NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Pixantrone monotherapy for treating relapsed or refractory aggressive non-Hodgkin's lymphoma

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Pixantrone has a conditional UK marketing authorisation as monotherapy for treating multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. The marketing authorisation is for third line and greater, and recognises that there is limited evidence on pixantrone use as fifth or any subsequent line of therapy. The intention-to-treat population in the PIX301 trial included a broader population than the marketing authorisation because it included additional histological subtypes. Therefore, the manufacturer provided post-hoc subgroup analyses for:
  - patients with aggressive B-cell lymphoma determined by onsite pathological review at study entry,
  - patients with aggressive B-cell lymphoma confirmed retrospectively by central independent pathological review and
  - patients with diffuse large B-cell lymphoma.

  The manufacturer has noted that marketing authorisation does not require central histological confirmation of diagnosis and that this is not clinical

practice. The ERG's view is that the subgroup of patients with aggressive B-cell lymphoma confirmed by central independent pathological review is more relevant to the appraisal scope, and the marketing authorisation because it retrospectively excludes patients who did not meet the inclusion criteria for PIX301 (for example, indolent disease). What is the Committee's view on the robustness and appropriateness of the evidence presented for the subgroups?

- Does the full trial population provide a reliable estimate of pixantrone's clinical effectiveness?
  - The PIX301 study randomised 140 of a planned 320 patients. The manufacturer's submission states that the study was considered sufficiently powered (about 80%) to detect a 15% difference in the complete or unconfirmed complete response rate, assuming a complete or unconfirmed complete response rate of at least 18% in the pixantrone arm.
  - However, the full publication of the trial states that a sample size of 70 patients per arm using the original assumptions would yield around 40% power and that the true proportion of patients with complete or unconfirmed complete response would have to have been 22% in the pixantrone group and 5% in the comparator group.
  - Actual response rates for the intention-to-treat population in the PIX301 trial were 20% in the pixantrone group and 5.7% in the comparator group.
- Rituximab is part of standard first-line treatment for aggressive B-cell non-Hodgkin's lymphoma in England and Wales. In the PIX301 trial, around 55% of patients had previously received rituximab treatment and subgroup results showed pixantrone had no statistically significant effect on progression-free survival in this subgroup. The Committee for Medicinal Products for Human Use noted a smaller benefit in the subgroup of patients who have previously received rituximab and concluded that an additional clinical trial should be conducted to confirm the benefit of pixantrone in this

subgroup, which forms the basis of the conditional marketing authorisation. Are the results from the PIX301 trial population or post-hoc subgroups according to lymphoma classification generalisable to the patient population with multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma in clinical practice in England and Wales?

Cost effectiveness

- In the base case of its economic model, the manufacturer used the subgroup with aggressive B-cell lymphoma determined by onsite pathological review that was receiving third- or fourth-line treatment. It considered that this subgroup was the closest to the population covered by the UK marketing authorisation. In its exploratory analyses, the ERG used the population with aggressive B-cell lymphoma (determined by central independent pathological review) for all lines of therapy in the PIX301 trial in its base case. Considering all subgroups, which is the most appropriate for assessing cost effectiveness in line with the marketing authorisation and NICE scope?
- The manufacturer used self-reported utility values for an elderly population receiving first-line treatment for aggressive non-Hodgkin's lymphoma. The ERG considered that using utility values for patients with chronic lymphocytic leukaemia receiving third-line therapy elicited from the general population using time trade-off was more relevant to the decision problem. Which utility values are more suitable for informing Committee's decision-making?
- The ERG noted that the results of the manufacturer's economic model may potentially be biased towards pixantrone as a result of an overestimation of the relative progression-free survival benefit of pixantrone versus treatment of physician's choice. The manufacturer indicated that the selected distribution fitted the data well and that overestimating the difference between the medians was because of the steps seen in the Kaplan–Meier curves around the median. Can the predictive equations used to calculate

progression-free survival and overall survival in the manufacturer's model be considered to generate reliable estimates?

- The manufacturer has modelled adverse events by applying disutilities that were limited to patients on original therapy (that is, excluding further lines of treatment). Is this assumption acceptable?

Other considerations:

- Does the Committee consider that pixantrone meets the end-of-life criteria, and if so, have all the end-of-life criteria been met and are the estimates robust?
- The manufacturer submission states that it was designed to reduce the cardiotoxicity associated with anthracyclines; however, the adverse-effect profile shows that more cardiac adverse events occurred in the pixantrone group than in the comparator group receiving treatment of physician's choice. What is the Committee's view on the innovative aspects of pixantrone raised by the manufacturer?

1 Background: clinical need and practice

1.1 Lymphomas are cancers of the lymphatic system (part of the body's immune system) and broadly comprise Hodgkin's lymphoma and non-Hodgkin's lymphoma. About 9 out of 10 people diagnosed with non-Hodgkin's lymphoma have a B-cell lymphoma. Non-Hodgkin's lymphoma can be fairly equally divided into indolent (low grade) and aggressive (high grade) lymphomas.

1.2 Non-Hodgkin's lymphoma accounts for approximately 4% of all cancers diagnosed in the UK, with around 10,800 new cases of non-Hodgkin's lymphoma registered in England and Wales in 2009, and around 3900 registered deaths in 2010. The incidence of non-Hodgkin's lymphoma increases with age and more than 70% of all non-Hodgkin's lymphoma is diagnosed in people over 60 years. Five-year survival rates in England and Wales for all types of non-

Hodgkin's lymphoma are over 60%. For patients with relapsed or resistant non-Hodgkin's lymphoma, survival at 2 years is less than 5–10%.

1.3 The optimum management of non-Hodgkin's lymphoma depends on its type and accurate disease staging. First-line treatment options for aggressive non-Hodgkin's lymphoma include combination chemotherapy regimens based on alkylating agents, without or with steroids. NICE technology appraisal guidance 65 recommends rituximab in combination with a regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) for the first-line treatment of people with CD20-positive diffuse large-B-cell (aggressive) lymphoma at clinical stages II, III or IV (that is, where the disease affects more than one group of lymph nodes in one region of the body).

1.4 For people with aggressive non-Hodgkin's lymphoma whose disease does not respond to first-line treatment, second-line treatment options include platinum-based chemotherapy with or without rituximab or single-agent chemotherapy (if combination chemotherapy is unsuitable). High-dose chemotherapy with stem cell support may then be considered as a subsequent line of therapy. Otherwise, single-agent chemotherapy is usually given when disease relapses or becomes refractory to prior treatments. Treatment options for multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma (the scope of this appraisal) include monotherapy with vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone or gemcitabine. The British National Formulary states anthracyclines such as doxorubicin are associated with dose-related, cumulative, and potentially life-threatening cardiotoxic side effects. The Summary of Product Characteristics for mitoxantrone notes that it is probable that the toxicity of doxorubicin and other

anthracyclines or anthracenediones is additive. Of the monotherapy treatment options named above, none are anthracyclines and only mitoxantrone is an anthracenedione.

2 The technology

2.1 Pixantrone (Pixuvri, Cell Therapeutics) is an aza-anthracenedione analogue and inhibitor of topoisomerase II. The recommended dosage is pixantrone 50 mg/m^2 on days 1, 8, and 15 of each 28-day cycle for up to 6 cycles. It is administered intravenously. Pixantrone has a conditional UK marketing authorisation 'as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy' (meaning that is conditionally approved for patients who have received at least 2 previous lines of therapy). The conditional marketing authorisation is linked to the provision of results from the phase III PIX306 trial investigating pixantrone plus rituximab versus gemcitabine plus rituximab for aggressive B-cell non-Hodgkin's lymphoma. The study will compare the two regimens in patients with relapsed or refractory diffuse large B-cell lymphoma (de novo or transformed), or follicular grade 3 lymphoma, who have previously received a rituximab-containing regimen and are not eligible for autologous stem cell transplant or high-dose chemotherapy. Patients with de novo diffuse large B-cell lymphoma or follicular grade 3 lymphoma must have received 1–3 treatment regimens and patients with transformed diffuse large B-cell lymphoma must have received at least 1–4 treatment regimens.

2.2 The summary of product characteristics states the most common toxicity with pixantrone is bone marrow suppression (particularly the neutrophil lineage) and that other toxicities such as nausea, vomiting, and diarrhoea were generally infrequent, mild, reversible, manageable, and expected in patients treated with cytotoxic agents. Although the occurrence of cardiac toxicity indicated by congestive heart failure appears to be lower than that expected with related drugs like anthracyclines, it recommends monitoring left ventricular ejection fraction. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Pixantrone is priced at £553.50 per 20 ml vial containing 29 mg free base pixantrone, which is equivalent to 50 mg pixantrone dimaleate (excluding VAT; costs from manufacturer's submission). The estimated cost of a course of treatment is £19,926.18 (costs calculated over 4 cycles using an average of 3 vials per dose based on the median length of treatment in the PIX301 trial). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of pixantrone dimaleate monotherapy within its licensed indication for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma in people for whom treatment with single agent chemotherapy is being considered. The decision problem addressed in the manufacturer's submission was in line with the final scope issued by NICE.

