Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma
STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 10/59

BMJ Technology Assessment Group

Title: Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma

Produced by: BMJ Technology Assessment Group (BMJ-TAG)

Authors: Steve Edwards, Head of BMJ-TAG, London

Samantha Barton, Senior Health Technology Assessment Analyst, BMJ-TAG, London

Leo Nherera, Senior Health Economist, BMJ-TAG, London

Nicola Trevor, Health Economics Lead, BMJ-TAG, London

Taryn Krause, Health Technology Assessment Analyst, BMJ-TAG, London

Elizabeth Thurgar, Senior Health Economist, BMJ-TAG, London

Correspondence to: Steve Edwards, Head of BMJ-TAG, BMJ Evidence Centre, BMJ Group, BMA House, Tavistock Square, London, WC1H 9JP.

Date completed: 13/02/2013

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 10/59.

Declared competing interests of the authors:
None.

Acknowledgements:
The ERG would like to thank Drs Robert Marcus (Consultant Haematologist) and Graham Collins (Consultant Haematologist) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report. The ERG would also like to thank Professor Matt Stevenson (Professor of Health Technology Assessment) for providing feedback on the economic sections of the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Edwards SJ, Barton S, Nherera L, Trevor N, Krause T, Thurgar EJ. Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma: A Single Technology Appraisal. BMJ-TAG, London, 2013

Contributions of authors:

Steve Edwards	Project lead: supervised the production of the final report; critical appraisal of the manufacturer's submission; critical appraisal of the clinical evidence; and critical appraisal of the economic evidence
Samantha Barton	Critical appraisal of the manufacturer's submission; critical appraisal of the clinical evidence; cross checking of manufacturer's search strategies; and drafted the summary and clinical results sections
Leo Nherera	Critical appraisal of the manufacturer's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; and drafted the economic analysis sections
Nicola Trevor	Critical appraisal of the manufacturer's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; and drafted the economic analysis sections
Taryn Krause	Critical appraisal of the manufacturer's submission; and critical appraisal of the clinical evidence
Elizabeth Thurgar	Critical appraisal of the manufacturer's submission; and critical appraisal of the economic evidence

All authors read and commented on draft versions of the ERG report

Table of contents

Abbreviations

ASCT	Autologous stem cell transplant
BNF	British National Formulary
BSA	Body surface area
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CI	Confidence Interval
CNS	Central nervous system
CR	Complete response
CRu	Complete response, unconfirmed
CT	Computed tomography
DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D	EuroQol 5 dimensions questionnaire
ERG	Evidence Review Group
FDA	Food and Drug Administration
GP	General Practitioner
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPI	International Prognostic Index
ITT	Intention-to-treat
IVRS	Interactive voice response system
kg	Kilogram
LDH	Lactate dehydrogenase
LYG	Life-years gained
LVEF	Left-ventricular ejection fraction
mg	Milligram
mL	Millilitre
mm	Millimetre
MS	Manufacturer's submission
MTA	Multiple Technology Appraisal
NHL	Non-Hodgkin's lymphoma
NHS	National Health Service

NICE	National Institute for Health and Clinical Excellence
NMA	Network meta-analysis
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PET	Positron emission tomography
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
R-CHOP	Rituximab added to cyclophosphamide, vincristine, doxorubicin and prednisolone
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TPC	Treatment of physician's choice
TTP	Time to progression
UK	United Kingdom
USA	United States of America
vs	versus
WHO	World Health Organization
WTP	Willingness-to-pay threshold

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The manufacturer of pixantrone (Pixuvri®; Cell Therapeutics Inc.) submitted to the National Institute for Health and Clinical Excellence (NICE) clinical and economic evidence in support of the effectiveness of pixantrone in the treatment of multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma (NHL).

In February 2012, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the use of pixantrone, recommending the granting of a conditional marketing authorisation for the use of pixantrone as a monotherapy for the treatment of multiply relapsed or refractory aggressive B-cell NHL.

The clinical evidence presented in the manufacturer's submission (MS) is derived from the PIX301 randomised trial. PIX301 enrolled patients with aggressive NHL (histologically determined by the pathology laboratory of the individual participating sites) that was sensitive to treatment with anthracyclines and who had received at least two prior chemotherapeutic regimens for their disease. Patients with NHLs developing from either B-cells or T-cells were eligible for randomisation in the PIX301 trial. Only 10% of patients in PIX301 were classified as having T-cell NHLs at baseline. The final scope issued by NICE specified the population of interest to be patients with multiply relapsed or refractory B-cell NHL. Given that the proportion of patients with T-cell derived NHLs is small, the Evidence Review Group (ERG) considers the population in PIX301 to be relevant to the decision problem. With the exception of health-related quality of life (HRQoL), all clinically relevant outcomes were reported within the MS.

The comparator in PIX301 was treatment of physician's choice (TPC). Patients randomly assigned to the TPC group received their physician's choice of single chemotherapeutic agent at predefined standard doses and schedules. Clinicians were able to choose from six chemotherapeutic agents (to be used as a monotherapy) that were approved for cancer indications other than aggressive NHL but with demonstrated activity in aggressive NHL. The six chemotherapeutic agents available matched the agents listed as comparators of interest in the final scope. Therefore, in terms of intervention and comparator, the ERG considers that the submitted evidence addresses the decision problem outlined in the final scope issued by NICE.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The PIX301 trial was a multicentre, international, parallel-group study that included 140 patients with multiply relapsed or refractory aggressive NHL. The trial was of open-label design. Patients were randomised (1:1) to pixantrone or to other single chemotherapeutic agent as chosen by the treating physician. Pixantrone was intravenously infused over 1 hour at a dose of 85 mg/m² (equivalent to 50 mg/m² of pixantrone in its base form) on days 1, 8, and 15 of a 28-day cycle, for up to six cycles.

Patients were initially evaluated histologically for aggressive disease at the pathology laboratory of the individual participating sites. Subsequently, histology was retrospectively reviewed at a central laboratory, where consensus from two of three pathologists was required to confirm a diagnosis of aggressive NHL. Of the 140 patients randomised, 104 patients were subsequently confirmed to have aggressive NHL. The manufacturer deemed it impractical to carry out central histological review prior to study entry, citing the unstable nature of aggressive NHL and the urgent need for treatment in this patient group as obstacles to central review before enrolment. The ERG considers retrospective histological review to be a pragmatic approach, but considers it important to evaluate data from the subgroup of patients with retrospective histological confirmation of disease, and, in particular, those with B-cell NHLs.

The primary outcome of PIX301 was the proportion of patients achieving complete response (CR) or unconfirmed CR (CRu) in the intention-to-treat (ITT) population (i.e., 140 patients) at the end of treatment, as evaluated by an Independent Assessment Panel (IAP) who were blinded to treatment allocation. In the ITT population, a statistically significantly larger proportion of patients in the pixantrone group achieved CR/CRu compared with the TPC group (14/70 [20.0%] with pixantrone vs 4/70 [5.7%] with TPC; p = 0.021). A prespecified secondary outcome evaluated the proportion of patients achieving CR/CRu in the subgroup of patients with retrospective histological confirmation of aggressive NHL at baseline by an independent central review panel (HITT population). The HITT population comprises a small number of patients with NHL subtype originating from T-cells (7 patients). In the HITT population, although a larger proportion of patients achieved CR/CRu in the pixantrone group at the end of treatment, the difference between groups was not statistically significant (9/54 [16.7%] with pixantrone vs 3/50 [6.0%] with TPC; p = 0.126). On request, the manufacturer helpfully provided data for the subgroup of patients with retrospective histological confirmation of aggressive B-cell NHL (hereafter referred to as histologically confirmed aggressive B-cell NHL). There was no statistically significant difference between pixantrone and TPC in the proportion of patients achieving CR/CRu at the end of treatment in this population (8/50 [16.0%] with pixantrone vs 3/47 [6.4%] with TPC; p = 0.202).

