no data available to support this assumption in aggressive NHL. However, since most patients go through end of life care, this drop in HRQL would be the same for almost all patients between treatment arms. Thus, patients would incur the same average utility decrement and undiscounted QALY reductions in both treatment arms. As a consequence, the model does not account for these HRQL changes incurred during end of life care.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

See Section 7.3.7. Briefly, the impact of Grade 1 AEs and Grade 2 AEs (except neuropathy, abdominal pain, vomiting, asthenia, pain in extremity and fatigue) was excluded from the analysis due to the expected minimal impact of those AEs on QoL. Additionally, most Grade 3 or 4 AEs that occurred in fewer than 5% of the clinical patients were excluded as AEs with such low incidence rates are also expected to minimally impact overall cost calculations.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

HRQL was assumed to depend only on the health states.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to be constant over time as long as patients are in a given health state. Due to the very short life expectancy in this patient population

and the disease progression, further deterioration of HRQL due to aging is not required to be taken into account. HRQL changes incurred during end of life care were not taken into account due to expected similarity of these changes for patients treated with either pixantrone or comparators (please see Section 7.4.11 for more details).

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values in Sections 7.4.3 to 7.4.8 have not been amended

## *7.5 Resource identification, measurement and valuation*

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

**NHS costs**

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The current clinical management of this condition requires patients to have a regular contact with the specialist oncology/haematology centres in the UK. This involves regular attendance at an outpatient clinic, CT scans and face to face consultation with a specialist (e.g., oncologist, haematologist, or radiologist) and with a nurse in hospital setting. At the cessation of active treatment, and from the start of palliative care, the majority of the disease management shifts to the community-based health care and to palliative care centres (e.g., palliative care specialist, specialist nurse, GP, district nurse). Various laboratory tests are also done (e.g., full blood cell counts, LDH, liver function, renal function, immunoglobulin, and calcium phosphate). At the time of progression, additional imaging tests are done (e.g., ECG, MUGA, MRI, PET-CT, bone marrow biopsy). Inpatient stay and residential care is more common while on active treatment, day care, home care, and hospice care after progression. Chemotherapy administration is accounted for separately.

In oncology, Payment by Results (PbR) tariffs for chemotherapy delivery are planned to be introduced in a staged way in 2013–2014[74]; however, until the introduction, NHS reference costs are the most appropriate for costing purposes.

NHS reference costs for 2010–2011[15] were used for hospital-based outpatient visits (non-admitted), which were assumed to be consultant led and face to face using the cost of follow-up attendance, since first attendance would have been at the time of diagnosis. Outpatient costs were employed for imaging and laboratory tests; however, in some cases for imaging, the cost of direct access and other types of access were also available. Where this was the case, the average cost of the different type of access was used, weighted by the activity to incorporate the variations seen in actual practice. For various laboratory tests, direct access pathology service costs were used as a proxy in the absence of other data. In all these cases, the outpatient costs were used, since inpatient stays were accounted for separately. Transfusion was assumed to be a day case for the same reason.

Outpatient costs used were from the NHS reference costs for chemotherapy administration. For complex regimens, the costs of 'Deliver complex Chemotherapy, including prolonged infusion treatment at first attendance' were incorporated for the administration of the initial drugs in the regimen and 'Deliver subsequent elements of a Chemotherapy cycle' for the subsequent drugs given separately. For monotherapies, the cost for 'Deliver simple Parenteral Chemotherapy at first attendance' was assumed. These assumptions were verified by a clinical expert based on his current clinical practice[23].

Inpatient stay for NHL can be either elective or non-elective; thus, the average costs weighted by activity were estimated from non-elective long stay, non-elective short stay, and elective stay. Inpatient stay for AEs was assumed to be non-elective, using the weighted average of short and long stay.

Hospice care was costed with the help of day case and regular day/night cases from the NHS Reference costs.

PSSRU 2011 was the source of cost for specialist nurse visits, hospice care worker visits, and residential care. As a consequence of the perspective chosen (NHS and PSS), the costs of care provided by local authorities were incorporated rather than the cost of care provided by the private sector. As no

cancer-specific costs were available, as a proxy, costs for residential care provided for older people in an establishment were used.

Drug costs were taken from the British National Formulary (BNF) No. 62[75]. In case of various brands being available the cheapest appropriate formulation was chosen.

For further details please see Appendices F, G, H and I. If required, costs were inflated to 2011-2012 costs. For inflators, see Appendix J.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The NHS reference costs currently cover a wide variety of conditions in oncology, including NHL and chemotherapy administration [NHS, 2011]. PbR tariffs for chemotherapy delivery is planned to be introduced in a staged way in 2013-2014[74]; however, until the introduction, NHS reference costs are the most appropriate for costing purposes.

**Resource identification, measurement and valuation studies**

7.5.3 Please provide a systematic search of relevant resource data for the UK.

Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A combined search for full economic evaluations and resource studies was carried out (previously reported in Section 7.1). Specific search terms were used to identify resource data (for example, cost*, budget*, expenditure, resource utiliz*, health resources, or medical resources); combined with terms for the population. The search strategy used has been reported in Appendix 13. The inclusion criteria used to identify studies for the review are provided in Table 35.

**Table 35: Eligibility criteria used in search strategy**

| | Inclusion criteria | Rationale |
|---|---|---|
| **Population** | Adults with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma who have had two or three lines of previous therapies. | Licensed indication of pixantrone is for the treatment of this population. |
| **Intervention** | N/A | N/A |
| **Comparison** | N/A | N/A |
| **Outcomes** | Any costs or resource utilisation data. | Outcomes relevant to resource data. |
| **Study Design** | N/A | N/A |
| **Country** | UK | Only UK data will be included to maximise relevance to the UK context. |
| **Language** | English | UK context only allowed the inclusion of English language articles. |
| **Publication Year** | 2000 to present | Resource studies from 2000 are included to maximise relevance to the resource utilisation of current practice. |

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Guidance on the economic models was provided by five clinical experts from England, who were selected based upon publication record in the field of aggressive NHL, prior collaboration, and referrals from other physicians. None of the experts noted any conflict of interest. Each expert was provided a discussion guide, with background on the modelling effort, a description of the proposed model structure (Section 7.2.2), and general questions on clinical treatment patterns for aggressive NHL in the UK. Furthermore, each expert was provided with a resource use questionnaire. Three of the clinical experts

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

provided detailed responses to the resource utilisation questionnaire, including the following specific information:

- Data on drug treatment pre- and post-progression, healthcare professional contacts (types of contact and frequency), patient monitoring during disease follow-up (type, proportion of patients receiving it and frequency), inpatient care (type, length, admission, frequency and follow-up), AEs (inpatient, outpatient care and drug treatments), use of personal and social services (type, frequency and funding), and composition of best supportive care (BSC)

The actual questionnaire used to inform the model is provided in Appendix D. Prior to the use of the questionnaire, it was discussed with and validated by one of the clinical experts.