Population	Adults with multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma

3.2 In its submission, the manufacturer presented several patient populations to address the decision problem. These comprised the intention-to-treat population and several post-hoc subgroups from the PIX301 trial. The different populations presented by the manufacturer are described in table 1. The manufacturer considered the population with aggressive B-cell lymphoma confirmed by onsite pathological review (third- and fourth-line treatment) to be the most relevant to the decision problem and used this in its economic model. The ERG considered the population with aggressive B-cell lymphoma confirmed by central independent pathological review for all lines of therapy in the PIX301 trial to be the most information to the decision problem and used it in its exploratory analyses.

Table 1 Different patient populations in the manufacturer's submission

Population	Details
UK marketing authorisation	• Adults with 'multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater' chemotherapy in patients who are refractory to last therapy'
NICE scope	• Adults with multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma
Manufacturer's submission	
Intention-to-treat population	• Adults with aggressive de novo or transformed non-Hodgkin's lymphoma that had relapsed after 2 or more chemotherapy regimens, including at least 1 standard anthracycline-containing regimen with a response that had lasted at least 24 weeks • Because this population included patients with indolent non-Hodgkin's lymphoma and with non-specified aggressive non-Hodgkin's lymphoma, and, therefore, the ERG considered the results from this population were not the most relevant to the decision problem
Aggressive B-cell lymphoma confirmed by onsite pathological review	• This group was defined by the manufacturer as diffuse large B-cell lymphoma, transformed indolent lymphoma and follicular lymphoma, grade III • The ERG noted that not all types of aggressive B-cell lymphoma were represented in the PIX301 trial • The manufacturer stated that performing central histological review before study entry was judged to be

	impractical because of a combination of the unstable nature of the disease and the urgent need for therapy, together with the large number of participating sites. • The ERG acknowledged retrospective histological review to be a pragmatic approach, but considered it important to evaluate data from the subgroup of patients with histologically confirmed disease
Aggressive B-cell lymphoma confirmed by onsite pathological review (third- and fourth-line treatment)	• Because of the wording of the UK marketing authorisation, the manufacturer considered this subgroup to be the most relevant to the decision problems and included it in its economic model • The ERG did not consider this population to be the most appropriate population for evaluation (see below)
Aggressive B-cell lymphoma confirmed by central independent pathological review	• The ERG noted that analysis of retrospective histological confirmation of aggressive disease by central independent pathological review revealed that, in the intention-to-treat population, 23% of patients in the pixantrone group and 29% of patients in the comparator group had disease that was subsequently determined not to be aggressive. • The ERG was aware that disease severity is an important factor in determining treatment strategy because patients without aggressive disease are likely to have a more favourable response than those whose disease is histologically confirmed as aggressive • The ERG concluded the patient population with aggressive B-cell lymphoma whose disease had been confirmed by central independent pathological review was the most appropriate for assessment and used it in its exploratory analyses
Aggressive B-cell lymphoma confirmed by central independent pathological review (third- and fourth-line treatment)	• The ERG noted that the clinical effectiveness for this subgroup were broadly similar to the subgroup of all patients with aggressive B-cell lymphoma confirmed by central independent pathological review in the PIX301 trial • The ERG did not comment on the appropriateness of restricting treatment to the third and fourth lines of therapy. However, the ERG included the population with aggressive B-cell lymphoma confirmed by central independent pathological review for all lines of treatment in the PIX301 trial in its exploratory analyses
Diffuse large B-cell lymphoma (confirmed by onsite pathological review)	• In the subgroup of patients with aggressive B-cell non-Hodgkin's lymphoma, 85% were diagnosed as having diffuse large B-cell lymphoma • This is therefore a smaller group than that covered by the UK marketing authorisation

The ERG noted that the full trial population of PIX301 included patients that would not be eligible for treatment according to the UK

marketing authorisation but, given the small proportion of patients with T-cell-derived non-Hodgkin's lymphoma in the PIX301 trial, concluded the trial population was relevant to the decision problem.

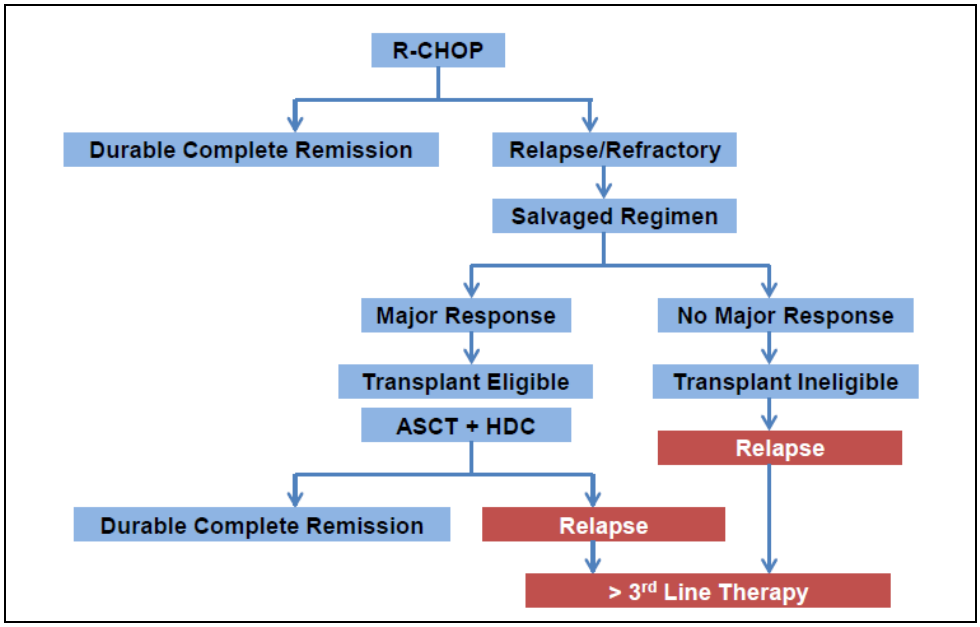
Intervention	Pixantrone
Comparators	• Vinorelbine • Oxaliplatin • Ifosfamide • Etoposide • Mitoxantrone • Gemcitabine
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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. Costs will be considered from an NHS and Personal Social Services perspective.

3.3 The manufacturer noted that, although they are all used in UK clinical practice, none of the comparator therapies specified in the decision problem has a UK marketing authorisation for treating non-Hodgkin's lymphoma in patients 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. Clinical specialist advice to the ERG emphasised that there is no consensus on the most appropriate therapy for third and subsequent lines of treatment in UK clinical practice. The ERG's clinical specialists indicated that third-line treatment is typically given with the goal of increasing progression-free survival while limiting toxicity. One clinical specialist indicated that, based on these considerations, this would most likely be a single chemotherapeutic agent such as gemcitabine, vinblastine and

vinorelbine. However, a second clinical specialist noted a preference for combination chemotherapy. The clinical specialists added that a combination regimen might be considered if a patient's previous response to treatment had lasted for more than 12 months. However, the ERG's clinical specialists stressed that there is no consensus on this strategy.

3.4 The UK marketing authorisation is for multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. The manufacturer advised that it expected pixantrone to be used as third-line therapy or greater for people with multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma (see figure 1) and that there are currently no other drugs licensed in the UK for this specific patient population (that is, third and subsequent lines of treatment). The ERG considered the manufacturer's proposed position of pixantrone in the treatment pathway to be appropriate and emphasised the lack of evidence for the other treatments for third and subsequent lines of therapy in aggressive non-Hodgkin's lymphoma.

Figure 1 Manufacturer's treatment algorithm



Key: ASCT, autologous stem cell transplant; HDC, high-dose chemotherapy; R-CHOP, rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone

Source: page 24 of the manufacturer's submission

3.5 The ERG concluded that the manufacturer's approach to the decision problem was appropriate, noting that the clinical trial population and reported outcomes to be relevant and that the 6 comparators matched those specified in the final scope.

4 Clinical-effectiveness evidence

4.1 The manufacturer's systematic review identified 1 randomised controlled trial, which was included in its submission. No other relevant randomised controlled trials or non-randomised controlled trials were identified. The manufacturer also included some supporting cardiotoxicity data from a randomised phase II study that did not meet the inclusion criteria of the literature review (it evaluated pixantrone in combination with other drugs, not as monotherapy).

4.2 PIX301 is a randomised, controlled, open-label phase III study that was conducted in 66 centres, including the USA and Europe. Eligible patients were adults with aggressive de novo or transformed non-Hodgkin's lymphoma that had relapsed after 2 or more chemotherapy regimens, including at least 1 standard anthracycline-containing regimen with a response that had lasted at least 24 weeks. Patients were randomised to either pixantrone (n=70) or to a physician's choice of single-agent comparators comprising vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab (n=70). Pixantrone was administered at a dosage of 85 mg/m^2 on Days 1, 8 and 15 of a 28-day cycle for up to 6 cycles. Comparators were administered at predefined standard dosages for up to 6 cycles. Follow-up was for 18 months after completing study treatment.

4.3 The primary outcome was complete and unconfirmed complete response that was determined by a blinded independent assessment panel. Secondary outcomes were overall survival, response rate lasting at least 4 months and progression-free survival. Other predefined end points were overall response rate, time to response, time to complete response, duration of response and relative dose intensity. The primary analysis was the intention-to-treat population. Secondary analyses included a prespecified analysis of the response and survival end points for the histologically confirmed intention-to-treat population (that is, where the lymphoma had been classified according to retrospective independent central pathology assessment).