Other prespecified secondary outcomes analysed in the ITT population included overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) lasting more than 4 months. Median overall survival (OS) was longer in the pixantrone group compared with the TPC group in the three patient populations analysed, but none of the differences between groups reached statistical significance and the median OS gain was less than 3 months in all analyses:

- ITT: 10.2 months with pixantrone vs 7.6 months with TPC (Hazard ratio [HR] 0.79; 95% Confidence Interval [CI]: 0.53 to 1.18);
- HITT: 7.5 months with pixantrone vs 6.2 months with TPC (HR 0.74; 95% CI: 0.48 to 1.14);
- subgroup of patients with histologically confirmed aggressive B-cell NHL: 8.1 months with pixantrone vs 6.3 months with TPC; (HR 0.72; 95% CI 0.45 to 1.13).

By contrast, PFS was statistically significantly prolonged with pixantrone in all three populations. In patients with histologically confirmed aggressive B-cell NHL, median PFS gain with pixantrone was 3.1 months (median PFS: 5.6 months with pixantrone vs 2.5 months with TPC; HR 0.51; 95% CI: 0.33 to 0.78) compared with 2.7 months in the ITT population (5.3 months with pixantrone vs 2.6 months with TPC; HR 0.60; 95% CI: 0.42 to 0.82). PFS in PIX301 included change in treatment without radiological confirmation of progression as a progressive event. Results from analyses in the ITT population that censored patients who initiated a different treatment are in accord with the prespecified analysis of PFS.

ORR at the end of treatment was higher in the pixantrone group compared with the TPC group in the ITT, HITT and histologically confirmed aggressive B-cell populations. The difference between groups reached statistical significance in the ITT (26/70 [37.1%] in the pixantrone group vs 10/70 [14.3%] in the TPC group; p = 0.003) and HITT (18/54 [33.3%] in the pixantrone group vs 8/50 [16.0%] in the TPC group; p = 0.045) populations but not in the subgroup of patients with histologically confirmed aggressive B-cell NHL (17/50 [34.0%] in the pixantrone group vs 8/47 [17.0%] in the TPC group; p = 0.066).

In the subgroup of patients who had received prior treatment with rituximab and who had histologically confirmed aggressive B-cell NHL, there was no significant difference between pixantrone and TPC in the proportion of patients achieving CR/CRu at the end of treatment (5/30 [16.7%] with pixantrone vs 2/26 [7.7%] with TPC; p = 0.431). Although median PFS and OS were longer in the pixantrone group for this subgroup of patients, the difference between groups did not reach statistical significance for either outcome (OS: 6.0 months with pixantrone vs 4.6 months with TPC; HR 0.85; 95% CI: 0.48 to 1.50; PFS: 3.5 months with pixantrone vs 2.3 months with TPC; HR 0.66; 95% CI: 0.38 to 1.14).

Most patients in PIX301 experienced an adverse event, but the incidence of Grade 3 or 4 adverse events was higher in the pixantrone group than the TPC group. The most frequently occurring Grade 3

or 4 adverse effects in the pixantrone group were neutropaenia and leukopaenia, both of which are recognised adverse effects of treatment. An independent cardiology review identified that there were 14 events (in 13 patients) considered likely (9 events in nine patients) or possibly (5 events in four patients) to be associated with pixantrone treatment, including two putative cases of congestive heart failure. The most frequent treatment-related adverse effect leading to discontinuation from pixantrone treatment was neutropaenia.

1.3 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer carried out a systematic review of the published literature which aimed to identify economic evaluations or costing studies relevant to the decision problem that is the focus of this Single Technology Appraisal (STA). No relevant publications were identified; therefore, the manufacturer carried out a *de novo* economic evaluation. The manufacturer's economic evaluation consisted of cost-utility analyses of the following patient populations:

- aggressive B-cell NHL (not retrospectively histologically confirmed) – manufacturer's base case;
- ITT (not retrospectively histologically confirmed);
- diffuse large B-cell lymphoma (DLBCL, not retrospectively histologically confirmed);
- histologically confirmed aggressive B-cell NHL (submitted at clarification).

As noted in Section 1.2, the ERG considers it important to evaluate data from the subgroup of patients with histologically confirmed disease. In addition, the ERG notes that, based on the licensed indication, the aggressive B-cell NHL (histologically confirmed) patient population is the most representative of the patient populations considered.

The manufacturer's cost-utility analyses were based on a semi-Markov model constructed in Microsoft© EXCEL, which considered treatment with pixantrone versus TPC; consistent with the treatment comparison considered in PIX301. The manufacturer's model consisted of four mutually exclusive health states "PFS, on 3rd (or 4th) line treatment", "PFS, discontinued 3rd (or 4th) line treatment", "Progressive disease (PD)" and the absorbing state of "Death". Patients were distributed across these four health states based on individual patient level data (IPD) from PIX301. The partition method was used to establish the location of each patient with respect to PFS, PD and death. In addition, Kaplan–Meier data were used to inform treatment discontinuation (ahead of progression). Benefits were assessed using quality adjusted life years (QALYs), in line with the reference case recommended by NICE. As no HRQoL data were gathered in PIX301, utility data were sourced from systematic and targeted reviews of the published literature carried out by the manufacturer. Standard UK-specific reference sources were used to inform the unit costs of treatment and other resources used in the manufacturer's model. Expert clinical opinion was used to inform the level of resource use

required by patients at various stages of their condition. Costs and benefits relevant to an NHS and personal social services (PSS) perspective were considered and discounted at a rate of 3.5% per annum. A lifetime (23 year) time horizon was used and outcomes were assessed weekly using a half-cycle correction.

The manufacturer estimated deterministic incremental cost-effectiveness ratios (ICERs) per QALY of £28,503, £32,830, £43,200 and £23,800 in the aggressive B-cell NHL (not retrospectively histologically confirmed), histologically confirmed aggressive B-cell NHL, ITT and DLBCL patient populations, respectively. Furthermore, the manufacturer carried out probabilistic analysis which revealed that each ICER was associated with large 95% CIs (generally dominance of pixantrone over TPC to approximately £300,000 per additional QALY). In addition, in support of the submitted economic evaluation, the manufacturer carried out several one-way sensitivity and scenario analyses which demonstrated that the relative PFS benefit of pixantrone versus TPC was a key driver of the cost-effectiveness result. Moreover, in both the aggressive B-cell NHL (not retrospectively histologically confirmed) and histologically confirmed aggressive B-cell NHL, the manufacturer's economic evaluation was biased towards pixantrone with respect to the relative (pixantrone versus TPC) PFS benefit.

1.4 ERG commentary on the robustness of evidence submitted by the manufacturer

1.4.1 Strengths

Clinical

PIX301 was a randomised controlled trial with blinded assessment of the primary outcome of proportion of patients achieving CR/CRu at the end of treatment. The PIX301 trial contributes to the limited evidence base available evaluating treatments for multiply relapsed or refractory aggressive NHL.

Economic

The ERG considers that the manufacturer's model was generally well-constructed and transparent and adhered to current best practice recommendations, particularly with respect to techniques used for extrapolation and the assessment of uncertainty. Furthermore, robust systematic reviews, the methods and results of which were clearly described, were carried out to identify parameter estimates for utility and cost.