**Intervention and comparators' costs**

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Drug and administration costs were calculated based on average dose per administration from the trial using the BNF[75] and the NHS reference costs[15]. Drug costs differ each week in the 3 week and 4 week treatment cycles according to the number of administrations each week for each drug specified in the trial. The appropriate Health Resource Groups (HRGs) for the administration costs were determined with the help of the type of regimen, the method and length of administration and the timing of the administrations. For details on the administration of the different comparators and regimens, their costs and the justification see Appendix M. For unit costs see Appendix F.

Without wastage, drug costs were estimated per mg or mL; they were derived from the pack price of an active component provided by the BNF[75] divided by the number of pills or vials and the strength of the active substance within a

unit. This calculation implied perfect vial sharing without wastage. This unit cost was multiplied by the dosage administered for each treatment component per administration and the number of combinations administered within a one-week cycle.

Wastage calculation required the following additional information:

- Pack/vial sizes available
- Distribution of the patient population across body surface area (BSA) bands defined by the dose and the available pack/vial sizes

The calculation was based on the method described by Sacco et al.[76], but in this case the distribution of BSA and weight was available from the trial. In the first step, the total mg/mL of the active ingredient was estimated from the different vial/pack sizes. Dividing the total mg/mL for each pack/vial combination with the dosage per kg or per $m^2$ gave the maximum weight or BSA of a patient for whom the given combination would suffice. Based on this, different bands of weight or BSA were calculated for each vial size or combination of vial sizes.

In the next step, the proportion of administrations in each band was determined from the PIX301 trial. Finally, the cost of each vial combination was calculated and these costs were weighted by the distribution of the administrations. Drug wastage is incorporated in the base case and is excluded in the sensitivity analyses.

**Table 36: Drug costs and administration schedule in the economic model**

| | Distribution of comparators | Average dose per administration per $m^2$/kg* | Treatment cycle | Week 1 | Week 2 | Week 3 | Week 4 | Drug cost per Administration | Administration cost first attendance | Administration cost subsequent attendance |
|---|---|---|---|---|---|---|---|---|---|---|
| Pixantrone | | 71.7 mg/$m^2$ | 4 weeks | 1 | 1 | 1 | - | £1,660 | £231 | £206 |
| Comparators | | | | | | | | | | |
| Vinorelbine | 16.4% | 14 mg/$m^2$ | 4 weeks | 1 | 1 | 1 | 1 | £86 | £231 | £206 |
| Oxaliplatin | 44.8% | 89.8 mg/$m^2$ | 3 weeks | 1 | - | - | | £546 | £302 | £206 |
| Ifosfamide | 17.9% | 2614 mg/$m^2$ | 4 weeks | 2 | - | - | - | £223 | £302 | £206 |
| Etoposide 100 mg | 6.0% | 100 mg/$m^2$ | 4 weeks | 5 | - | - | - | £26 | £231 | £206 |
| Etoposide 50 mg | 7.5% | 30 mg/$m^2$ | 4 weeks | 7 | 7 | 7 | - | £7 | £163 | £163 |
| Mitoxantrone | 6.0% | 13 mg/$m^2$ | 3 weeks | 1 | - | - | | £185 | £231 | £206 |
| Gemcitabine | 1.5% | 984.6 mg/$m^2$ | 4 weeks | 1 | 1 | 1 | | £282 | £231 | £206 |

* Skipped and reduced doses in the PIX301 trial are included

**Health-state costs**

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Resource costs in the model were assigned by type of treatment (active vs.. palliative) and if patients were on initial treatment, except for personal and social services. Personal and social services were £476.42 per 28 days for stable health state on treatment, £119.10 for stable health state on palliative care and £1993.89 for progressive health state.

**Table 37: Disease management costs by type of treatment in the economic model**

| Type of Treatment | Items | Cost | Reference |
|---|---|---|---|
| Active Treatment | Health professional contacts | Per 28 days<br>£788.96 on treatment<br>£220.38 post treatment | Please see Appendix G for detailed values and section 6.5.1 for the description treatment pattern |
| | Disease follow-up | Per 28 days<br>£86.63 | |
| | Hospital related costs | Annual<br>£2,357.28 | |
| Palliative Care | Health professional contacts | Per 28 days<br>£990.74 | |
| | Disease follow-up | Per 28 days<br>£18.44 | |
| | Hospital related costs | Annual<br>£1,982.03 | |

### Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The total cost per adverse event is described in Table 38 below. For detailed resource use and costs, please see Appendix H. The cost of the specific AEs were weighted by their distribution among all AEs to estimate the cost per AE for each comparator and were multiplied by the probability of an AE occurring in the given treatment arm. Please see Appendix H for AE rates.

**Table 38: List of adverse events and summary of costs included in the economic model**

| Adverse Event | Cost |
|---|---|
| **Grade 2** | |
| Neuropathy (Grade 2)* | £6 |
| Abdominal pain (Grade 2) | £4 |
| Vomiting (Grade 2) | £49 |
| Asthenia (Grade 2) | £49 |
| Pain in extremity (Grade 2) | £4 |
| Fatigue (Grade 2) | £56 |
| **Grade 3/4** | |
| Abdominal Pain | £4 |
| Anaemia | £129 |
| Anorexia | - |
| Asthenia | £49 |
| Back Pain | £4 |
| Bronchitis | - |
| Cellulitis | £953 |

| Adverse Event | Cost |
|---|---|
| Dehydration | £869 |
| Dyspnoea | £265 |
| Ejection Fraction Decreased | - |
| Fatigue | £56 |
| Febrile Neutropenia | £1,627 |
| Hypotension | £653 |
| Leukopenia | - |
| Lymphopenia | - |
| Malignant Neoplasm Progression | - |
| Mucosal Inflammation | - |
| Nausea | - |
| Neutropenia | £245 |
| Pain In Extremity | £4 |
| Platelet Count Decreased | £573 |
| Pleural Effusion | - |
| Pneumonia | £889 |
| Pyrexia | £915 |
| Renal Failure | £590 |
| Thrombocytopenia | - |
| Vomiting | £558 |
| Weight Decreased | - |

*Only used for ITT patient population (see subgroups).

### Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Personal and social services: costs, including residential care, day care, home care and hospice care, were incorporated, see section 7.5.6.