4.4 It was initially planned that 320 patients would be recruited but slow accrual resulted in early closure of study enrolment. The manufacturer's submission stated that, with a final enrolment of 140 patients, the study was considered sufficiently powered (about

80%) to detect a 15% difference in the complete or unconfirmed complete response rate, assuming a complete or unconfirmed complete response rate of at least 18% in the pixantrone arm. However, the full publication of PIX301 reported that, according to the original sample size assumptions, a sample of 70 patients per group would have about 40% power. It further stated that to achieve 81% power with 70 patients per group, the true proportion of patients with a complete or unconfirmed complete response would have to have been 22% in the pixantrone group and 5% in the comparator group.

4.5 The manufacturer reported that baseline demographic and disease characteristics were similar in the two arms (see table 2 for baseline lymphoma classification according to onsite pathological review). Previous treatment for non-Hodgkin's lymphoma, including median number and category of previous chemotherapy, was broadly similar for both groups (see pages 66–7 of the manufacturer's submission for further details).

Table 2 Lymphoma categorisation at baseline (onsite pathological review)

	Pixantrone (n=70)	**Treatment of physician's choice[a] (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 not otherwise characterised	3 (4.3%)	7 (10.0%)
Anaplastic large cell lymphoma/null cell/primary systemic	3 (4.3%)	1 (1.4%)

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab
Data are presented as n (%)
Source: page 64 of the manufacturer's submission
Shading indicates categories of lymphoma that are not covered by pixantrone's UK marketing authorisation

4.6 The manufacturer's submission reported that at the end of treatment and end of study, confirmed and unconfirmed response rates for the intention-to-treat population were statistically significantly higher for the pixantrone group than the comparator group receiving treatment of physician's choice (table 3).

Table 3 Manufacturer's results for confirmed and unconfirmed response rates in PIX301: intention-to-treat population

	End of treatment			End of study		
	Pixantrone (n=70)	**TPC[a] (n=70)**	**p-value**	**Pixantrone (n=70)**	**TPC[a] (n=70)**	**p-value**
Complete or unconfirmed complete response	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
Complete response	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
Unconfirmed complete response	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

[a] TPC (treatment of physician's choice) was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

Data are presented as n (%, confidence interval)
End of study refers to analyses of treatment and 18-month follow-up
Source: page 77 of the manufacturer's submission

4.7 The manufacturer's submission described the results for progression-free and overall survival in the intention-to-treat population (table 4). Median progression-free survival was statistically significantly longer for patients receiving pixantrone than a comparator drug. However, there was no statistically significant difference in overall survival between the 2 groups.

Table 4 Manufacturer's results for progression-free and overall survival: intention-to-treat population

	Pixantrone (n=70)	Treatment of physician's choice[a] (n=70)	Hazard ratio (95% CI)	Log-rank p-value
Progression-free survival, months (95% CI)	5.3 (2.3–6.2)	2.6 (1.9–3.5)	0.60 (0.42–0.82)	0.005
Overall survival, months (95% CI)	10.2 (6.4–15.7)	7.6 (5.4–9.3)	0.79 (0.53–1.18)	0.251

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

Key: CI, confidence interval
Source: pages 78–9 of the manufacturer's submission

4.8 The manufacturer's submission provided the results of the other prespecified end points for the intention-to-treat population. The overall response rate — comprising the total proportion of patients with complete response, unconfirmed complete response and partial response — was statistically significantly higher in the pixantrone arm than the comparator arm at the end of treatment (37.1% [95% CI 25.9–49.5] versus 14.3% [95% CI 7.1–24.7], p=0.003) and at end of study (40.0% [95% CI 28.5–52.4] versus 14.3% [95% CI 7.1–24.7], p=0.001). There were no statistically significant between-group differences in time to overall response, time to complete response and duration of response (see page 80 of the manufacturer's submission for details). However, more patients in the pixantrone group than the comparator group had a response lasting at least 4 months (17.1% versus 8.6%). Median relative dose intensity was 90.6% in the pixantrone group and greater than 93% in the comparator group for all drugs except vinorelbine.

4.9 Aggressive histological features were identified onsite in all patients before treatment was given and confirmed by central independent pathological review in 54 (77%) of 70 patients in pixantrone arm

and 50 (71%) of 70 patients in the comparator arm receiving treatment of physician's choice. Of the remaining 36 patients, reasons for non-confirmation included low-grade histology (n=13) and lack of consensus (n=10). Out of 140 patients, 36 patients completed 6 cycles of protocol treatment, and 104 patients discontinued early. The most common reason for early discontinuation in both groups was disease progression or relapse. After completing study treatment, 95 patients entered follow-up and 26 of these completed 18 months of follow-up.

4.10 The manufacturer identified a post-hoc subgroup of patients with aggressive B-cell lymphoma (classed as diffuse large B-cell lymphoma, transformed indolent lymphoma or follicular lymphoma [grade III]) confirmed by onsite pathological review. It advised that this subgroup was similar to the population eligible for treatment according to pixantrone's UK marketing authorisation, and that it was used in the base case of the manufacturer's cost-effectiveness analysis. Response rates at end of study were statistically significantly higher and progression-free survival was statistically significantly longer in patients who had received pixantrone than those who had received a comparator drug (table 5). The manufacturer advised that median overall survival was not included because the aggressive B-cell lymphoma analyses were exploratory.

Table 5 Manufacturer's results for response rates and progression-free survival in PIX301: post-hoc subgroup with aggressive B-cell lymphoma confirmed by onsite pathological review

	Pixantrone (n=64)	Treatment of physician's choice (n=62)	p-value	Hazard ratio (95% confidence interval)
Complete or unconfirmed complete response	15 (23.4%, 13.8–35.7)	5 (8.1%, 2.7–17.8)	0.027	–
Overall response rate	26 (40.6%, 28.5–53.6)	10 (16.1%, 8.0–27.7)	0.003	–
Median progression-free survival, months	5.7 (2.4–6.5)	2.5 (1.9–3.5)	0.002	0.56 (0.38–0.81)

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

Data are presented as n (%, confidence interval) or median (95% confidence interval)
Overall response rate is patients with complete, unconfirmed complete, or partial response
Source: page 82 of the manufacturer's submission

4.11 In a further analysis of patients with aggressive B-cell lymphoma confirmed by onsite pathological review who received pixantrone or a comparator as third- or fourth-line therapy (which the manufacturer stated was more closely aligned with pixantrone's marketing authorisation), the group receiving pixantrone had a statistically significantly higher complete response or unconfirmed complete response rate and overall response rate, and statistically significantly longer progression-free survival (table 6). Overall survival in this population was numerically higher in the pixantrone arm than the comparator arm. The manufacturer's submission did not state if the results were for end of treatment or end of study.

Table 6 Manufacturer's results for response rates and progression-free survival in PIX301: post-hoc subgroup with aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line therapy)

	Pixantrone (n=50)	Treatment of physician's choice (n=49)	p-value	Hazard ratio (95% confidence interval)
Complete or unconfirmed complete response	28.0%	4.0%	0.002	–
Overall response rate	48.0%	12.2%	<0.001	–
Median progression-free survival, months	5.8	2.8	0.002	Not stated
Median overall survival, months	13.9	7.8	p=0.275	0.76 [95% confidence interval 0.47 to 1.24]

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

Data are presented as n (%, confidence interval) or median (95% confidence interval)
Overall response rate is patients with complete, unconfirmed complete, or partial response
Source: page 78 of the manufacturer's submission

4.12 In response to clarification questions, the manufacturer provided results for the post-hoc subgroup of patients with aggressive B-cell lymphoma whose disease had been histologically confirmed by central independent pathological review (table 7). At the end of the study, there was no statistically significant difference in complete or unconfirmed complete response rates between the pixantrone and comparator groups but the overall response rate was statistically significantly higher in the pixantrone group. Progression-free survival was statistically significantly longer in the pixantrone arm versus the comparator arm but there was no statistical difference in overall survival between the 2 groups.

Table 7 Manufacturer's results for response rates and progression-free survival in PIX301: post-hoc subgroup with aggressive B-cell lymphoma confirmed by central independent pathological review

	Pixantrone (n=50)	Treatment of physician's choice[a] (n=47)	p-value	Hazard ratio (95% confidence interval)
Complete or unconfirmed complete response	9	4	0.236	–
Overall response rate	18	8	0.041	–
Median progression-free survival, months	5.6 (0.7–24.0)	2.5 (0–24.0)	–	0.51 (0.33–0.78)
Median overall survival, months	8.1 (0.8–24.0)	6.3 (0.1–24.0)	–	0.72 (0.45–1.13)

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

Data are presented as n-numbers or median (95% confidence interval)
Overall response rate is patients with complete, unconfirmed complete, or partial response
Source: page 5 of appendix X in the manufacturer's clarification response

4.13 At the clarification stage, the manufacturer provided results for a subgroup of patients with aggressive B-cell lymphoma confirmed by central independent pathological review who were receiving third- or fourth-line therapy (table 8). Clinical effectiveness results for patients receiving third- or fourth-line treatment were similar to those for the overall subgroup of patients with histologically confirmed aggressive B-cell non-Hodgkin's lymphoma, with most results not reaching statistical significance but the direction of effect favouring pixantrone.