1.4.2 Weaknesses

Clinical

Only one small RCT (140 patients randomised) is available for the comparison of pixantrone monotherapy various other single chemotherapy agents as a third and subsequent line treatment. As highlighted by the manufacturer, there is a lack of consensus among clinicians on which treatments should be used for third and subsequent line therapy. The ERG's clinical experts advised that treatment options for patients with multiply relapsed or refractory aggressive NHL are limited, and treatment strategies are likely to vary from setting to setting. It is unclear how frequently a monotherapy would be the preferred treatment option as a third or subsequent line treatment in patients with multiply relapsed or refractory aggressive disease.

The PIX301 trial is likely to be underpowered to detect a difference between pixantrone and TPC for the primary outcome assessed of proportion of patients achieving CR/CRu in the ITT population at the end of treatment as evaluated by an IAP. As a result of slow accrual, only 140 patients (out of a planned 320 patients) were recruited and randomised. Furthermore, histology of aggressive NHL was initially carried out at the individual participating sites, with subsequent review by a central panel. Of the 140 patients randomised, only 104 were subsequently histologically confirmed as having aggressive NHL. Therefore, the ITT population comprises patients without aggressive NHL and results in the full trial population might not reflect benefit of pixantrone in patients with aggressive B-cell NHL. Power to detect a difference between pixantrone and TPC is reduced further in analyses based on data from subgroups of patients with retrospective histological confirmation of disease.

The primary outcome evaluated in the PIX301 trial was CR/CRu, which is not considered to be as appropriate as OS or PFS in trials evaluating treatments for cancer. In addition, HRQoL data were not collected during PIX301.

The ERG considers that there is uncertainty around the clinical benefit associated with pixantrone in patients who have previously been treated with rituximab. In the UK, patients with multiply relapsed or refractory aggressive NHL will have received rituximab as a component of their standard care. In addition, only a small proportion of patients in the PIX301 trial were recruited from Western Europe (38/140), which included seven patients from the UK. Compared with the Rest of World subgroup, patients from Western Europe had more severe disease, being later stage patients with highly aggressive disease, and had been more heavily pretreated with multiple combination regimens (including rituximab). In the Western Europe subgroup, out of 26 patients, only one patient in the pixantrone group achieved CR/CRu at the end of treatment (1/16 [6.3%] with pixantrone vs 0/10 [0%] with TPC; 6.3%; 95% CI: –5.6% to 18.1%). Moreover, results of analyses of median OS and PFS favour TPC in this subgroup of patients (OS: HR 1.73; 95% CI: 0.70 to 4.32; PFS: HR 1.23; 95% CI:

0.54 to 2.81). The ERG's clinical expert indicated that the Western Europe subgroup could potentially have more severe disease than a patient who would typically be eligible for treatment with pixantrone in the UK. That is, compared with the Western Europe subgroup, patients in clinical practice in the UK might have received fewer lines of treatment before being considered eligible for treatment with pixantrone, with pixantrone potentially being given as a third-line treatment rather than fourth or fifth line treatment.

Comparative clinical effectiveness results for most subgroups presented (e.g., histologically confirmed aggressive B-cell NHL, prior treatment with rituximab, and geographic region) are based on *post hoc* subgroup analyses. Moreover, as subgroups, the power to detect a difference is reduced further, the number of patients in the analysis is generally small, and there is increased uncertainty around the robustness of the result. In the case of subgroups based on retrospective histological confirmation of disease and prior rituximab treatment, because randomisation was not stratified by these factors, there is the potential for unbalanced groups. For these reasons, the ERG considers that results of the subgroup analyses should be interpreted with caution.

Economic

The uncertainty associated with the limited clinical data available to inform the manufacturer's economic evaluation is propagated throughout the economic model, resulting in wide CIs around the probabilistic ICERs. In particular, ICERs associated with *post hoc* subgroup analyses.

When compared with the clinical trial result, both the manufacturer's base case analysis and the analysis carried out in the histologically confirmed aggressive B-cell patient population (i.e., the patient population most relevant to the decision problem) were biased towards pixantrone as a result of overestimation of the relative PFS benefit of pixantrone versus TPC.

The absence of relevant HRQoL data from clinical trials resulted in a variety of sources being used to inform the utility and disutility values used in the manufacturer's economic evaluation. The ERG identified several values that may not have been appropriate for use in the patient population that is the focus of this STA.

1.4.3 Areas of uncertainty

The ERG considers that the key area of uncertainty relevant to the decision problem relates to the clinical benefit of pixantrone in patients who have previously been treated with rituximab. No statistically significant differences were found between pixantrone and TPC in response (CR/CRu), OS, or PFS in patients who had received prior rituximab.

In the Western Europe subgroup, results for median PFS and OS favour TPC. Based on differences in baseline severity of disease between the Western Europe subgroup and the Rest of World subgroup,

the ERG considers that it is unclear whether the results of the Western Europe subgroup are applicable to patients in the UK.

1.5 Key issues

The ERG considers the key issues to be:

- uncertainty around the clinical benefit of pixantrone in patients who have received prior treatment with rituximab;
- use of CR/CRu as a primary outcome;
- the likelihood that PIX301 was underpowered to detect a difference in primary outcome of proportion of patients achieving CR/CRu at end of treatment in the ITT population;
- retrospective histological confirmation of disease, a consequence of which was that the ITT population includes patients without aggressive NHL;
- high levels of uncertainty, represented by large CIs surrounding the probabilistic ICER estimates in all patient populations considered by the manufacturer.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG considered that the assessment of cost-effectiveness in the population of patients with B-cell NHL, histologically confirmed as aggressive, is the most relevant analysis to the decision problem that is the focus of this STA. Following detailed examination of the MS and economic evaluation, the ERG identified several areas of inaccuracy or uncertainty associated with the manufacturer's model. In particular, structural assumptions made regarding treatment discontinuation and utility, disutility and cost parameters used. Where possible, the ERG assessed the impact of areas of inaccuracy or uncertainty on the manufacturer's cost-effectiveness result, using sensitivity or scenario analyses. Of these analyses, the use of utility values, representing patients with PFS or PD, from a population of patients on third-line treatment for chronic lymphocytic leukaemia (CLL), rather than first-line treatment for NHL, had the largest impact on the ICER (increasing from £32,830 to £60,129 in the histologically confirmed aggressive B-cell NHL population). Collectively the other sensitivity analyses carried out by the ERG (on disutility and unit cost values) increased the ICER by a further £25 (from £60,129 to £60,154).

In addition, the ERG was unable to assess the impact of some areas of inaccuracy or uncertainty. In particular, the cost-effectiveness of pixantrone in a population of patients with histologically confirmed aggressive B-cell NHL who had received prior treatment with rituximab. However, based on inspection of the clinical trial results, it is likely that the ICER in this patient population may be substantially higher; however, the ERG notes that the evidence base in this patient population is weak and that any findings may be a result of random chance. The ERG considers that the remaining areas of uncertainty, such as structural assumptions made regarding treatment discontinuation, are likely to have a minimal impact on the cost-effectiveness result.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problems

In the Context section of the manufacturer's submission (MS; Section 2), the manufacturer provides an overview of the key aspects of aggressive non-Hodgkin's lymphoma (NHL) relevant to the decision problem, including classification systems used to categorise lymphomas, staging of the disease and prognosis in relapsed or refractory aggressive NHL. However, there is little discussion of incidence or prevalence of NHL in the UK. The Evidence Review Group (ERG) considers it useful to augment some areas of the manufacturer's description of the underlying health problem.