## *7.6 Sensitivity analysis*

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The various sensitivity analyses have explored the main areas of uncertainty contained within the model. Structural uncertainty was explored by assessing the change in the results using alternative distributions for OS and PFS. Beside the lognormal distribution used in the base case, generalised gamma and log-logistic distributions were also explored. Generalised gamma gave the best fit according to visual inspection and statistical criteria; however, it was not considered clinically plausible. The log-logistic distribution had a very

similar fit to the lognormal distribution, but also was not considered clinically plausible (see Section 7.3.7).

The alternative definition of PFS was also considered in the sensitivity analyses, where besides death and progression, treatment switch was also incorporated as a PFS event (see Section 7.3.1).

An important structural assumption was the combination of CR, PR and SD into a single health state (stable/no progression). This could potentially exclude the clinical decision to consider patients' eligibility for stem cell transplant in case of CR, which could significantly increase overall survival [Personal communications, Drs. Follows, Illidge, Chau]. Due to the low patient numbers achieving CR, PR and SD this assumption was not tested. However due to the significantly fewer patient achieving CR/CRu in the chemotherapeutic agent arm compared to the pixantrone arm (24.3% vs.. 7.1%, p=0.009 in the pixantrone and chemotherapeutic agent arm respectively)[2], not taking the potential stem cell transplant into account was a conservative assumption. In addition very few patients achieved CR/CRu in the comparator arm of the PIX301 trial (17 vs.. 5 in the pixantrone and chemotherapeutic agent arm respectively)[2] compromising the reliability of the calculations (see Section 7.2.3).

Additional structural uncertainties have not been specifically explored. However, the model used in the economic analysis has been validated by clinical experts practicing in England and many of its assumptions have been used in the previous published economic evaluations in different patient populations with NHL[48,49,50,51,52].

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

One-way sensitivity analyses are provided for all major model variables in order to identify model drivers and examine key areas of uncertainty within the model. Minor variables e.g. utility decrements for each AE, unit costs and resource use for non-drug resources were incorporated in aggregate form, such as average utility decrement for AEs with each comparator, or professional and social services in stable health state on active treatment. Where possible, 95% confidence intervals were estimated with the help of the standard errors. In the absence of any published ranges or literature findings, extremes of mean +/- 20% were selected as reasonable upper and lower bounds. The alternative utility inputs for each health state were also tested in sensitivity analysis.

The most important parameters were varied as shown in Table 39 below. For an extensive list of the variables, the base case value, upper and lower bounds and scenario analyses for utility inputs, please see Appendix N.

For parameters of the distribution, since they are not independent, Cholesky decomposition of the covariance matrix was employed[77]. Variance-covariance matrices were estimated from the PIX301 trial (please see Appendix O).

For the treatment discontinuation the Kaplan-Meier estimates were multiplied by a factor of 1 in the base case. For the deterministic analysis, this factor was changed to 0.8 for lower bound and 1.2 for the upper bound.

In addition, numerous scenario analyses were performed to investigate the effect of changing the base case assumptions. The most important variables and assumptions that were subjected to scenario analysis are presented in Table 39. For the full list please see Appendix N.

**Table 39: Model parameters varied in deterministic sensitivity analysis**

| Variable | Base case | Parameter change | Rationale |
|---|---|---|---|
| Time horizon | Life time | 1–3 years | Full possible range of time horizons |
| Discount rate | 3.5% | 0%–6% | NICE reference case |
| Distribution used for OS | Lognormal | Generalised | Parametric fittings provide good |

| Variable | Base case | Parameter change | Rationale |
|---|---|---|---|
| | | gamma loglogistic | goodness of fit and commonly used parametric fittings (see Section 7.6.1) |
| Distribution used for PFS | Lognormal | Generalised gamma loglogistic | Parametric fittings provide good goodness of fit and commonly used parametric fittings (see Section 7.6.1) |
| Alternative PFS definition | Death and progressive disease | Death, progressive disease and treatment switch | Although not consistent with model structure, it was the primary definition in the PIX301 trial [PIX301 CSR, 2010] (see Section 7.6.1) |
| Utilities | Stable disease:0.81<br>Progressive disease: 0.60 | Stable disease: 065 - 0.85<br>Progressive disease: 0.47-0.76 | Utility estimates based on patients from similar clinical conditions and treatments |

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was undertaken with 5,000 simulations.

For the probabilistic analysis, a gamma distribution was applied to the costs [Briggs et al. 2006], the length of AEs, and the number of AEs. Due to the limitations of Excel 2007, however, where as a result of the small standard error, the gamma distribution returned an error message, a normal distribution was incorporated. A normal distribution was applied for BSA. For utilities and the proportion of male patients, a beta distribution was assumed[77]. Since the proportion of subsequent treatments both pre- and post-progression needs to add up to 100%, a Dirichlet distribution was employed.

For parameters of the distributions, since they are not independent, Cholesky decomposition of the covariance matrix was employed[78]. Time horizon and

discount rates were excluded from PSA, since they are not subject to parameter uncertainty. Drug costs and the number of administration per cycle according to dosing schedule were also excluded, for the same reason. See Appendix O for further details of the PSA.

## *7.7 Results*

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

**Clinical outcomes from the model**

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The modeled medians are similar to the ones reported in the EXTEND trial. For OS, the model slightly underestimates the median OS with pixantrone,

while overestimating it for the standard care comparator arm, reducing the advantage of pixantrone. For PFS, the model overestimates the median for the pixantrone arm and slightly underestimates it for the comparator arm. This is due to the steps seen in the Kaplan-Meier curves at the median (please see section 7.37). These steps have been smoothed out for the model.

**Table 40: Summary of model results compared with clinical data**

| Outcome | Pixantrone arm | | Comparator arm | |
|---|---|---|---|---|
| | **Clinical trial result (median)** | **Model result (median)** | **Clinical trial result (median)** | **Model result (median)** |
| Progression-free survival | 6.4 months | 7.8 months | 3.5 months | 3.2 months |
| Overall survival | 13.8 months | 13.1 months | 7.6 months | 9.2 months |

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

See Appendix L for details

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Utilities were assigned to the stable/no progression and progressive/relapse disease health states as described in section 6.4. Utility decrements of AE were applied to the proportion of patients who experienced an AE in a given cycle. Markov traces of QALY accrual in pixantrone arm and the comparator arm for the first 52 weeks are presented in Appendix L.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Results of the economic evaluations are shown in Table 41 and Table 42. Over the lifetime time horizon, discounted (at 3.5% per annum), mean life-years (LYs) gained for patients on pixantrone was 2.42 years. Mean discounted LYs for patients receiving the comparator was 1.71 years. Of these, 1.41 and 0.48 LYs were accrued pre-progression for patients receiving pixantrone, and comparator respectively.