Table 8 Manufacturer's results for response rates and progression-free survival in PIX301: post-hoc subgroup with aggressive B-cell lymphoma confirmed by central independent pathological review (third- or fourth-line therapy)

Outcome	Pixantrone (n=39)	Treatment of physician's choice (n=39)	p-value or hazard ratio (95% CI)
Complete or unconfirmed complete response	9 (23.1%)	2 (5.1%)	0.047
Overall response rate	17 (43.6%)	5 (12.8%)	0.005
Median progression-free survival (range), months	5.7 (0.7 to 24.0)	2.8 (0.0 to 13.5)	0.44 (0.27 to 0.71)
Median overall survival (range), months	11.9 (1.1 to 24.0)	7.0 (0.2 to 24.0)	0.67 (0.40 to 1.12)

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

Key: CI, confidence interval

Source: Pages 9–10 of appendix X in the manufacturer's clarification response

4.14 The manufacturer provided results for the post-hoc subgroup of patients with diffuse large B-cell lymphoma confirmed by onsite pathological review. At the end of the study, response rates were statistically significantly higher and progression-free survival was statistically significantly longer in patients who had received pixantrone than those who had received a treatment of physician's choice (table 9).

Table 9 Manufacturer's results for response rates and progression-free survival in PIX301: post-hoc subgroup with diffuse large B-cell lymphoma confirmed by onsite pathological review

	Pixantrone (n=53)	Treatment of physician's choice[a] (n=51)	p-value	Hazard ratio (95% confidence interval)
Complete or unconfirmed complete response	10 (18.9%, 9.4–32.0%)	2 (3.9%, 0.5–13.5%)	0.029	–
Overall response rate	18 (34.0%, 21.5–48.3%)	7 (13.7%, 5.7–26.3%)	0.021	–
Median progression-free survival, months	4.6 (2.3–6.5)	2.1 (1.8–3.2)	<0.001	0.47 (0.30–0.71)

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

Data are presented as n (%, confidence interval) or median (95% confidence interval)
Overall response rate is patients with complete, unconfirmed complete, or partial response
Source: page 84 of the manufacturer's submission

4.15 At clarification, the manufacturer provided subgroup analyses that showed the influence of previous rituximab therapy pixantrone's efficacy in the subgroup of patients who had aggressive B-cell non-Hodgkin's lymphoma confirmed by central independent pathological review (table 10). There was no significant difference between pixantrone and the comparator arm in the proportion of patients achieving complete or unconfirmed complete response at the end of treatment. Median progression-free survival and median overall survival were longer in the pixantrone group for this subgroup of patients, but the between-group difference did not reach statistical significance for either outcome.

Table 10 Manufacturer's results for post-hoc subgroup of patients with aggressive B-cell non-Hodgkin's lymphoma confirmed by central independent pathological review who had previously received rituximab

	Pixantrone (n=30)	Treatment of physician's choice[a] (n=26)	p-value	Hazard ratio (95% confidence interval)
Complete or unconfirmed complete response	5/30 (16.7%)	2/26 (7.7%)	p=0.431	–
Median progression-free survival, months	3.5	2.3		0.66 (0.38 to 1.14)
Median overall survival, months	6.0	4.6		0.85 (0.48 to 1.50)

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab
Source: page 9 of appendix X in the manufacturer's clarification response

Overview of efficacy data

4.16 The clinical-effectiveness data for all the different populations presented in the manufacturer's submission are summarised below: response rates in table 11, progression-free survival in table 12 and overall survival in table 13.

Table 11 Response rates at end of study for the different PIX301 patient populations in the manufacturer's submission

	Pixantrone	Treatment of physician's choice[a]	Absolute difference between arms	p-value
Intention-to-treat population				
Complete or unconfirmed complete response	17/70 (24.3%)	5/70 (7.1%)	17.2%	0.009
Overall response rate	28/70 (40.0%)	10 (14.3%)	25.7%	0.001
Aggressive B-cell lymphoma confirmed by onsite pathological review				
Complete or unconfirmed complete response	15/64 (23.4%)	5/62 (8.1%)	15.3%	0.027
Overall response rate	26/64 (40.6%)	10/62 (16.1%)	24.5%	0.003
Aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line therapy[b]				
Complete or unconfirmed complete response	n[b]/50 (28.0%)	n[b]/49 **(**4.0%**)**	24.0%	0.002
Overall response rate	n[b]/50 (48.0%)	n[b]/49 (12.2%)	35.8%	<0.001
Aggressive B-cell lymphoma confirmed by central independent pathological review				
Complete or unconfirmed complete response	9/50 (18.0%)	4/47 (8.5%)	9.5%	0.236
Overall response rate	18/50 (36.0%)	8/47 (17.0%)	19.0%	0.041
Aggressive B-cell lymphoma confirmed by central independent pathological review (third- or fourth-line therapy				
Complete or unconfirmed complete response	9/39 (23.1%)	2/39 (5.1%)	18.0%	0.047
Overall response rate	17/39 (43.6%)	5/39 (12.8%)	30.8%	0.005
Diffuse large B-cell lymphoma confirmed by onsite pathological review				
Complete or unconfirmed complete response	10/53 (18.9%)	2/51 (3.9%)	15.0%	0.029
Overall response rate	18/53 (34.0%)	7 /51(13.7%)	20.3%	0.021

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

[b] It is assumed the results from patients with aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line therapy) are end of study (this is not explicitly stated in the manufacturer's submission). The number of patients responding to each treatment was not reported.

Data are presented as n/N (%)

Overall response rate is patients with complete, unconfirmed complete, or partial response

Sources: Data compiled from the manufacturer's submission and clarification response, and the ERG report

Table 12 Progression-free survival for the different PIX301 patient populations in the manufacturer's submission

	Pixantrone	Treatment of physician's choice[a]	Absolute difference between arms	Hazard ratio (95% CI)
Intention-to-treat population	5.3 (2.3–6.2), n=70	2.6 (1.9–3.50), n=70	2.7 months	0.60 (0.42–0.82)
Aggressive B-cell lymphoma confirmed by onsite pathological review	5.7 (2.4–6.5), n=64	2.5 (1.9–3.5), n=62	3.2 months	0.56 (0.38–0.81)
Aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line therapy)[b]	5.8 (95% CI not given), n=50	2.8 (95% CI not given), n=49	3.0 months	Not stated
Aggressive B-cell lymphoma confirmed by central independent pathological review	5.6 (0.7–24.0), n=50	2.5 (0–24.0), n=47	3.1 months	0.51 (0.33–0.78)
Aggressive B-cell lymphoma confirmed by central independent pathological review (third- or fourth-line therapy)	5.7 (0.7–24.0), n=39	2.8 (0.0–13.5), n=39	2.9 months	0.44 (0.27 to 0.71)
Diffuse large B-cell lymphoma confirmed by onsite pathological review	4.6 (2.3–6.5), n=53	2.1 (1.8–3.2), n=51	2.5 months	0.47 (0.30–0.71)

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

[b] It is assumed the results from patients with aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line therapy) are end of study (this is not explicitly stated in the manufacturer's submission). The number of patients responding to each treatment was not reported.

Data are presented as median in months (95% confidence interval), n. Data for the group with aggressive B-cell lymphoma confirmed by central independent pathological review (third- or fourth-line therapy) are presented as median (range), n. Sources: Data compiled from the manufacturer's submission and clarification response, and the ERG report

Table 13 Overall survival for the different PIX301 patient populations in the manufacturer's submission

	Pixantrone	Treatment of physician's choice[a]	Absolute difference between arms	Hazard ratio
Intention-to-treat population	10.2 (6.4–15.7), n=70	7.6 (5.4–9.3), n=70	2.6 months	0.79 (0.53–1.18)
Aggressive B-cell lymphoma confirmed by onsite pathological review	Not available	Not available	Not available	Not available
Aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line therapy)[b]	13.9 (95% CI not given), n=50	7.8 (95% CI not given), n=49	6.1 months	0.76 (0.47 to 1.24)
Aggressive B-cell lymphoma confirmed by central independent pathological review	8.1 (0.8–24.0), n=50	6.3 (0.1–24.0), n=47	1.8 months	0.72 (0.45–1.13)
Aggressive B-cell lymphoma confirmed by central independent pathological review (third- or fourth-line therapy)	11.9 (1.1 to 24.0), n=39	7.0 (0.2-24.0) n=39	4.9 months	0.67 (0.40 to 1.12)
Diffuse large B-cell lymphoma confirmed by onsite pathological review	Not available	Not available	Not available	Not available

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

[b] It is assumed the results from patients with aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line therapy) are end of study (this is not explicitly stated in the manufacturer's submission). The number of patients responding to each treatment was not reported.

Data are presented as median (95% confidence interval), n. Data for the group with aggressive B-cell lymphoma confirmed by central independent pathological review (third- or fourth-line therapy) are presented as median (range), n

Sources: Data compiled from the manufacturer's submission and clarification response, and the ERG report

Safety data

4.17 The manufacturer's submission described the adverse effects in the PIX301 trial for 68 patients in the pixantrone group and 67 patients in the comparator group who received treatment of physician's choice. One dose reduction was allowed for patients

who had neutropenia during treatment, and reductions were similar in the pixantrone and groups (18% versus 15%). Dose delay was more frequent with pixantrone (40% versus 22%).