In 2009, NHL was the fifth most common cancer in the UK, with 12,294 new cases of NHL reported (equivalent to 4% of all new cases of cancer).[(1)] Furthermore, NHL is one of the most common causes of cancer death in the UK, accounting for 3% of all cancer deaths; in 2010, 4,452 deaths were attributed to NHL in the UK.[(1)] Age-standardised relative survival rates for NHL in England indicate that 76% of men are expected to survive NHL for 1 year, falling to 61.5% survival at 5 years. Survival rates for women are marginally higher, with 78.9% expected to survive for 1 year, falling to 65.7% survival at 5 years. Data indicate that men are more likely to develop NHL than women; of new cases reported in 2009, 54% were in men versus 46% in women.[(1)] Incidence of NHL is strongly correlated with age, with the highest incidences occurring in older men and women and about 60% of cases of NHL are diagnosed in people aged over 65 years. Age is also an important prognostic factor in some types of NHL, with older patients having a poorer outcome.[(2)]

The aetiology of NHL is not clear. However, risk of developing NHL is increased in people with a weakened immune system, such as those who have an infection that affects the immune system (e.g., HIV or AIDS), those who are immune-suppressed (e.g., receiving drugs post-organ transplant), and those with an autoimmune disease (e.g., rheumatoid arthritis or coeliac disease).[(3)] Exposure to chemicals used in agriculture (e.g., pesticides and insecticides) has also been linked to an increased risk of NHL. The incidence of NHL has increased steadily in the UK since the mid-1970s, a trend that has also been observed globally. Cancer Research UK (CRUK) reports that between 1975–1977 and 2007–2009 European age standardised rates increased by more than two and a half times.[(1)] The underlying cause of the trend in increased NHL incidence is unclear. It should be noted that advances in diagnosis and classification of NHL are thought to account for a fraction, but not all, of the observed trend towards steady increase in incidence.[(1)]

NHL, as the manufacturer identifies, comprises multiple types of cancer originating in the lymphatic system.[(4)] To expand on the manufacturer's description of the underlying disease, the ERG considers it useful to briefly describe the pathology of NHLs. As part of the immune system, the lymphatic

system comprises infection-fighting white blood cells (lymphocytes), of which there are two main types, B-lymphocyte cells (B-cells) and T-lymphocyte cells (T-cells). In lymphoma, lymphocytes divide abnormally, and continue to divide, and then collect in a specific area, for example, a lymph node. It is the accumulation of these abnormal cells that leads to lymphoma. In the UK, most NHLs originate from abnormal division of B-cells (about 85% of cases),[4] whereas NHLs arising from T-cells are more common in teenagers and young adults.[3] Although NHL typically arises in a lymph node (nodal lymphoma), as the lymphatic system is spread throughout the body, NHL can arise in almost any tissue (extranodal lymphoma). About 1 in 3 patients with NHL will have some extranodal lymphoma.[3]

There are multiple types of NHL, and, as recognised by the manufacturer, there are numerous complex classification systems available to categorise NHL type. Classification of NHL type is an important initial step as treatment strategies vary depending on the type of lymphoma. Disparity in the definitions of individual lymphomas across the systems available, together with advances in histological methods, adds further complexity to the interpretation and generalisation of results of studies in patients with NHL. Within the MS, the manufacturer presents a comprehensive description of the most widely accepted methods used to classify NHL in recent years, including the REAL (proposed in 1994),[5] and World Health Organization (WHO) (published in 2001) classification systems;[6] the WHO system is based in the underlying principles of the REAL classification system. As the manufacturer identifies, the WHO classification of lymphomas was updated in 2008,[7] and is becoming accepted as the International standard classification system; to illustrate the multitude of subtypes of lymphoma that occur, the lymphoma types described in the WHO system are listed in Appendix 1. In the WHO system, categorisation of lymphoma type is based on various factors:

- cellular histology;
- immunophenotyping (phenotyping of molecules on the cellular surface of the lymphoma);
- cytogenetics (presence of genetic abnormalities specific to lymphomas);
- patient's age, gender and medical history (e.g., past illnesses or drug therapies);
- clinical features of the lymphoma (e.g., site of origin of the lymphoma or site to where the lymphoma has spread).

In addition to distinguishing NHLs by origin of cell type, it is important to also identify the speed of lymphoma growth. NHLs that grow slowly are referred to as "low grade" or indolent, whereas tumours that grow rapidly are referred to as "high grade" or aggressive. Over time, an indolent NHL may transform into an aggressive NHL. Within the aggressive NHLs, there are several distinct subtypes of lymphoma, which require different treatment strategies. Moreover, aggressive NHLs grow at varying rates, and the level of aggression is an important prognostic factor.[2]

Typically, indolent NHLs respond to treatment but follow a relapsing and remitting course. Cure is not usually possible unless a patient presents with localised (Stage I) disease, or is eligible for treatment with autologous stem cell transplant (ASCT). Patients with indolent NHLs may have a median survival rate of between 10 and 20 years. By contrast, although aggressive NHLs are more likely to cause death in the shorter term if untreated, a large proportion of patients with aggressive NHLs will be classed as cured after intensive chemotherapeutic treatment (~50–60%);[3;4] that is, the patient does not have any clinical symptoms of disease for a prolonged period (typically, 5 years). However, as the manufacturer identifies, a substantial proportion of patients who achieve an initial response to treatment do relapse (>30%),[8] with most relapses occurring within 2 years after completion of treatment. About 10% of patients fail to respond to initial chemotherapy, which is referred to as refractory disease (<50% decrease in lesion size with chemotherapeutic treatment or the appearance of new lesions[9]).[4] As the manufacturer identifies, following relapse in patients with aggressive NHL, at least 60% of patients remain sensitive to conventional chemotherapy treatment. However, patients with relapsed or resistant NHL have a poor prognosis (survival at 2 years is <5–10% with salvage chemotherapy).[10]

Of particular relevance to the decision problem that is the focus of this STA are the subtypes of NHLs that have been identified to be aggressive, which, as the manufacturer recognises, include:

- diffuse large B-cell lymphoma (DLBCL);
- mediastinal large B-cell lymphoma;
- diffuse mixed cell lymphoma;
- Burkitt's lymphoma;
- anaplastic large cell lymphoma.

DLBCL is the most common aggressive NHL, affecting ~30% of patients with NHL and 80% of patient with aggressive NHL.[3]

As the manufacturer highlights, treatment strategies for NHL are dependent on the stage of a patient's tumour. In NHL, stage of tumour is based on the Ann Arbor system, which is a four-point scale that evaluates the number of sites affected (scale presented in Appendix 2).[11] In aggressive NHL, which is the focus of this STA, the International Prognostic Index (IPI) is used as an aid in determining a patient's prognosis. The IPI considers the stage of tumour as evaluated by the Ann Arbor system, in addition to a patient's age and performance status (based on Eastern Cooperative Oncology Group [ECOG] score), the number of extranodal sites involved, and lactate dehydrogenase (LDH) levels (indicative of level of aggression).[2] In younger patients, the system is adjusted for age and is based on only tumour stage, performance status, and LDH levels. The IPI comprises four prognostic categories: low risk; low–intermediate risk; high–intermediate risk; and high risk. A score of one is assigned to each negative prognostic factor, and thus, as the manufacturer recognises, the higher the

score, the poorer the prognosis (5-year survival rates summarised in Table 1). The introduction of rituximab led to improvements in treatment outcome, and there has been debate as to what extent prognostic factors change with a novel treatment strategy. A retrospective analysis of patients with DLBCL and treated with R-CHOP led to the suggestion of a revised IPI with only three risk groups: very good (4-year PFS 94%, and OS 94%); good (4-year PFS 80%, and OS 79%), and poor (4-year PFS 53%, and OS 55%).[12]

Table 1. Prognosis in aggressive non-Hodgkin's lymphoma based on International Prognostic Index score[2]

Categorisation	Score	Survival rate at 5 years
All patients		
Low risk	0 / 1	73%
Low–intermediate risk	2	51%
High–intermediate risk	3	43%
High risk	4 / 5	26%
Age-adjusted patients		
Low risk	0	83%
Low–intermediate risk	1	69%
High–intermediate risk	2	46%
High risk	3	32%

In summary, the ERG considers the manufacturer's description of the underlying health problem to be accurate and relevant to the decision problem that is the focus of this STA.