When considering quality-adjusted life years (QALYs) based on utilities, pixantrone resulted in a discounted mean of 1.75 QALYs, while the comparator arm yielded 1.13 QALYs. This corresponds to a QALY gain of 0.62 among patients receiving pixantrone. The QALY gain in the pixantrone arm is mainly attributable to QALY gains during the stable/no progression stage similarly to LYs.

Mean total costs incurred over the life-time time horizon (discounted at 3.5% per annum) among patients receiving pixantrone was £86,288. Mean total cost incurred by patients receiving the comparator was £68,650. Overall, treatment with pixantrone increased total direct costs by £17,638 compared to the comparator.

**Table 41: Discounted model outputs by clinical outcomes - pixantrone**

| Outcome | LY | QALY | Cost (£) |
|---|---|---|---|
| **Discounted** | | | |
| Progression-free survival | 1.41 | 1.15 | 39,535 |
| Post-progression survival | 1.01 | 0.60 | 46,753 |
| Overall survival | 2.42 | 1.75 | 86,288 |
| **Undiscounted** | | | |
| Progression-free survival | 1.56 | 1.26 | 41,255 |
| Post-progression survival | 1.27 | 0.76 | 57,956 |
| Overall survival | 2.83 | 2.02 | 99,210 |
| LY, life years<br>QALY, quality-adjusted life year | | | |

**Table 42: Discounted model outputs by clinical outcomes – comparator**

| Outcome | LY | QALY | Cost (£) |
|---|---|---|---|
| **Discounted** | | | |
| Progression-free survival | 0.48 | 0.39 | 12,364 |
| Post-progression survival | 1.23 | 0.74 | 56,285 |
| Overall survival | 1.71 | 1.13 | 68,650 |
| **Undiscounted** | | | |
| Progression-free survival | 0.49 | 0.40 | 12,529 |
| Post-progression survival | 1.44 | 0.86 | 64,959 |
| Overall survival | 1.93 | 1.26 | 77,488 |
| LY, life years<br>QALY, quality-adjusted life year | | | |

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the

model by category of cost. Suggested formats are presented below.

The QALY gain in the stable/no progression stage accounts for all of the overall QALY gain in the pixantrone patients.

The increase in cost is largely driven by drug cost, which accounts for 89% of the increase. From a health state perspective, the increase is driven by higher stable/no progression cost, which accounts for 154% of the total cost increase. See Table 43–Table 45 below.

**Table 43: Summary of QALY gain by health state**

| Health state | QALY pixantrone | QALY comparator | Increment | Absolute increment | Absolute increment (%) |
|---|---|---|---|---|---|
| Discounted | | | | | |
| Stable/No progression | 1.15 | 0.39 | 0.76 | 0.76 | 123% |
| Progressed/Relapse | 0.60 | 0.74 | -0.14 | 0.14 | 23% |
| Total | 1.75 | 1.13 | 0.62 | 0.62 | 100% |
| Undiscounted | | | | | |
| Stable/No progression | 1.26 | 0.40 | 0.86 | 0.86 | 113% |
| Progressed/Relapse | 0.76 | 0.86 | -0.10 | 0.10 | 13% |
| Total | 2.02 | 1.26 | 0.76 | 0.76 | 100% |

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

**Table 44: Summary of cost by health state**

| Health state | Cost (£) pixantrone | Cost (£) comparator | Increment (£) | Absolute increment | Absolute increment (%) |
|---|---|---|---|---|---|
| Discounted | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Stable/No progression | 39,535 | 12,364 | 27,171 | 27,171 | 154% |
| Progressed/Relapse | 46,753 | 56,285 | -9,532 | 9,532 | 54% |
| Total | 86,288 | 68,650 | 17,638 | 17,638 | 100% |
| Undiscounted | | | | | |
| Stable/No progression | 41,255 | 12,529 | 28,726 | 28,726 | 132% |
| Progressed/Relapse | 57,956 | 64,959 | -7,004 | 7,004 | 32% |
| Total | 99,210 | 77,488 | 21,723 | 21,723 | 100% |
| Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee | | | | | |

**Table 45: Summary of predicted resource use by category of cost**

| Item | Cost (£) pixantrone | Cost (£) comparator | Increment (£) | Absolute increment | % Absolute increment |
|---|---|---|---|---|---|
| Drug costs | 16,793 | 1,175 | 15,618 | 15,618 | 89% |
| Administration costs | 2,173 | 1,758 | 414 | 414 | 2% |
| AE costs | 371 | 285 | 87 | 87 | 0% |
| Post-treatment drug & administration costs | 2,916 | 2,603 | 312 | 312 | 2% |
| Post-progression drug & administration costs | 4,068 | 4,214 | -146 | 146 | 1% |
| Pre-progression non-drug costs | 17,282 | 6,542 | 10,740 | 10,740 | 61% |
| Post-Progression non-drug costs | 41,928 | 51,287 | -9,359 | 9,359 | 53% |
| One-off progression costs | 757 | 784 | -27 | 27 | 0% |

| Item | Cost (£) pixantrone | Cost (£) comparator | Increment (£) | Absolute increment | % Absolute increment |
|---|---|---|---|---|---|
| Total | 86,288 | 68,650 | 17,638 | 17,638 | 100% |
| Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee | | | | | |

### Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The base case for the analysis is the aggressive B-cell population. From an incremental perspective, the analysis results yield an overall ICER of £28,423/QALY compared to the comparator arm, as summarised in Table 46 below.

**Table 46: Aggressive B-cell population cost-effectiveness summary results**

| Treatment | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£)/QALY |
|---|---|---|---|---|---|---|---|
| Pixantrone | 86,288 | 2.42 | 1.75 | 17,638 | 0.71 | 0.62 | 28,423 |
| Comparator | 68,650 | 1.71 | 1.13 | | | | |
| ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | |

### Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

A series of one-way sensitivity analyses were run where a single parameter at a time was varied to test its impact on the model results. Results are shown in Table 47 below and Appendix N.

Among parameters in model settings, time horizon has the biggest impact on ICER. The ten-year time horizon decreased the ICER versus chemotherapeutic agents to £25,944/QALY. This is due pixantrone increasing survival pre-progression, rather than post-progression. Thus with a shorter time horizon, the advantages of pixantrone are still taken into account, while the disadvantages post-progression decrease with the shorter time horizon. The 0–6% discount rate used for cost and health affected the ICER by +23% to -11% and -19% to +13% respectively. Methodological assumptions on modelling OS and PFS have a major impact on the ICER. Changing the approach from log-normal distribution to generalised gamma distribution for both OS and PFS leads to an ICER of £1,159/QALY. Using a log-logistic function fit for both OS and PFS leads to an ICER of £35,126/QALY versus chemotherapeutic agents.