4.18 A similar number of patients experienced an adverse event of any grade but there was a higher incidence of grade 3 and 4 adverse events in the pixantrone group versus the comparator group (table 14). Neutropenia occurred more frequently in the pixantrone group and was the most common adverse event of any grade (50.0% versus 23.9%) and the most common grade 3 or 4 adverse event (41.2% versus 19.4%). Grade 3 or 4 febrile neutropenia was also higher in the pixantrone group than the comparator group (7.4% versus 3.0%), and more patients in the pixantrone group than the comparator group received an immunostimulant (51.5% versus 26.9%). The manufacturer reported that severity of neutropenia did not increase with increasing cycle number and that the overall rates of grade 3 and 4 infections were similar in the 2 groups. It further stated that the common adverse events were similar to those expected in a heavily pretreated patient population, reflective of pixantrone's intended use in UK clinical practice (that is, third and subsequent lines of therapy). For a detailed table of common any-grade adverse events and all grade 3 or 4 adverse events in the PIX301 trial, see pages 93–5 of the manufacturer's submission.

Table 14 Summary of safety data from the PIX301 trial

	Pixantrone (n=68)	Treatment of physician's choice[a] (n=67)
Any adverse event	66 (97.1%)	61 (91.0%)
Grade 3 or 4 event	52 (76.5%)	35 (52.2%)
Treatment-related adverse event	55 (80.9%)	38 (56.7%)
Serious adverse event	35 (51.5%)	30 (44.8%)
Death within 30 days of last dose	10 (14.7%)	12 (17.9%)

[a] Treatment of physician's choice was 1 of: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine and rituximab

4.19 Approximately 40% of patients in the 2 treatment arms presented with cardiac history at study enrolment and cardiac risk factors were also similar in the 2 groups. The manufacturer states that pixantrone is an innovative treatment because it has been specifically designed to reduce cardiotoxicity associated with anthracyclines without compromising efficacy. More cardiac adverse events occurred in the pixantrone group (24 patients [35.3%] than the comparator group that received treatment of physician's choice (14 patients [20.9%]). Thirteen (19.1%) patients in the pixantrone group experienced decreases in left ventricular ejection fraction compared with 7 in the comparator group (see page 98 of the manufacturer's submission for details). The manufacturer provided supporting cardiotoxicity data from the randomised open-label phase II PIX203 trial, which closed before enrolment completed. The study compared the combination of cyclophosphamide, pixantrone, vincristine, prednisone and rituximab with the standard of care R-CHOP as first-line treatment in patients with diffuse large B-cell lymphoma (see pages 102–6 of the manufacturer's submission). The results of the PIX203 trial broadly supported those of PIX301.

4.20 The ERG considered that the manufacturer had included trials that were relevant to the decision problem in its analysis. No additional relevant trials were identified and the ERG found the manufacturer's systematic review followed standard practices.

4.21 The ERG had concerns about the generalisability of the PIX301 trial population to clinical practice in England and Wales. It noted that only 7 of 140 patients in the trial were recruited from the UK. The remaining patients were recruited from North America (n=8),

Western Europe (n=31) and Rest of World (n=94). It further noted that patients from Western Europe were heavily pretreated and may have had more severe disease than patients typically eligible for treatment with pixantrone in the UK.

4.22 The ERG had specific concerns about the potential effect of previous rituximab therapy on the response to pixantrone in UK clinical practice because rituximab is given as part of standard first-line treatment in the UK. However, only 37.2% of patients in the PIX301 trial had previously received biological therapy because rituximab was not available in all participating countries. It considered that the clinical benefit of pixantrone in patients who have previously been treated with rituximab was a key area of uncertainty, given that there were no statistically significant differences between the pixantrone and comparator arms for complete or unconfirmed complete response, progression-free survival or overall survival in the subgroup of patients with aggressive B-cell lymphoma confirmed by central independent pathological review who had previously received rituximab.

4.23 The ERG considered whether the treatments of physician's choice in the PIX301 trial represented UK clinical practice. The ERG noted there is no consensus on which chemotherapy should be used following failure of second-line treatment and there is lack of comparative data on clinical effectiveness. The ERG concluded that the choice of treatment in the comparator arm of the PIX301 trial was unlikely to be a key issue and that, because of the small numbers receiving each treatment, the choice of treatment in the comparator group could not be reliably analysed.

4.24 The ERG reviewed the appropriateness of the outcomes used in the PIX301 trial. It highlighted that the assessment report published

by the Committee for Medicinal Products for Human Use had stated that although progression-free survival or overall survival would have been more appropriate as a primary end point, the use of complete or unconfirmed complete response was not a major concern because of the positive results with pixantrone in the heavily pretreated population of the PIX301 trial.

4.25 The ERG expressed concerns about the statistical power of PIX301 to detect a difference between treatment groups. According to the manufacturer's revised power calculation, 81% power with 70 patients per group (the intention-to-treat population) would be achieved if the true proportion of patients with complete or unconfirmed complete response was 22% in the pixantrone group and 5% in the comparator group. However, the observed proportions of patients achieving complete or unconfirmed complete response in the intention-to-treat population were 20.0% in the pixantrone group and 5.7% in the comparator groups. The ERG noted that the difference between groups did not always reach statistical significance, and that results of the analyses in the subgroups confirmed by central independent pathological review should be interpreted with caution as they are likely to be underpowered to detect a difference between treatment groups. Taken as whole, the ERG concluded it had reservations about whether superior efficacy of pixantrone had been demonstrated.

4.26 The ERG was concerned about the reliability of the diagnosis of aggressive non-Hodgkin's lymphoma at study entry. It noted that central independent pathological review by consensus was undertaken retrospectively, rather than at enrolment, and that only 104 of the 140 patients who were randomised had subsequent confirmation of aggressive disease. Consequently, it felt that results from the full trial population might not reflect the benefit of

pixantrone in patients with aggressive B-cell lymphoma. It acknowledged the reasons of impracticality given by the manufacturer but considered it important to evaluate data from the subgroup of patients with disease confirmed by central independent pathological review. However, it noted that, as a subgroup analysis, the statistical power of the PIX301 trial would be diminished compared with the intention-to-treat population.

4.27 The ERG considered the different patient populations in the subgroup analyses presented by the manufacturer. The ERG viewed the data from the post-hoc subgroup of patients with aggressive B-cell NHL that was histologically confirmed by central independent pathological review to be more relevant to the decision problem than the other 2 subgroups categorised according to type of lymphoma determined by onsite pathological review (patients with aggressive B-cell non-Hodgkin's lymphoma and patients with diffuse large B-cell lymphoma). The ERG noted that analysis of retrospective histological confirmation of aggressive disease by central independent pathological review revealed that, in the intention-to-treat population, 23% of patients in the pixantrone group and 29% of patients in the comparator group had disease that was subsequently determined not to be aggressive. The ERG was aware that disease severity is an important factor in determining treatment strategy because patients without aggressive disease are likely to have a more favourable response than those whose disease is histologically confirmed as aggressive.

4.28 The ERG considered the statistical robustness of the subgroup analyses. It observed that the comparative clinical effectiveness results for most subgroups presented were based on post-hoc subgroup analyses and that the number of patients in the analysis was generally small, increasing uncertainty around the results. In

the case of subgroups based on retrospective histological confirmation of aggressive disease and previous rituximab treatment, it noted the potential for unbalanced groups because randomisation had not been stratified by these factors. The ERG concluded that the results of subgroup analyses should be interpreted with caution.

4.29 The ERG considered that the adverse events reported to occur more frequently in the pixantrone group that the comparator group receiving treatment of physician's choice were consistent with the common adverse effects associated with pixantrone as reported in the Summary of Product Characteristics.

5 Comments from other consultees

5.1 The patient and professional groups stated that treatment options are limited for patients who relapse post-transplant or those ineligible for transplant who relapse following standard chemotherapy and that the prognosis is poor. The professional groups stated these are clinical trials, if available, or symptomatic management. They noted that the PIX301 trial is the only randomised prospective trial in this patient population and consequently provides a new standard of care. They added that the trial population, including the 15% of patients who had relapsed post-transplant, reflected current UK practice, and that the comparator agents are presently used in clinical practice (although a robust evidence base is lacking). The professional groups indicated that they felt pixantrone was especially appropriate for people whose lymphoma has previously been sensitive to anthracycline treatment but who are unable to receive further anthracycline therapy because of cumulative cardiac toxicity, and people with pre-existing heart conditions, who might be more

susceptible to the cardiotoxic effects of anthracyclines. They identified other groups that might derive particularly benefit, such as people with comorbidities, and noted that pixantrone's adverse effects are likely to be comparable to alternative regimens.

5.2 The patient groups described the outcomes that are particularly valued by patients. Increased survival is important because the achievement of extra months of life can improve the mental health of the person and their family. Improving or maintaining quality of life is also critical because the symptoms experienced by people with relapsed or refractory aggressive lymphoma are often severe and debilitating. They noted that pixantrone may achieve partial or complete remission, which would alleviate such symptoms more effectively than symptom control measures alone. They noted that, unlike some other therapies, pixantrone can be administered in a day-case setting, which means that people can spend more time at home with their families, which is very important for their quality of life. Other potential benefits to quality of life are less toxicity than other available salvage therapies, with less time in hospital. It was observed that pixantrone's adverse effects such as myelosuppression are familiar to people with lymphoma and are generally tolerable in exchange for the potential benefit from a life-prolonging treatment.