2.2 Critique of manufacturer's overview of current service provision

In the Context section, the manufacturer discusses approaches to the treatment of aggressive NHL, including National Institute for Health and Clinical Excellence (NICE) guidance on the use of rituximab. In addition, the manufacturer outlines the proposed position of pixantrone in the treatment pathway, and estimates the number of patients in the UK who would be eligible for treatment.

As the manufacturer highlights, there is no NICE guideline on the treatment of aggressive NHL, either for first or subsequent lines of treatment. NICE has issued service guidance on improving outcomes in haematological cancers in general, addressing areas such as medical diagnosis and management, but no recommendations are available on chemotherapeutic agents for treatment.[13]

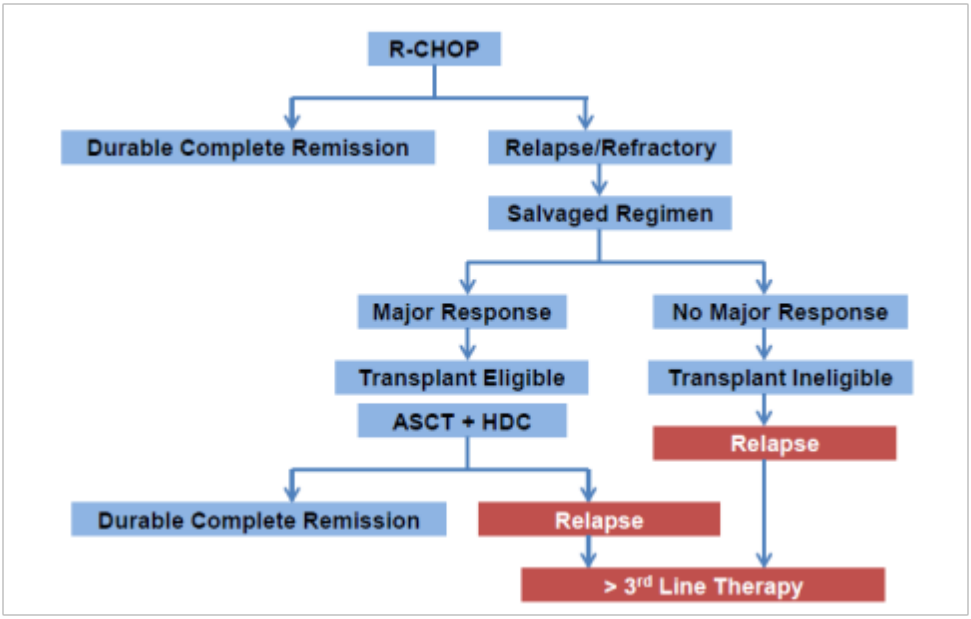
The manufacturer also discusses NICE recommendations on the use of rituximab in the treatment of NHL, which has been the focus of one STA in aggressive NHL (TA65).[14] Rituximab was recommended by NICE for use in the first-line treatment of DLBCL (clinical Stage II, III, or IV) in combination with the CHOP regimen (cyclophosphamide, vincristine, doxorubicin and prednisolone).[14] The manufacturer highlights that the use of rituximab as a first-line treatment of

aggressive NHL is not of relevance to the decision problem that is the focus of this STA. The ERG acknowledges the manufacturer's point but considers it pertinent to the decision problem note that first-line treatment of aggressive NHL with rituximab added to an anthracycline-based regimen is standard clinical practice in the UK (discussed in more detail in Section 4). The manufacturer also highlights guidance on the use of rituximab in the treatment of relapsed or refractory Stage III or IV follicular lymphoma (TA137).[15] The ERG considers it important to note that follicular lymphoma is categorised as an indolent type of NHL. However, indolent B-cell lymphomas, such as follicular lymphoma, are commonly associated with transformation to aggressive disease, but it is generally considered good practice to confirm histologically the conversion to aggressive disease. Although the key trial evaluated in TA137 included a patient population with Stage III or IV follicular lymphoma, the histology of follicular lymphoma was not reported as aggressive but as indolent, and, as such, the ERG does not consider guidance issued in TA137 to be relevant to the decision problem that is the focus of this STA.

In the MS, the manufacturer presents a treatment algorithm for aggressive NHL to illustrate the anticipated position of pixantrone (reproduced in Figure 1). To validate the manufacturer's treatment algorithm, the ERG sought expert advice on clinical practice in the UK for the treatment of aggressive NHL. In brief, first-line treatment of aggressive NHL typically involves rituximab added to an anthracycline (e.g., doxorubicin)-based regimen, and is given with curative intent. In the presented algorithm, the manufacturer lists R-CHOP as the first-line treatment. The ERG's experts fed back that, although R-CHOP is typically the first-line treatment in DLBCL, other anthracycline-based regimens might be the first-line treatment of choice in other subtypes of aggressive B-cell NHL.

For patients who relapse or are refractory to first-line treatment, the manufacturer indicates that second-line treatment involves salvage chemotherapy, which the ERG's clinical advisors highlighted would most likely be an established platinum-based regimen (e.g., RICE [rituximab, ifosfamide, cytarabine, and etoposide] or R-DHAP [rituximab added to dexamethasone, cytarabine, and cisplatin]). Patients who have a major response to salvage chemotherapy, and are eligible, would go on to receive ASCT. However, of the patients receiving second-line chemotherapeutic treatment, about half of patients are ineligible for ASCT because of advanced age (>65 years) or considerable co-morbidities (e.g., major organ dysfunction). Moreover, not all eligible patients will undergo ASCT. As the manufacturer reports, it has been estimated that 25% of patients will respond to second-line chemotherapy and continue to treatment with ASCT, with only 10% of patients achieving remission.[9] Relapse after ASCT is generally associated with a poor prognosis, with a median survival of only 4–6 months.[16] Thus, most patients receiving second-line treatment go on to receive third-line therapy. The ERG's clinical advisor fed back that the numbers reported for proportion of patients undergoing and responding to ASCT reflect clinical results observed in UK clinical practice.

Figure 1. Manufacturer's treatment algorithm for aggressive non-Hodgkin's lymphoma (reproduced from MS; Figure 1, pg 24)



The manufacturer has positioned pixantrone as a treatment option for multiply relapsed or aggressive B-cell NHL, and the Committee for Medicinal Products for Human Use (CHMP) has recommended conditional approval for the use of pixantrone in this indication.[17] The CHMP added the caveat that clinical benefit of pixantrone "has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy". Considering third-line treatment, the manufacturer asserts that there are limited treatment options for patients with multiply relapsed or refractory aggressive NHL, and that there is a lack of consensus among clinicians as to which treatments should be used for third and subsequent line therapy. Moreover, as the manufacturer identifies, no intervention has as yet been licensed in Europe for the third-line treatment of relapsed or refractory aggressive NHL. The ERG's clinical advisors support the statements made by the manufacturer, emphasising that there is no consensus in UK clinical practice as to which is the most appropriate therapy for third and subsequent lines. Factors that influence choice of treatment are a patient's clinical well-being, the clinician's preference for treatment, and setting-specific clinical practice. A survey commissioned by the manufacturer identified numerous different treatment regimens used in the third and fourth-line treatment of aggressive B-cell NHL (Table 2). However, the clinical experts consulted by the ERG considered that, of the listed treatments, only DHAP, ICE (ifosfamide, carboplatin, and etoposide), CHOP, and ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin) regimens would be likely to be used in UK clinical practice, and would most likely be used as second-line treatments with a view to proceeding to ASCT. Moreover, the ERG notes that none of the treatment options listed is a comparator in the key trial (PIX301) from which submitted evidence on the clinical effectiveness of pixantrone is derived.[18]

Table 2. Treatment approaches for aggressive B-cell lymphoma (reproduced from the MS; Table 8, pg 28)

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
Survey of 251 haemato-oncologists and oncologists across five countries in the European Union (France, Germany, Italy, Spain, UK). Abbreviations used in table: CHOP, cyclophosphamide, vincristine, doxorubicin and prednisolone; DHAP, dexamethasone, cytarabine, and cisplatin; EPOCH, etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone; ESHAP, etoposide, methylprednisolone, high-dose cytarabine and cisplatin; HyperCVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICE, ifosfamide, carboplatin, etoposide.	