Among the utility inputs, the stable/no progression utility influences the ICER more. When the stable/no progression utility decreases to 0.62, the ICER increases to £39,454/QALY. When the stable/no progression utility increases to 0.94, the ICER decreases to £23,720/QALY versus chemotherapeutic agents. In scenario analysis, when the baseline utilities are reduced to 0.65 for stable/no progression state and 0.47 for progressive disease state, the ICER rises to £35,248/QALY versus chemotherapeutic agents. When the baseline utilities are increased to 0.85 for stable/no progression state and 0.73 for progressive disease state, the ICER decreased to £28,056/QALY versus chemotherapeutic agents.

Cost inputs overall have a relatively small impact on the model result except for the drug cost of pixantrone. Decrease of pixantrone drug cost by 20% leads to an ICER of £23,011/QALY and increase of pixantrone drug cost by 20% yields an ICER of £33,836/QALY.

**Table 47: Aggressive B-cell population One-way sensitivity analysis results**

| Parameter | Baseline value | Alternate value | ICER (£/QALY) |
|---|---|---|---|
| **All parameters at baseline values** | | | 28,423 |

| Parameter | Baseline value | Alternate value | ICER (£/QALY) |
|---|---|---|---|
| Time horizon | life time | 10 year | 25,944 |
| Health discount rate | 3.5% | 0.0% | 23,083 |
| | | 6.0% | 32,231 |
| Cost discount rate | 3.5% | 0.0% | 35,005 |
| | | 6.0% | 25,384 |
| Parametric fitting for OS and PFS | log-normal | Generalised Gamma | 1,159 |
| | | Log-logistic | 35,126 |
| PFS definition | Death and progressive disease | Death, progressive disease and treatment switch* | 56,189 |
| Progression free survival: pixantrone | Mean | 2.5% Lower | Dominant |
| | | 97.5% Upper | 90,914 |
| Progression free survival: comparator | Mean | 2.5% Lower | 54,934 |
| | | 97.5% Upper | 17,880 |
| Overall survival: pixantrone | Mean | 2.5% Lower | 54,085 |
| | | 97.5% Upper | Less costly and less effective |
| Overall survival: comparator | Mean | 2.5% Lower | Less costly and less effective |
| | | 97.5% Upper | 47,673 |

*This scenario, although used as primary analysis in the PIX301 trial, for modeling purposes double counts discontinuations and assumes all patients discontinue only at progression.

**Table 48: Aggressive B-cell population utility scenario analysis results**

| Description of data sources | Pre-progression Utility | Post-progression utility | ICER |
|---|---|---|---|
| Base case | | | |
| Self-reported quality of life during chemotherapy in elderly patients with | 0.81 | 0.6 | 28,432 |

| | | | |
|---|---|---|---|
| aggressive non-Hodgkin lymphoma | | | |
| Alternative utility scenarios | | | |
| 2nd line treatment in patients with chronic myelogenous leukiemia, | 0.85 | 0.73 | 28,056 |
| 3rd line treatment in patients with chronic lymphocytic leukemia | 0.65 | 0.47 | 35,248 |
| 1st line maintenance treatment in patients with Follicular lymphoma | 0.78 | 0.62 | 29,994 |
| 1st line treatment in patients with metastatic renal cell carcinoma | 0.70 | 0.59 | 33,913 |
| 2nd line treatment in patients with renal cell carcinoma | 0.76 | 0.68 | 31,730 |
| 2nd line treatment in patients with malignant melanoma | 0.80 | 0.76 | 30,662 |

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

PSA was performed by varying uncertain model parameters simultaneously and randomly within their probability distributions (see section 6.6.2). 5,000 iterations were run in the PSA. Figure 26 presents the ICER scatter plot for pixantrone compared to the comparator arm. The x-axis represents incremental outcomes in terms of QALYs, while the y-axis represents incremental costs. Each point on the chart represents a single probabilistic iteration of the model.

The plot indicates that in 92% of the model iterations pixantrone yields more QALYs than the comparator arm at higher cost. Figure 27 presents cost-effectiveness acceptability curves for each model comparator. The x-axis represents a health care payer's willingness to pay for an additional unit of health outcome, while the y-axis represents the probability of cost-effectiveness. At a willingness to pay value above £30,000/QALY, pixantrone

is more likely to be cost-effective than the comparators. The probability of pixantrone being cost-effective at £30,000/QALY threshold is 53% and at £50,000/QALY threshold 78%.