6 Cost-effectiveness evidence

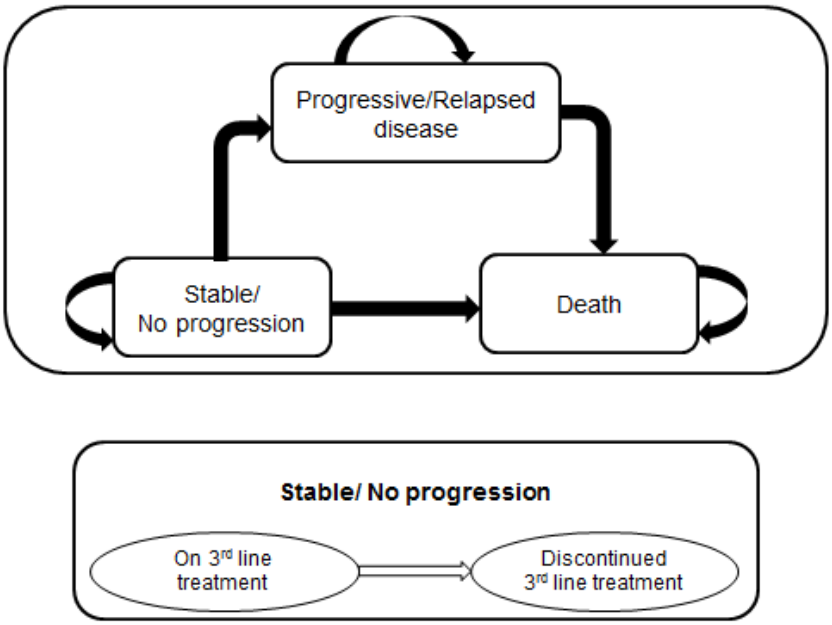
6.1 The manufacturer did not identify any published economic evaluations or costing studies that were relevant to the decision problem and submitted a de novo economic analysis that assessed the cost effectiveness of pixantrone compared with treatment of physician's choice in treating multiply relapsed or refractory aggressive B-cell lymphoma. The manufacturer advised that the

base-case model considered patients who had received 2 or 3 prior therapies and were sensitive to treatment with anthracyclines because this population was consistent with pixantrone's UK marketing authorisation for treating multiply relapsed or refractory aggressive non-Hodgkin's lymphoma (the marketing authorisation notes that a treatment benefit has not been established when used as fifth-line or greater chemotherapy in patients who are refractory to their last therapy). The clinical data for this population were derived from the PIX301 trial. The analysis was conducted from an NHS and Personal and Social Services perspective and a lifetime horizon of 23 years was used. Weekly cycles were chosen to capture the 4-week treatment cycles of pixantrone and 3-week treatment cycles of some of the comparator treatments and a half-cycle correction was applied. Costs and benefits were discounted at 3.5% per annum.

6.2 The manufacturer created a semi-Markov model that contained 3 health states: stable or no progression, progressive or relapsed disease and death (figure 2). The stable or no progression health state had 2 distinct subpopulations. The first of these was patients on initial third- or fourth-line treatment. The second was patients who had discontinued third- or fourth-line treatment (due to complete response, adverse event, completion of 6 months' treatment or a non-clinical reason but had not experienced progression. All patients entered the model in the on-treatment subpopulation within the stable or no progression health state. During each cycle, patients could remain in on-treatment subpopulation in this health state, discontinue treatment and move into the other subpopulation in this health state, progress and move into the progressive disease health state, or die. Patients who discontinued treatment before progression remained at risk of progression or death and were unable to start treatment that line of

treatment again. Following progression, patients were at risk of death and unable to return to the stable or no progression health state. It was assumed that the original therapy was stopped following disease progression and patients received further treatment or palliative care. Adverse events were captured as events within the model by applying a utility decrement (disutility).

Figure 2 Structure of manufacturer's economic model



Source: page 123 of the manufacturer's submission

6.3 The manufacturer outlined how the transition between health states was calculated from the clinical data for any given weekly cycle. It noted that semi-Markov models allow the use of a partition approach, which has been used extensively in oncology because it is particularly suited to progressive conditions like aggressive B-cell lymphoma, where there are ongoing risks that may vary over time. The distribution of the patient cohort between the different health states defined by these curves was estimated by calculating the area under the survival curves at each cycle. The progression-free survival curve defined the stable or no progression state, while the

progressed state was defined by subtracting those patients who remain progression free from all surviving patients.

6.4 Clinical parameters for progression-free survival and overall survival were incorporated into the base case of the manufacturer's economic model through statistical analysis of patient-level data from the aggressive B-cell population of the PIX301 trial. Predictive equations for progression-free survival and overall survival were derived by fitting the patient-level data and extrapolating beyond the data from the PIX301 trial (around 2 years). A log-normal distribution was employed in the base case for both progression-free survival and overall survival.

6.5 Further clinical parameters were incorporated into the base case of the manufacturer's economic model. The cycle probability of treatment discontinuation distinguished between patients remaining on initial treatment and those who discontinued while stable. The frequency and duration of adverse events (grades 2–4) before progression while taking initial treatment were based on the PIX301 trial. Grade 3 and 4 adverse events occurring in at least 5% of the total patient population were considered to have cost and utility consequences. Some grade 2, and rarer grade 3 and 4, adverse events were included if considered important by clinical specialists in England. Other data from the PIX301 trial that were used to inform the model were mean dose for the comparator treatments plus gender, body surface area and mean time on treatment.

6.6 There were no patient-reported outcomes in the PIX301 trial and the manufacturer did not identify any utility data for any line of treatment in aggressive non-Hodgkin's lymphoma in its systematic literature review for studies on health-related quality of life. Utilities 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 including diffuse large B-cell lymphoma, chronic myelogeneous leukemia, chronic lymphocytic leukaemia, follicular lymphoma, renal cell carcinoma and melanoma (table 15). The manufacturer considered that the self-reported quality of life in elderly patients with aggressive diffuse large B-cell lymphoma provided the estimation closest to the PIX301 trial population and employed these values (pre-progression 0.81, post-progression 0.60) in its base-case analysis. The manufacturer did not provide a rationale for this decision. Utility values were assumed to depend only on the health state and any adverse events experienced, but not the treatment arm. Based on expert clinical opinion, the manufacturer assumed no difference in baseline health-related quality of life between the two subpopulations in the stable or no progression health state. All stable/no progression patients were assumed to have similar quality of life (that is, there was no difference according to complete response, partial response or stable disease).

Table 15 Manufacturer's summary of utility values for health states

Description of data sources	Pre-progression utility	Post-progression utility	Reference	Justification and analysis
1st-line treatment in elderly patients with aggressive non-Hodgkin lymphoma (self-reported quality of life during chemotherapy)	0.81	0.60	Doorduijn et al., 2005 in Groot et al., 2005;62-63	Used in the base case because this population of elderly patients with diffuse large B-cell lymphoma was considered most relevant to the PIX301 study population
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 leukaemia	0.65	0.47	Ferguson et al., 200880	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, 201181,64,45	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

6.7 The manufacturer determined disutilities associated with each adverse event that was included the model from relevant literature from other oncology indications. If no utility decrements were available, the maximum value of the range identified was assumed to keep the calculations conservative.

6.8 Adverse events were modelled by the manufacturer as events rather than as health states and assumed to be time independent because adverse events are likely to be experienced at different stages of treatment. Any grade 1–4 adverse event that occurred in less than 5% of the trial population was assumed to have no impact on quality of life. Because no disutility values were available specifically for grade 2 and grade 3/4 adverse events, they were assumed to be the same for each grade (see pages 134–5 of the manufacturer's submission and page 20 of the manufacturer's clarification response). Within a health state, disutilities relating to an adverse event were applied to the proportion of patients assumed to experience the adverse event as weighted average disutilities. For each treatment, the manufacturer calculated a weighted average of grade-specific disutilities that were weighted by the number of events of that particular grade. The disutility for each adverse event was then applied for the duration of that specific type of event. The manufacturer's model limited the consideration of adverse events to patients on original therapy (pixantrone or treatment of physician's choice).

6.9 Costs captured within the manufacturer's model included drugs and their administration, plus those associated with health state and disease management, including adverse events (table 16). Drug and administration costs were calculated based on average dose per administration from the trial using the British National Formulary No. 62 and the NHS reference costs. From the second attendance onwards, administration costs were £206 for each attendance for all drugs except etoposide 50 mg (£163). Drug costs per administration supplied in the manufacturer's submission were: £1660 for pixantrone, £86 for vinorelbine, £546 for oxaliplatin, £223 for ifosfamide, £26 for etoposide 100 mg, £7 for etoposide 50 mg, £185 for mitoxantrone and £282 for gemcitabine. At clarification,

the manufacturer corrected an error in the vial price, which had been mistakenly quoted £343.80 (based on the vial size given in pixantrone base) instead of £553.50 (equivalent to 50 mg pixantrone dimaleate). It advised that this error had a minimal impact on the cost-effectiveness estimates (which increased by 0.3%) because the drug costs in the model had been calculated based on cost per administration. The total number of administrations varied according to the dosing schedule for each drug. Drug wastage was incorporated in the base case. 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. End of life care was excluded from the calculations since it affected only the last few weeks of life and estimates would be similar for pixantrone and its comparators. Within a health state, costs for managing an adverse event were applied to the proportion of patients assumed to experience the adverse event. Details of the costs for managing adverse events are on pages 173–4 of the manufacturer's submission.