The ERG's clinical experts indicated that third-line treatments are typically considered to be palliative, and treatment is given with the goal of increasing progression-free survival while limiting toxicity. One clinical expert indicated that, based on these considerations, the preference would most likely be for a single chemotherapeutic agent. Typical agents used include gemcitabine, vinblastine, and vinorelbine. However, a second expert fed back that they would only rarely use a monotherapy, with preference for combination chemotherapy. Expert opinion was 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 experts stressed that there is no consensus on this strategy and this may not be standard in all clinical settings.

The manufacturer comments that there is a lack of evidence on comparative clinical effectiveness of treatments (either as monotherapy or combination regimens) used as third and subsequent line therapies, which is consistent with a review evaluating the effectiveness of interventions for relapsed DLBCL;[4] the review identified no RCTs evaluating third and subsequent line treatments. The ERG's clinical advisors also concur with the manufacturer on this point. Clinical experts also stressed, as recognised by the manufacturer, that there is a clinical unmet need in multiply relapsed or refractory aggressive NHL.

Overall, the ERG considers the manufacturer's overview of current service provision to be an accurate, relevant representation of clinical practice in the UK for the treatment of aggressive NHL.

The ERG considers the proposed position of pixantrone in the treatment pathway to be appropriate and considers it important to emphasise the lack of an evidence base on the treatments available for third and subsequent lines of therapy in aggressive NHL.

In terms of resources required to administer pixantrone within the National Health Service (NHS), the manufacturer proposes that additional infrastructure will not be required as reconstitution and administration of pixantrone is similar to that of other chemotherapeutic agents used in the proposed setting. The manufacturer indicates that pixantrone should be administered in a hospital setting by clinicians "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". The manufacturer notes that additional resource might be necessary to manage neutropaenia (low neutrophil count), which is listed in the Summary of Product Characteristics as a common adverse effect of pixantrone treatment.[19] As identified by the manufacturer, neutropaenia can be managed by treatment with a granulocyte colony-stimulating factor agent, such as filgrastim. In addition, the manufacturer comments that, although pixantrone is associated with low rates of chemotherapy induced nausea and vomiting, treatment with an anti-emetic could be required. The ERG's clinical expert advised that the manufacturer's proposal that additional infrastructure would not be necessary and that minimal additional resource would be required to introduce pixantrone to the NHS is appropriate.

The manufacturer estimates the number of patients potentially eligible for treatment with pixantrone to be between ~550 and ~730 patients (ERG's calculation based on data presented within MS). The manufacturer states: "based on the incidence data from the EU Cancer Observatory 2008 … 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[20]". The ERG was unable to validate the manufacturer's estimate. However, the ERG's clinical expert indicated that it would be difficult to obtain an accurate estimate of the number of patients potentially eligible for treatment with pixantrone, and that the manufacturer's estimate seems reasonable.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

The manufacturer provided a summary of the final decision problem issued by the National Institute for Health and Clinical Excellence (NICE; manufacturer's submission [MS], pg 35),[21] together with a brief description of the rationale for any deviation from the decision problem (Table 3).

Table 3. Summary of decision problem as outlined in the manufacturer's submission (adapted from MS; pg 35)

	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	Indication is 3rd line plus, as 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; • Oxaliplatin; • Ifosfamide; • Etoposide; • Mitoxantrone; • Gemcitabine.	• Vinorelbine; • Oxaliplatin; • Ifosfamide; • Etoposide; • Mitoxantrone; • 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 • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • 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 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	The economic evaluation will be a cost effectiveness analysis, with the results presented as incremental cost per quality-adjusted life year gained. 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. Costs will be considered from an NHS and Personal Social Services perspective.	
Subgroups to be considered	None specified	Two subgroups of patients are considered: • Aggressive B-cell NHL; • 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	Guidance will only be issued in accordance with the marketing authorisation	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.[a]

[a] Additional text supplied by the manufacturer in support of the case for consideration of pixantrone under the End of Life Policy.

Overall survival in the PIX301 trial for this patient population was less than a year (median overall survival was 10.2 (6.4 to 15.7) vs 7.6 (5.4 to 9.3) months for pixantrone and standard care, respectively) log rank p-value = 0.251; HR = 0.79 (95% CI: 0.53 to 1.18), while median progression-free survival was less than 6 months; 5.3 (2.3 to 6.2) vs 2.6 (1.9 to 3.5) for pixantrone and standard care, respectively) p = 0.005; HR = 0.60 (95% CI: 0.42 to 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 fulfil the need as a standard salvage therapy that leads to improved outcomes with manageable toxicities.

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
Abbreviations used in table: DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; NHL, non-Hodgkin's lymphoma; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; UK, United Kingdom.

3.1 Population

In the summary of the decision problem (Table 1), the manufacturer identifies that the final scope issued by NICE listed the population of interest as "adults with multiply relapsed or refractory aggressive B-cell non-Hodgkin lymphoma".[21] The ERG notes that the manufacturer indicates that the submitted evidence addresses multiply relapsed or refractory aggressive NHL, with no restriction of the population of interest to B-cell NHLs.

The key trial (PIX301[18]) that forms the basis of the direct clinical evidence submitted by the manufacturer enrolled patients with aggressive *de novo* or transformed NHL (according to the Revised European–American Lymphoma and World Health Organization classification). Key eligibility criteria for randomisation in PIX301 were:

- relapse 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;
- presence of at least one objectively measurable lesion as demonstrated by computed tomography (CT), spiral CT, or magnetic resonance imaging could be followed for response as a target lesion;
- life expectancy of at least 3 months.

Patients with NHLs originating from either B-cells or T-cells were eligible for randomisation in the PIX301 trial. Only 10% of patients in PIX301 were classified as having T-cell NHLs, which reflects the relative proportion of B-cell to T-cell NHLs typically observed in UK clinical practice.[3] However, the conditional approval issued by the Committee for Medicinal Products for Human Use (CHMP) specifies that pixantrone is indicated for treatment of adult patients with multiply relapsed or refractory aggressive B-cell NHLs.[17] For the decision problem that is the focus of this Single Technology Appraisal (STA), the Evidence Review Group (ERG) considers the restriction of the population to patients with aggressive B-cell NHLs to be appropriate. The ERG considers it important to note that patients with Burkitt's lymphoma were excluded from PIX301. Burkitt's lymphoma is a highly aggressive NHL originating from B-cells that occurs most frequently in children and young adults. In addition, as patients with T-cell NHLs were randomised in PIX301, albeit a small proportion, data on clinical effectiveness in aggressive B-cell NHLs are based on a *post hoc* subgroup analysis.