**Figure 26: ICER scatter plot**

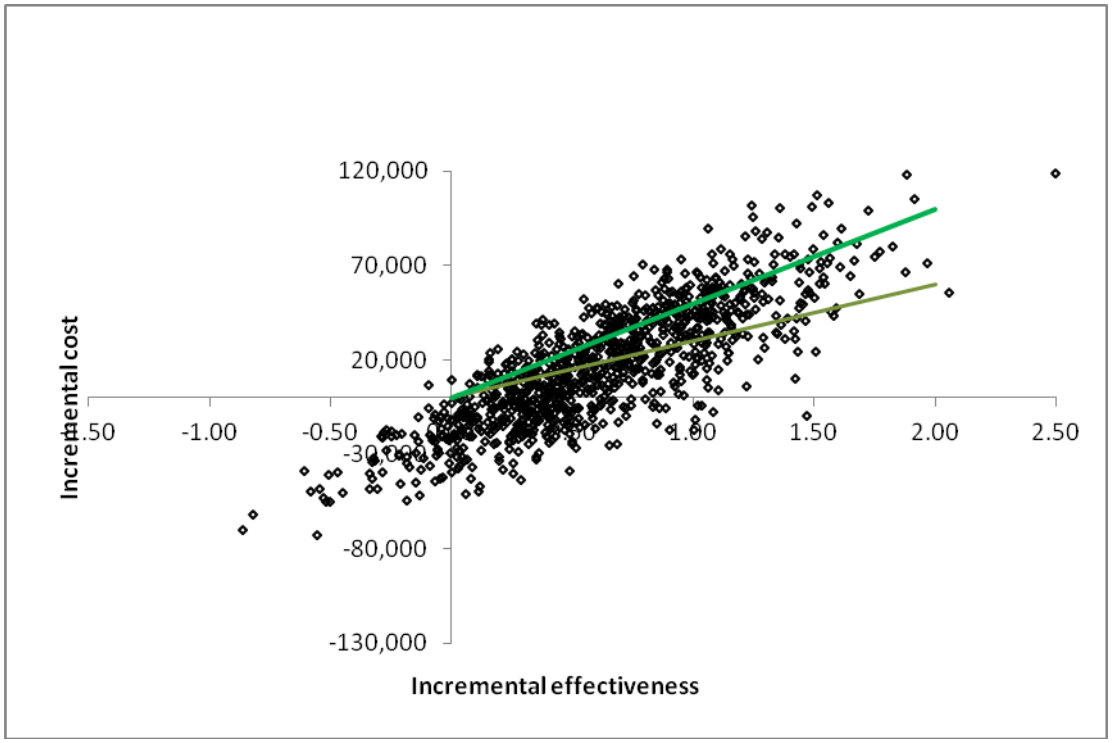
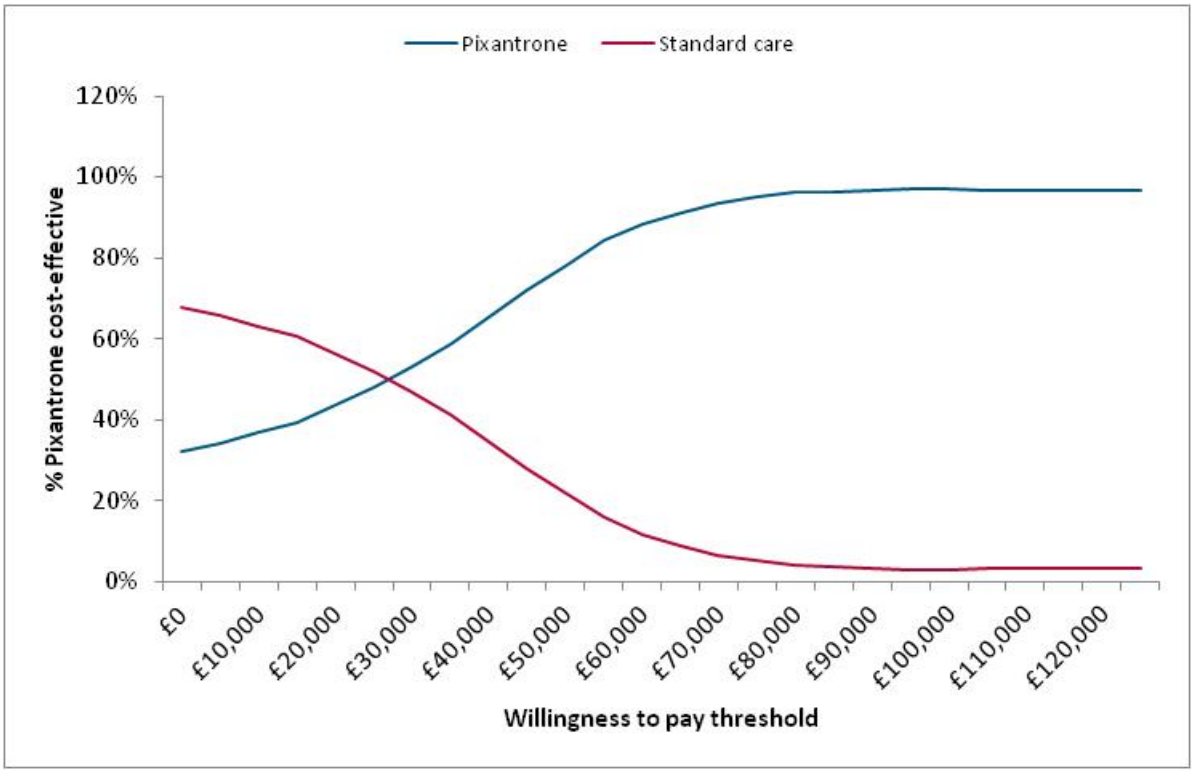


**Figure 27: Cost effectiveness acceptability curves**




7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

See Section 7.7.7 for sensitivity analysis results pertaining to alternate statistical distributions.

7.7.10 What were the main findings of each of the sensitivity analyses?

The key drivers of model result are time horizon, parametric fitting methodology for OS and PFS, utility input of stable/no progression health state, and the drug cost of pixantrone.

Methodological assumptions on modelling OS and PFS have a big impact on the ICER. Changing the approach from log-normal distribution to generalized gamma distribution for both OS and PFS leads to an ICER of £1,159/QALY.

Using a log-logistic function fit for both OS and PFS leads to an ICER of £35,126/QALY versus comparators. Varying utility input of stable/no progression health state by 5% more and less than the base case input resulted in ICERs of £39,454and £23,720 respectively.

Varying the drug cost of pixantrone by 20% more and less than the base case input resulted in ICERs of £23,011and £33,826 respectively. The impact of the other cost, resource use, and utility inputs to the model result is minimal, varying the ICER by less than 2% from the base case result.

Probabilistic sensitivity analysis showed that pixantrone is more likely to be cost-effective at a willingness to pay threshold above £30,000. The probabilities of pixantrone to be more cost-effective at £20,000, £30,000 and £50,000 are 43.8%, 53.0% and 78.2% respectively.

7.7.11 What are the key drivers of the cost-effectiveness results?

The key driver of the results were the OS and PFS parameters, the utility estimate for the stable/no progression health state, the time horizon, the discounts rate and the cost of pixantrone for further details see section 7.7.10 and Appendix N.

## *7.8 Validation*

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Prior to determining final results, the structure and programming of the completed Microsoft Excel model was validated by two modelling experts not involved in this study, and a variety of stress tests were performed to ensure that the model results were reflective of the inputs entered. For example, both extreme values and equal values across treatment arms were input and actual results were compared against results expected from a properly functioning model. In situations where actual results diverged from expected results, debugging was performed to investigate and remedy the discrepancy.

Statistical fittings for PFS and OS were validated by comparison of observed median PFS and OS for the pixantrone and comparator arms to values derived from the predictions. The median survival of 10.2 months and 7.6 months for the pixantrone and comparator arms, respectively, were similar to the values of 10.4 months and 7.9 months for the comparator arms derived from the model.

Predicted OS and PFS survival curves from the parametric fittings, as well as major model assumptions (see Section 7.3.8) were validated by clinical experts practicing in England.

As a last step in the model validation process, the model was reviewed by an independent health economics consultancy, BresMed, who were not previously involved with the project, using the Drummond checklist and Glasgow checklist, as well as a proprietary internal checklist. Following this review discussions were held and changes made to the model and documentation accordingly.

## *7.9 Subgroup analysis*

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.

- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

The intended-to-treatment population from PIX301 trial and the population with diffuse large B-cell lymphoma were analyzed in the subgroup analysis. Diffuse large B-cell lymphoma accounted for 74% of the PIX301 trial population and was a predefined subgroup.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Patient characteristics of the intended-to-treatment population from PIX301 trial were described in detail in section 6.3.4 Tables 14 – 17 and Appendix A.

Patient characteristics of the diffuse large B-cell lymphoma population from the PIX301 trial are described in Table 49 below.

**Table 49: PIX301 Baseline demographic characteristics (patients with diffuse large B-cell lymphoma)**

| | **Pixantrone** (N=53) | **Comparator** (N=51) |
|---|---|---|
| **Age at Randomisation (years)** | | |
| Mean (SD) | 58.2 (14.4) | 55.9 (13.1) |
| Median (range) | 60.0 (18-80) | 58.0 (26-77) |
| **Age Category at Randomisation, n (%)** | | |
| <=60 | 29 (54.7%) | 29 (56.9%) |
| > 60 | 24 (45.3%) | 22 (43.1%) |
| **Sex, n (%)** | | |
| Male | 34 (64.2%) | 28 (54.9%) |
| Female | 19 (35.8%) | 23 (45.1%) |

| | | |
|---|---|---|
| **Race, n (%)** | | |
| Caucasian | 37 (69.8%) | 32 (62.7%) |
| Black | 0 | 0 |
| Asian | 9 (17,.0%) | 10 (19.6%) |
| Hispanic | 4 (7.5%) | 5 (9.8%) |
| Native American | 0 | 1 (2.0%) |
| Other | 3 (5.7%) | 3 (5.9%) |
| **Baseline ECOG Performance Status, n (%)** | | |
| 0 | 18 (34.0%) | 16 (31.4%) |
| 1 | 21 (39.6%) | 21 (41.2%) |
| 2 | 14 (26.4%) | 13 (25.5%) |
| 3 | 0 | 1 (2.0%) |
| **Geographic Region, n (%)** | | |
| North America | 3 (5.7%) | 4 (7.8%) |
| Western Europe | 18 (34.0%) | 14 (27.5%) |
| Rest of World | 32 (60.4%) | 33 (64.7%) |
| **Weight (kg)** | | |
| Mean (SD) | 70.9 (16.2) | 69.0 (16.6) |
| Median (range) | 70.0 (45-117) | 65.0 (37-115) |

SD=standard deviation
Fisher exact test was used to compare proportions between the group and a two-sided student's t-test was used in the comparison of means between treatment groups.
Source: 14.1.3 and 14.1.3.4 [PIX301 CSR]

7.9.3 Please describe how the statistical analysis was undertaken.

Statistical analysis of patient-level data was performed as described in section 6.3.6 for both subgroup populations.What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

From an incremental perspective, the analysis results of the ITT population yield an overall ICER of £43,102/QALY compared to the comparator arm, as summarised in Table 50 below.

**Table 50: ITT population cost-effectiveness summary results**

| Treatment | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£)/QALY |
|---|---|---|---|---|---|---|---|
| Pixantrone | 76,942 | 2.03 | 1.45 | 19,809 | 0.56 | 0.46 | 43,102 |
| Comparator | 57,132 | 1.47 | 0.99 | | | | |
| ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | |

The analysis results of the diffuse large B-cell lymphoma population yield an overall ICER of £23,699/QALY compared to the comparator arm, as summarised in Table 51 below.

**Table 51: Diffuse large B-cell lymphoma population cost-effectiveness summary results**

| Treatment | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER (£)/QALY |
|---|---|---|---|---|---|---|---|
| Pixantrone | 62,795 | 1.70 | 1.25 | 9,841 | 0.44 | 0.42 | 23,699 |
| Comparator | 52,953 | 1.26 | 0.83 | | | | |
| ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years | | | | | | | |

7.9.4 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

No other obvious subgroups were identified and there were no additional subgroups requested in the scope.

## *7.10 Interpretation of economic evidence*

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No previously published literature provides evidence related to treatment of aggressive NHL patients following third-line or later therapy. This is most likely due to there being no licensed treatments for this difficult to treat patient group.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The primary economic evaluation considers aggressive B-cell lymphoma patients treated with pixantrone or comparator as a third- or fourth-line therapy, as specified in Section 4. This sub-population more closely resembles the licensed indication of pixantrone. The evaluation is based on data from the PIX301 trial, the only available clinical data source for pixantrone, which applies only to patients who had treatment with greater than two prior chemotherapy regimens. In addition, a subgroup analysis considers patients with DLBCL who received pixantrone or comparator as third- or later-line of treatment.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strengths of the evaluation are as follows:

- The model structure is simple but captures key elements of clinical progression and management of aggressive NHL

- The model was informed by statistical analysis of patient-level data rather than aggregate or summary data sets, enabling greater precision in model inputs derived from statistical analyses of those data
- This evaluation is the first evaluation of the cost effectiveness of therapies for aggressive NHL for patients who have failed two or more prior treatment regimens. No prior model has been published for this patient population.
- The model evaluates the effect on model predictions of variation in the parametric fitting for PFS and OS, a key uncertainty associated with the methodology
- Model structure, major assumptions and OS and PFS predictions were validated by clinical experts in England
- Robust and thorough sensitivity and scenario analyses have been performed on model parameters for which there were data gaps (e.g., utilities for health states), enabling an understanding of the key cost drivers of the predicted economic outcomes.
- The model was reviewed by an independent health economics consultancy, BresMed, who were not previously involved with the project, using the Drummond checklist and Glasgow checklist, as well as a proprietary internal checklist.

The primary weaknesses of this evaluation are as follows:

- A relative scarcity of clinical trial and real-world data in patients failing two or more lines of treatment for aggressive NHL was available to inform the modelling, necessitating reliance on data from a single RCT
- Patient numbers in the PIX301 clinical trial were relatively low
- The trial had a two year duration, necessitating extrapolation to lifetime clinical outcomes based on statistical methodologies.

- Assumptions related to health state utilities were required due to the absence of HRQL data for the population considered.

While the evaluation was based on the best available data and informed by the opinions of practicing clinical experts in England, the assumptions should be considered when reviewing the predicted model outcomes.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The robustness of the results could be enhanced by the collection of additional data. Specifically, the following types of data would be useful:

- HRQL data for the patient population of interest (aggressive NHL patients who have failed two or more lines of treatment)

- Longer term (greater than two years) survival data, perhaps via a retrospective database analysis, would be valuable to help validate the choice of the lognormal distribution for the parametric fittings of OS and PFS used in the model base case, or to determine whether an alternate choice (e.g., generalised gamma) is more appropriate

- A patient chart review would be valuable to inform data gaps in costs of the management of the disease and AEs, however due to small patient number in this patient population the chart review would be time consuming and would require the inclusion of a large number of centres including hospitals and palliative care centres.