Table 16 Disease management costs in the manufacturer's model

Type of treatment	Items	Cost
Active treatment	Health professional contacts	£788.96 on treatment (per 28 days) £220.38 post treatment (per 28 days)
	Disease follow-up	£86.63 (per 28 days)
	Hospital-related costs	£2,357.28 (annual)
Palliative care	Health professional contacts	£990.74 (per 28 days)
	Disease follow-up	£18.44 (per 28 days)
	Hospital-related costs	£1,982.03 (annual)

6.10 The manufacturer advised that predicted median progression-free survival and predicted median overall survival were similar to the results reported in the PIX301 study. Compared with the clinical trial results, the manufacturer noted that the model slightly

underestimates the median overall survival with pixantrone (13.1 months versus 13.8 months) while overestimating it for the comparator (9.2 months versus 7.6 months). It reported that, conversely, the model overestimates the median progression-free survival for the pixantrone arm (7.8 months versus 6.4 months) and slightly underestimates it for the comparator arm (3.2 months versus 3.5 months).

6.11 The manufacturer presented base-case analyses for pixantrone compared with treatment of physician's choice in patients with aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line treatment) (table 17).

Table 17 Manufacturer's base-case 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[a]
Treatment of physician's choice	68,650	1.71	1.13				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

[a] Using the correct vial price supplied at clarification increases the ICER from £28,423 to £28,503

6.12 The manufacturer undertook a probabilistic sensitivity analysis to explore uncertainty. This analysis showed that the probability of pixantrone being cost effective versus treatment of physician's choice in patients with aggressive B-cell lymphoma confirmed by onsite pathological review (third- or fourth-line treatment) is 43.8% at £20,000 per QALY gained, 53.0% at £30,000 per QALY gained and 78.2% at £50,000 per QALY gained.

6.13 The manufacturer tested the robustness of the model using one-way sensitivity analyses and reported that the key drivers of the cost-effectiveness estimates produced using its economic model

were the parametric fitting methodology for progression-free survival and overall survival, the utility estimate for the stable or no progression health state, the time horizon and the cost of pixantrone (table 18).

Table 18 Manufacturer's one-way sensitivity analyses on the base case

Parameter	Baseline value	Alternative value	ICER (£ per QALY gained)
All parameters at baseline values			28,423
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	1159
		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[a]
		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

[a] Greater benefit at lower cost

6.14 The manufacturer provided alternative utility scenarios using data from published sources for similar patient populations, and for disease areas with similar characteristics. These were second-line

treatment in patients with chronic myelogenous leukaemia, third-line treatment in patients with chronic lymphocytic leukaemia, first-line maintenance treatment in patients with follicular lymphoma, first-line treatment in patients with metastatic renal cell carcinoma, second-line treatment in patients with renal cell carcinoma and second-line treatment in patients with malignant melanoma. The results ranged from £28,056 per QALY gained to £35,248 per QALY gained.

6.15 The manufacturer provided subgroup analyses for the cost effectiveness of pixantrone compared with treatment of physician's choice in the intention-to-treat population, patients with diffuse large B-cell lymphoma and patients with aggressive B-cell non-Hodgkin's lymphoma confirmed by central independent pathological review (table 19). In comparison with the base case ICER of £28,423 per QALY gained (incremental costs £17,638; incremental QALYs 0.62) for the population with aggressive B-cell lymphoma confirmed by onsite pathological review), the ICERs were higher for the intention-to-treat population (£43,102 per QALY gained [incremental costs £19,809; incremental QALYs 0.46]) and aggressive B-cell non-Hodgkin's lymphoma (£32,728 per QALY gained [incremental costs £14,809; incremental QALYs 0.45]) but lower for the population with diffuse large B-cell lymphoma confirmed by central independent pathological review (£23,699 per QALY gained [incremental costs £9841; incremental QALYs 0.42]).

Table 19 Manufacturer's subgroup analyses

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr.costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Intention to treat							
Pixantrone	76,942	2.03	1.45	19,809	0.56	0.46	43,102
Treatment of physician's choice	57,132	1.47	0.99				
Diffuse large B-cell lymphoma confirmed by onsite pathological review							
Pixantrone	62,795	1.70	1.25	9,841	0.44	0.42	23,699
Treatment of physician's choice	52,953	1.26	0.83				
B-cell non-Hodgkin's lymphoma confirmed by central independent pathological review							
Pixantrone	60,918	1.64	1.22	14,809	0.50	0.45	32,728
Treatment of physician's choice	46,109	1.13	0.77				

Key: ICER, incremental cost-effectiveness ratio; incr., incremental; LYG, life years gained; QALYs, quality-adjusted life years

6.16 Overall, the ERG considered the manufacturer's model adhered to current best practice recommendations, was generally well constructed and largely transparent. The ERG considered that an important limitation of the manufacturer's base-case analysis was the use of data from patients whose disease had not been histologically confirmed as aggressive. The ERG indicated that the subgroup of patients with aggressive B-cell non-Hodgkin's lymphoma confirmed by central independent pathological review for all lines of therapy in the PIX301 trial was the most informative to the decision problem because it excluded patients who had retrospectively confirmed as having disease that was irrelevant to the decision problem (for example, indolent disease). However, the ERG noted a high level of uncertainty surrounding the manufacturer's estimate of cost-effectiveness in this patient population because post-hoc subgroup data were used to inform the evaluation and the subgroups were not powered to detect a

difference in efficacy between treatment with pixantrone versus treatment of physician's choice.

6.17 The ERG considered that the utility weights used by the manufacturer in its economic model may be inappropriate. It noted that these values were from a population of patients receiving first-line treatment for aggressive non-Hodgkin's lymphoma and derived from a study that had initially been rejected by the manufacturer in its systematic review. It further noted that the reported utility values are higher than UK time trade-off values for healthy elderly patients.

6.18 The ERG indicated that the manufacturer's assessment of uncertainty was very detailed and that the probabilistic and one-way sensitivity analyses, including various scenario analyses, were satisfactorily reported. It noted that, with the exception of parameters used to inform progression-free survival and overall survival estimates, the manufacturer's cost-effectiveness estimate was relatively insensitive to changes in individual parameters in the manufacturer's base case (aggressive B-cell lymphoma confirmed by onsite pathological review [third- or fourth-line treatment]) and in the subgroup of patients with aggressive B-cell lymphoma confirmed by central independent pathological review were similar to those. For the latter subgroup, which it considered to be more appropriate, the ERG noted that only 6 of 102 one-way sensitivity analyses produced a deterministic ICER greater than £35,000 per QALY gained.

6.19 The ERG noted that the results of the manufacturer's economic model may potentially be biased towards pixantrone as a result of an overestimation of the relative progression-free survival benefit of pixantrone versus treatment of physician's choice for the

populations with aggressive B-cell lymphoma (whether confirmed by onsite or central independent pathological review). Clinical specialist opinion received by the ERG expressed concern that the data used in the model may not be sufficient to reach reasonable conclusions about the clinical or cost-effectiveness of pixantrone.

6.20 The ERG examined the manufacturer's probabilistic sensitivity analyses. It noted that the mean probabilistic ICER of £28,846 per QALY gained was highly consistent with the deterministic ICER (£28,423 per QALY gained) but indicated there was a substantial amount of uncertainty in the manufacturer's cost-effectiveness results, as shown by the wide 95% confidence interval (ranging from dominance of pixantrone over treatment of physician's choice to £308,681 per QALY gained). The ERG was also aware that pixantrone was either less costly and less effective than, or dominated by, treatment of physician's choice in approximately 9% of the 5000 simulations.

6.21 The ERG identified further areas of inaccuracy or uncertainty in the assumptions and parameter estimates used in the manufacturer's model and indicated the most significant of these were structural assumptions made regarding treatment discontinuation, disutility and the cost parameters used:

- The potential double-counting of treatment discontinuation as a result of disease progression.
- The exclusion of adverse event disutilities for patients on further lines of therapy.
- Discrepancies between the manufacturer's and ERG's interpretation of the literature regarding disutilities for adverse events.

- The use of weighted average adverse event rates to inform costs and disutilities associated with adverse events for patients on original therapy.
- The potential inclusion of missing data to inform average adverse event costs.
- The exclusion of costs associated with the treatment of leukopaenia and thrombocytopaenia.
- The use of costs from BNF 62 rather than BNF 64.

6.22 The ERG calculated the deterministic ICER for the manufacturer's base case (the population with aggressive B-cell lymphoma) using the correct drug costs supplied by the manufacturer at clarification. It noted that this resulted in an ICER of £28,503 per QALY gained (incremental costs £17,688; incremental QALYs 0.62). This value was close to the ICER derived from the incorrect drug costs that was presented in the manufacturer's submission (£28,423 per QALY gained).

6.23 The ERG carried out exploratory sensitivity analyses to investigate the impact of alternative assumptions or parameters on the manufacturer's cost-effectiveness results, which were combined to provide revised cost-effectiveness estimates. The ERG judged the population with aggressive B-cell lymphoma confirmed by central independent pathological review for all lines of therapy in the PIX301 trial to be the most relevant to the decision problem (because it excluded patients who had retrospectively confirmed as having disease that was not relevant to the decision problem [for example, indolent disease]) and implemented it in all its exploratory analyses.