Patients eligible for enrolment in PIX301 had failed at least two previous lines of chemotherapeutic treatment and are, therefore, receiving pixantrone as a third or subsequent line treatment. As noted in Section 2.2, recommendations on treatment strategies for multiply relapsed or refractory aggressive NHL are not available, and there is no consensus on the most appropriate treatment for this population. Based on clinical expert opinion, the ERG considers that the population in PIX301 is representative of patients in the UK who would be eligible for, and most likely to receive, treatment with pixantrone as a single agent. Although not specified in the final scope, based on advice from clinical experts, the ERG considers the subgroup of patients who have received prior rituximab treatment is of particular relevance as rituximab forms part of the standard of care in the UK for the first-line treatment of aggressive NHL.

3.2 Intervention

The ERG notes that the MS provides an overview of the regulatory status and mode of action of pixantrone. Pixantrone does not currently have a UK marketing authorisation for the treatment of multiply relapsed or refractory aggressive NHL, but, as noted earlier, the CHMP has issued a conditional approval for the use of pixantrone monotherapy in this indication.[17] In 2010, the US Food and Drug Administration (FDA) rejected the manufacturer's application for use of pixantrone in the USA, recommending that the manufacturer carry out an additional trial to demonstrate the safety and effectiveness of pixantrone.[22;23] The FDA also raised concerns that only 140 of a planned 320 patients had been recruited for the trial, and, of those recruited, only 8 patients were enrolled from the USA. Pixantrone is given intravenously on days 1, 8, and 15 of each 28-day cycle for up to 6 cycles, at a dose of 85 mg/m^2 (equivalent to 50 mg/m^2 pixantrone base).[19]

Pixantrone is an analogue of mitoxantrone and was designed to reduce the cardiotoxicity associated with anthracyclines and anthracenediones while improving, or at least maintaining, clinical effectiveness. Anthracyclines, such as doxorubicin, are highly effective anticancer agents and are a key component of standard chemotherapies used in the treatment of NHL. However, their clinical usefulness is limited by the associated irreversible and accumulative cardiac adverse effects that may lead to congestive heart failure. Anthracycline-associated cardiotoxicity is related to a patient's cumulative lifetime dose, and, once the recommended dose for a particular anthracycline has been reached, treatment is typically stopped. Most patients previously treated with an anthracycline are unlikely to be eligible for further treatment with this class of agent should their disease relapse. While it is known that anthracyclines elicit their chemotherapeutic effect primarily through inhibition of DNA synthesis, transcription and replication, the pathological mechanisms underlying the cardiotoxic effects are not yet fully understood.[24] It is known that anthracyclines generate oxygen-derived free radicals, which, as well as directly damaging DNA, are thought to damage the membranes of the heart.[24]

Pixantrone belongs to a class of compounds called aza-anthracenediones. The manufacturer highlights that pixantrone is the first compound in this drug class to reach advanced clinical development. Like anthracyclines, pixantrone elicits a clinical effect through disruption of DNA synthesis. The manufacturer states that the structure of pixantrone increases the stability of DNA adduct formation while reducing formation of oxygen-derived free radicals. Therefore, pixantrone is associated with less cardiotoxicity than related anthracycline compounds and might provide an alternative option for heavily treated patients, and particularly those who have received prior anthracycline.

3.3 Comparators

The final scope issued by NICE indicated that pixantrone monotherapy should be evaluated against various other single chemotherapeutic agents:[21]

- vinorelbine;
- oxaliplatin;
- ifosfamide;
- etoposide;
- mitoxantrone;
- gemcitabine.

As noted earlier, no therapy has been granted a licence for the treatment of multiply relapsed or refractory aggressive NHL, and, furthermore, there is no clinical consensus on the appropriate treatment for this population. The ERG's clinical experts expressed different preferences for interventions used for third and subsequent line treatment, with one expert expressing a preference for a monotherapy and the other combination chemotherapy treatment. However, experts agreed that treatment would be determined by the individual patient. Chemotherapeutic agents highlighted by the ERG's clinical experts as being used as a monotherapy in this setting were gemcitabine, vinorelbine, and vinblastine. The ERG notes that vinblastine is not listed as a comparator of interest in the final scope, which in the view of the ERG, supports the opinion that there is considerable disparity in treatments used in this population in UK clinical practice.

The comparator group in PIX301 is treatment of physician's choice (TPC). Clinicians were able to choose from six chemotherapeutic agents (to be used as a monotherapy) approved for cancer indications other than aggressive NHL but with demonstrated activity in aggressive NHL. The six agents available were the agents listed as comparators in the final scope;[21] gemcitabine was available as a treatment option to clinicians only in the USA. Etoposide could be administered orally or intravenously. In addition to the six interventions listed, clinicians in the USA were also given the option to treat patients with rituximab. Treatments were given at prespecified standard doses and

schedules based on available evidence. The CHMP considered the choice of single arm comparator from a prespecified list to be acceptable.[17]

In the case of aggressive NHL, the choice of a comparator group comprising a diverse set of treatments is in line with guidance from the CHMP on choice of reference treatment in clinical trials evaluating interventions in cancer, which states: "If, for a specific target population, there is no regimen with an evidence-based favourable benefit-risk relationship, a regimen used in clinical practice with a well-documented and benign safety profile is acceptable. Alternatively, "investigator's best choice" among a few selected regimens with these characteristics (may include BSC) is acceptable. In these cases, superior efficacy has to be shown versus the pooled results in the reference arm".[25]

In the MS, the manufacturer presents data for the TPC group as a complete group, rather than as individual treatments. The most common treatment administered in the TPC group was oxaliplatin, which was treatment chosen for 45% of patients. None of the patients in the TPC group received rituximab, and only one patient received gemcitabine. Given the distribution of treatments within the TPC group (discussed in greater detail in Section 4.2.1), the ERG considers the manufacturer's approach to present data on clinical effectiveness from the complete TPC group rather than individual treatment subgroups to be pragmatic and appropriate. However, the ERG considers it important to note that considering the clinical effectiveness data in the TPC group as a complete data set precludes differentiation of patient responses to individual treatments, and thus comparative clinical effectiveness of pixantrone against individual treatments.

3.4 Outcomes

In the clinical section of the MS, with the exception of health-related quality of life (HRQoL), the manufacturer has provided direct evidence for pixantrone versus TPC on the outcomes listed in the final scope issued by NICE, which were:[21]

- overall survival (OS);
- progression-free survival (PFS);
- response rate;
- adverse effects of treatment;
- HRQoL.

The pre-specified primary outcome reported in the key trial submitted as direct evidence (PIX301[18]) is rate of complete response (CR) or unconfirmed CR (CRu) at the end of treatment in the intention-to-treat (ITT) population, as evaluated by an Independent Assessment Panel (IAP). CR and CRu were assigned as per the Report of the International Workshop to Standardize Response Criteria, which are also known as the International Working Group (IWG) criteria.[26] The CHMP did not consider the

choice of CR/CRu for the primary outcome acceptable for a single Phase III trial, commenting that PFS or OS would have been more appropriate. However, the CHMP stated that, because of the positive results associated with pixantrone in PIX301, the use of CR/CRu as the primary outcome was not a key concern.[17] As noted by the manufacturer, the IWG response criteria for NHL were revised in 2007, subsequent to the initiation of the PIX301 trial (commenced in 2004).[27] The updated IWG response criteria removed the outcome of CRu and introduced the use of positron emission tomography (PET). The potential implications of this change for interpretation of the clinical effectiveness results from PIX301 are discussed in more detail in Section 4.2.1.