# Section C – Implementation

# 8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

An estimate of the number of patients eligible for treatment is provided below in Table 52

**Table 52: Estimation of the eligible patient population**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Eligible population | 1,650 | 1,665 | 1,682 | 1,698 | 1,715 |

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Patients are assumed to currently receive chemotherapeutic agents used as initial line of treatments in the PIX301 trial[2] (Table 53). Since none of the current agents are new on the market, the market share of the different options is assumed to be constant. Pixantrone is expected to become available in the UK to refractory or relapsed NHL patients who previously failed to respond to two or more lines of treatment. An initial 5% uptake of pixantrone is assumed in the first year, which increases by an additional 5%

annually, yielding 25% of eligible patients taking pixantrone in the fifth year (See section 8.3 for more details).

**Table 53: Currently available standard care**

| Treatment options | Proportion of patients |
|---|---|
| Vinorelbine | 16.42% |
| Oxaliplatin | 44.78% |
| Ifosfamide | 17.91% |
| Etoposide 100 mg | 5.97% |
| Etoposide 50 mg | 7.46% |
| Mitoxantrone | 5.97% |
| Gemcitabine | 1.49% |

8.3 What assumption(s) were made about market share (when relevant)?

As pixantrone is the only new treatment expected to be made available to the patient population evaluated, the current market share is assumed to be 0% in the first year, and assumed to increase up to 25% of the eligible population in the first five years following introduction. See Table 54.

**Table 54: Projected market share for total population**

| Drug | Current status | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|
| Pixantrone | 0% | 5% | 10% | 15% | 20% | 25% |
| Comparators | 100% | 95% | 90% | 85% | 80% | 75% |

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The analysis calculates the budget impact for pixantrone based on the cost-effectiveness model, estimating the market uptake of pixantrone compared to the comparator arm. Drug costs and total health care costs, which include administration costs, routine follow-up costs, hospitalisations, AE management, and the cost of personal and social services, are considered, as presented in Section 7.

Please see section 8.5 for more details.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

As discussed in detail in Section 7.5.1, costs used as inputs for the budget impact model are the same as those used in the cost effectiveness model. For these estimated costs, the unit costs are taken from the National Schedule of Reference Costs Year: 2010–11[15] (for inpatient stay, outpatient visits, imaging and laboratory tests), British National Formulary (BNF)[75] (for drugs), the PSSRU[78] (for nurse visits and personal and social care) and the National Audit Office.

8.6 Were there any estimates of resource savings? If so, what were they?

Due to the later progression of patients starting on pixantrone, savings were seen in the post-progression related costs, such as drug and administration costs, non-drug costs, and one-off costs for progression.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS in England and Wales resulting from the introduction of pixantrone is shown in Table 55. The budget impact analysis shows that a total of between 83 and 429 patients will be

treated with pixantrone over the next 5 years according to the projected market share and the proportion of patients eligible for treatment.

The budget impact, assuming patients continue to receive only the comparators in the model, was calculated to be approximately £374 million compared with approximately £367 million with the introduction of pixantrone, resulting in a net budget impact of approximately £13 million. Based on drug cost only, this represents an increase of £7 million over the next 5 years for the NHS in England and Wales.

The total cost per patient in the first five years after starting on either pixantrone or standard care, broken down according to the stage of disease is presented in Table 56 and Table 57.

**Table 55: Budget impact results for the base case (Aggressive B-cell population)**

| Year | 1 | 2 | 3 | 4 | 5 | Total |
|---|---|---|---|---|---|---|
| **Budget impact with comparator arm** | £ 44,665,420 | £ 64,946,802 | £ 78,732,058 | £ 88,877,116 | £ 96,807,283 | £ 374,028,679 |
| **Budget impact with projected market shares for pixantrone** | £ 45,621,003 | £ 66,696,385 | £ 81,255,713 | £ 92,212,623 | £ 101,026,256 | £ 386,811,980 |
| **Difference (projected market share vs.. current market share)** | £ 955,583 | £ 1,749,583 | £ 2,523,655 | £ 3,335,507 | £ 4,218,973 | £ 12,783,301 |

**Table 56: Annual total cost per patient for patients starting on pixantrone**

| Cycle | Year | Pre-progression non-drug costs | Post-progression non-drug costs | Progression costs | Pre-progression drug costs | Pre-progression administration costs | AE costs | Post-treatment drug & administration costs | Post-progression drug & administration costs | Total costs |
|---|---|---|---|---|---|---|---|---|---|---|
| 52.18 | 1 | £8,943 | £4,195 | £488 | £16,898 | £2,186 | £374 | £2,943 | £2,626 | £38,653 |
| 104.36 | 2 | £2,935 | £6,029 | £143 | £0 | £0 | £0 | £0 | £769 | £9,876 |
| 156.54 | 3 | £1,722 | £5,399 | £61 | £0 | £0 | £0 | £0 | £329 | £7,511 |
| 208.71 | 4 | £1,142 | £4,643 | £33 | £0 | £0 | £0 | £0 | £175 | £5,992 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 260.89 | 5 | £813 | £3,991 | £20 | £0 | £0 | £0 | £0 | £105 | £4,929 |

**Table 57: Annual total cost per patient for patients starting on comparators**

| Cycle | Year | Pre-progression non-drug costs | Post-Progression non-drug costs | Progression costs | Pre-progression drug costs | Pre-progression administration costs | AE costs | Post-treatment drug & administration costs | Post-progression drug & administration costs | Total costs |
|---|---|---|---|---|---|---|---|---|---|---|
| 52.18 | 1 | £5,576 | £11,182 | £700 | £1,180 | £1,765 | £286 | £2,618 | £3,762 | £27,070 |
| 104.36 | 2 | £661 | £10,935 | £71 | £0 | £0 | £0 | £0 | £379 | £12,046 |
| 156.54 | 3 | £218 | £7,643 | £17 | £0 | £0 | £0 | £0 | £89 | £7,966 |
| 208.71 | 4 | £95 | £5,558 | £6 | £0 | £0 | £0 | £0 | £31 | £5,689 |
| 260.89 | 5 | £48 | £4,212 | £2 | £0 | £0 | £0 | £0 | £13 | £4,277 |

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not applicable, none have been identified

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## *Related procedures for evidence submission*

## *Cost-effectiveness models*

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission.

There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

### *Disclosure of information*

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential

information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been

put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.