6.24 In light of its conclusion that the utility values used by the manufacturer may have been inappropriate, the ERG investigated

the effect of a further alternative utility values on the manufacturer's base case, using utility data from chronic lymphocytic leukaemia patients receiving third-line therapy to inform the utility of profession-free survival and progressive disease. In the population of patients with aggressive B-cell lymphoma confirmed by retrospective central independent pathology review, using the alternative utility data markedly increased the ICER for pixantrone compared with treatment of physician's choice to £60,129 per QALY gained (incremental costs £14,855; incremental QALYs 0.247).

6.25 In further sensitivity analyses, the ERG varied other parameters where it perceived inaccuracy or uncertainty (table 20). Adding alternative estimates of disutility for selected adverse events, using costs from BNF 64, including costs for leukopaenia and thrombocytopaenia and excluding missing data had little effect with a cumulative ICER of £62,465 per QALY gained (incremental costs £14,857; incremental QALYs 0.452[1]).

[1] After this document was issued, it was noted that the incremental costs and QALYs quoted in section 6.25 are incorrect and should read £15,087 and 0.247 (as reported in table 20).

Table 20 ERG's sensitivity and scenario analyses on the manufacturer's economic evaluation in a population of patients with histologically confirmed aggressive B-cell NHL: individual and cumulative impact

Analysis	Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALYs)	Cumulative ICER
Manufacturer's estimate	TPC	46,109	0.766	–	–	–	32,830
	Pixantrone	60,964	1.218	14,855	0.452	32,830	
ERG's sensitivity analyses							
PFS and PD utility from CLL patients on 3rd line therapy	TPC	46,109	0.377	–	–	–	60,129
	Pixantrone	60,964	0.624	14,855	0.247	60,129	
ERG alternative utility values for anaemia, renal failure, weight loss and Grade 3 vomiting	TPC	46,109	0.766	–	–	–	60,147
	Pixantrone	60,964	1.218	14,855	0.452	£32,836	
Using drug costs from BNF 64	TPC	46,140	0.766	–	–	–	60,154
	Pixantrone	60,997	1.218	14,857	0.452	32,833	
ERG's scenario analyses[a]							
Inclusion of costs for leukopaenia and thrombocytopaenia[b]	TPC	46,240	0.377	–	–	–	61,533
	Pixantrone	61,437	0.624	15,197	0.247	61,533	
Exclusion of potentially missing data	TPC	46,381	0.377	–	–	–	62,465
	Pixantrone	61,468	0.624	15,087	0.247	61,086	

[a] Applied to ERG's base case ICER.

[b] As provided by the manufacturer at clarification, £227.25 and £1,626.79 for thrombocytopaenia and leukopaenia, respectively.

Abbreviations used in table: BNF, British National Formulary; CLL, chronic lymphocytic leukaemia; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; Incr., incremental; LYG, life years gained; NHL, non-Hodgkin's lymphoma; PD, progressive disease; PFS, progression free survival; QALYs, quality adjusted life years; TPC, treatment of physician's choice.

6.26 The ERG also commented on what the likely effect on the base-case ICER would be of varying other parameters that it was not able to assess (table 21). Compared with the base case, it considered that it was likely that there would be a substantial increase in the ICER for patients previously treated with rituximab

(in line with UK clinical practice) because of a reduced benefit in this patient population.

Table 21 ERG's opinion of likely impact of varying miscellaneous parameters

Parameter	ERG's opinion of likely effect on ICER	ERG's reasoning
Treatment effectiveness in a patient population previously treated with rituximab	Substantial increase	Reduced benefit in this patient population
Removal of double counting of treatment discontinuation as a result of disease progression	Small decrease	A higher proportion of patients receiving treatment of physician's choice discontinued because of disease progression. 'Stable or no progression, discontinued treatment' state was associated with a higher overall utility because adverse event-related disutilities for later lines of treatment were excluded
The use of overall survival data from combination rather than monotherapies	Small increase	Prolonged sojourn in the progressive disease health state
The application of adverse event related disutilities for patients on further lines of therapy	Small decrease	The group receiving treatment of physician's choice experiences higher levels of discontinuation and spends longer in the progressive disease health state
Use of accurate timing of each adverse event experienced across the course of original treatment	Minimal increase or decrease	Not specified
Age adjustment of utility data	Minimal increase or decrease	Not specified

6.27 The ERG undertook probabilistic sensitivity analyses in the population of patients with aggressive B-cell lymphoma confirmed by retrospective central independent pathological review and found that the mean probabilistic ICER was £62,000 per QALY gained (ranging from dominated to £373,454 per QALY gained). It noted that the ICER had a 95% chance of falling between the dominance of pixantrone over treatment of physician's choice and £373,454 per additional QALY. The ERG observed that the wide confidence interval associated with the probabilistic ICER, reflects the underlying uncertainty surrounding the data upon which the

manufacturer's economic evaluation is based. Furthermore, the ERG noted that these analyses do not account for the potentially inferior treatment effect likely to be seen in patients previously treated with rituximab.

7 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The manufacturer highlighted that median overall survival in the PIX301 trial was less than 12 months for both arms. However, in the intention-to-treat population, mean overall survival is projected to be 28.6 (standard deviation 7.1) months and 20.0 (standard deviation 4.7) months in the pixantrone and treatment of physician's choice groups. Estimated mean overall survival is considerably longer for the intention-to-treat population than for patients with aggressive B-cell lymphoma confirmed by central independent pathological review (11.3 [standard deviation 8.80] months with pixantrone and 8.9 [standard deviation 7.91] months with treatment of physician's choice). Taken together, the ERG agrees with the manufacturer that the life expectancy of patients with aggressive non-Hodgkin's lymphoma and who have received at least two prior chemotherapeutic regimens is likely to be less than 24 months.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In the population that the manufacturer included in the base case of its economic model (patients with aggressive B-cell lymphoma confirmed by onsite pathological review receiving third- or fourth-line therapy), overall survival was 13.9 months in the pixantrone arm and 7.8 months in the comparator arm (hazard ratio 0.76 [95% confidence interval 0.47 to 1.24], p=0.275). The ERG noted that median life extension with pixantrone in the subgroup of patients with aggressive B-cell non Hodgkin's lymphoma confirmed by central independent pathological review was reported to be 1.8 months (median overall survival: 8.1 months with pixantrone vs 6.3 months) but the difference between groups did not reach statistical significance. There was no statistically significant difference in overall survival between the pixantrone and comparator arms of the PIX301 trial in any of the groups presented in the manufacturer's submission. Extrapolation of data from patients with aggressive B-cell non-Hodgkin's lymphoma confirmed by central independent pathological review generated a mean overall survival gain of 7.2 (standard deviation 7.4) months with pixantrone (mean overall survival [standard deviation]: 22.6 [6.2] months with

	pixantrone vs 15.2 [4.1] months with treatment of physician's choice), but the difference between groups was not statistically significant. When data on extrapolated mean overall survival from the intention-to-treat population and the subgroup of patients with histologically confirmed aggressive B-cell non-Hodgkin's lymphoma are considered, the gain with pixantrone is longer than 3 months, but the difference between treatment groups did not reach statistical significance.
The treatment is licensed or otherwise indicated for small patient populations	The manufacturer estimated that 1650 patients per year would be eligible for treatment with pixantrone. Based on the data reported by the manufacturer, the ERG calculated that approximately 550–730 patients could be eligible for treatment with pixantrone. The ERG agrees with the manufacturer that pixantrone has conditional approval for what could be considered a small patient population.

8 Equalities issues

8.1 No equalities issues were raised during the scoping process or in the evidence submissions.

9 Innovation

9.1 Pixantrone is the only drug with a UK marketing authorisation for the treatment of multiply relapsed or refractory non-Hodgkin's lymphoma and it was designed to reduce the cardiotoxicity associated with anthracyclines. Although anthracycline therapy is included as part of standard first-line treatment, most patients are not able to receive further anthracycline treatment if their disease relapses because of the risk of cumulative toxicities. The manufacturer states that pixantrone is the only anthracycline-like agent that can be used to treat non-Hodgkin's lymphoma in people who have received up to the maximum lifetime dose of an anthracycline. The Summary of Product Characteristics for mitoxantrone, an anthracenedione with a UK marketing authorisation for treating non-Hodgkin's lymphoma, recommends

added caution in patients who have previously received anthracyclines but does not mention a maximum lifetime dose.

10 Authors

Linda Landells
Technical Lead

with input from the Lead Team (Daniele Bryden, Alan Rigby, David Chandler).

Appendix A: Supporting evidence

Related NICE guidance

Published

- Temsirolimus for the treatment of relapsed or refractory mantle cell lymphoma. NICE technology appraisal guidance 207 (2010). Available from www.nice.org.uk/guidance/TA207
- Rituximab for aggressive non-Hodgkin's lymphoma. NICE technology appraisal guidance 65 (2003). Available from www.nice.org.uk/guidance/TA65
- Haemato-oncology: Improving outcomes in haemato-oncology cancer. Cancer Service Guidance CSGHO (2003). Available from www.nice.org.uk/guidance/CSGHO