Prespecified secondary outcomes in PIX301 were:

- OS (defined as the interval between the date of randomisation and death from any cause);
- CR/CRu rate in histologically confirmed patients (i.e., patients whose lymphoma had been reviewed retrospectively by an independent, central panel);
- overall response (ORR) lasting at least 4 months (ORR defined as the percentage of patients who achieved CR, CRu, or partial response);
- PFS.

PFS is defined as the interval between the date of randomisation and the first documented progression of disease or death (MS; pg 61). Subsequently in the MS (MS; pg 71), and in publications relating to the PIX301 trial, it is reported that patients who commenced a different treatment during the follow-up period were also classified as having progressed, irrespective of whether disease progression had been confirmed radiologically.[17;18;28] As the manufacturer notes, inclusion of initiation of alternative therapy as an event in the outcome of PFS is not usual in trials evaluating treatments for cancer. The potential implications of this issue for interpretation of the clinical effectiveness results are discussed in greater detail in Section 4.3.1.

OS is considered to be the most reliable endpoint in trials evaluating interventions in cancer, and is generally the preferred endpoint.[29] Long follow-up periods and potential confounding from post-progression therapies can hinder the collection and analysis of survival data. Clinical trials frequently measure validated surrogate endpoints that have been identified as being correlated with clinical outcome, that is, the surrogate outcome is likely to predict clinical result. Considering aggressive NHL, a study by Lee *et al*.[30] highlights that surrogate end points in trials of relapsed or refractory aggressive NHL have not been evaluated. Of particular relevance to the decision problem is that the guidance from the FDA indicates that ORR (combination of complete and partial responses) is considered a direct measure of the antitumor activity of a drug but not as a measure of the stability of disease.[29] Clinical benefit in tumour response does not necessarily lead to benefit in OS.

Various data on safety and tolerability are presented within the MS, including data on common adverse events and on cardiotoxicity.

Other than HRQoL, which was not recorded during PIX301, the ERG considers the outcomes reported to be appropriate and clinically meaningful to the decision problem.

3.5 Time frame

In the PIX301 trial, after the last treatment for disease progression and survival, patients were followed up for 18 months. At the last follow-up assessment, of 140 patients randomised, 99 patients had died (70.7%). Of patients entering the follow-up period (67.9%), the median follow-up was 9.6 months (0.2 months to 18.0 months) in the pixantrone group and 8.2 months (0.8 months to 18.0 months) in the TPC group (data provided by manufacturer on request). Patients with multiply relapsed NHL typically have a poor prognosis. The ERG considers the time frame of the PIX301 trial (treatment period followed by 18 months of follow-up) to be sufficient to capture clinical benefit associated with treatment with pixantrone.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

4.1.1 Description and discussion of appropriateness of manufacturer's search strategy

The manufacturer provided the search terms and strategies implemented in the manufacturer's review of the literature as an Appendix (Appendix 2 of the MS). The manufacturer searched the literature to identify relevant randomised controlled trials (RCTs) and non-randomised clinical trials assessing the clinical effectiveness of pixantrone monotherapy and relevant comparators in the treatment of patients with multiply relapsed or refractory non-Hodgkin's lymphoma (NHL). In addition to the comparators available as treatment of physician's choice (TPC) in the PIX301 trial,[18] the manufacturer also searched the literature for data on bendamustine, bortezomib, and lenalidomide.

The manufacturer listed the specific databases searched, the time period covered by the searches, and the date the searches were run. For the review of the literature on the clinical effectiveness of the listed interventions, the manufacturer supplemented the search by reviewing the websites of various relevant organisations, including American Society of Clinical Oncology, European Association for Cancer Research, and European Society for Medical Oncology. The manufacturer also searched ClinicalTrials.gov and company websites of manufacturers of interventions identified as being of interest. Reference lists of identified studies and systematic reviews were hand searched for additional relevant studies.

Within the searches, the manufacturer used multiple search terms for NHL and for pixantrone. However, search terms of other listed interventions were limited to the common drug name. The manufacturer restricted the search for studies on the clinical effectiveness to citations published from January 1995; restriction applied to all databases. The manufacturer carried out the electronic literature search of MEDLINE and EMBASE in December 2011, and of CENTRAL in November 2011. The Evidence Review Group (ERG) notes that the span of the manufacturer's search did not capture the full publication of PIX301,[18] which was published in May 2012. A published systematic review of interventions in the treatment of relapsed diffuse large B-cell lymphoma (DLBCL; search date January 2010) reported no RCTs evaluating monotherapy treatments in this population.[4] It should be noted that inclusion criteria for this review were published systematic reviews and RCTs in any language, including unblinded studies, and containing more than 50 individuals per treatment arm of whom more than 80% were followed up and a minimum follow-up period of 2 years. The ERG considers that the manufacturer's restriction of the span of the search is unlikely to have resulted in publications relevant to the decision problem being missed.

Due to time constraints, the ERG was unable to replicate the manufacturer's search and appraisal of identified abstracts for all databases. However, the ERG carried out a separate search of MEDLINE, EMBASE and the Cochrane Library in January 2013 to update the manufacturer's search. The ERG used the manufacturer's search terms, and considers that all studies relevant to the clinical effectiveness of pixantrone monotherapy in the treatment of multiply relapsed or refractory aggressive NHL are likely to have been identified. In addition, the ERG identified no systematic review evaluating monotherapy treatment in multiply relapsed or refractory aggressive NHL. In summary, the ERG considers that the manufacturer searched the key electronic databases, including MEDLINE, EMBASE, and the Cochrane Library, and that the search strategies used were appropriate for the decision problem that is the focus of this Single Technology Appraisal (STA).

4.1.2 Inclusion criteria used in study selection

Inclusion criteria applied by the manufacturer for their systematic review are summarised in Table 4. Although the manufacturer did not specify exclusion criteria for the review, based on the manufacturer's description of the systematic review process, the ERG considers the exclusion criteria to be implicit (e.g., studies published in a non-English language were excluded).

Table 4. Eligibility criteria applied in the manufacturer's systematic review of the literature on clinical effectiveness (reproduced from MS; Table 10, pg 44)

Categorisation	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 • Bortezomib • Etoposide • Gemcitabine • Ifosfamide • Lenalidomide • Mitoxantrone • Oxaliplatin • Pixantrone dimaleate • Rituximab • 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 • Placebo • 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 • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life • Stable disease • 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	• RCTs • Non-RCTs: a trial with a concurrent control group where participants were assigned by investigators non-randomly to treatment groups	As the majority of studies in this population are not RCTs, non-RCTs 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
Abbreviations used in table: RCT, randomised controlled trial; UK, United Kingdom.		

The ERG considers the manufacturer's inclusion criteria, and accompanying rationales, to be mostly appropriate. With reference to the exclusion of non-English language studies, given the anticipated paucity of studies evaluating interventions in the population of interest, the ERG considers that studies in any language and meeting the other inclusion criteria would be of relevance to the decision problem. However, given the acknowledged lack of evidence in the specified population, the ERG considers it is unlikely that key studies have been omitted from the MS.

The ERG considers that the clinical-effectiveness literature review process, as described in the MS and Appendix 2 of the manufacturer's accompanying documentation, follows standard systematic review practices.

4.1.3 Included and excluded studies in review of clinical effectiveness

The manufacturer provided a single flow diagram that encompassed the review of the literature for evidence on clinical effectiveness, health-related quality of life (HRQoL), economics, and resources (MS; Figure 4, pg 46). The diagram included a summary of the results of each individual search. The flow diagram provided by the manufacturer indicates that six publications were identified by the review of the clinical effectiveness literature. As highlighted earlier, the manufacturer's search of the literature was carried out prior to publication of results of the PIX301 trial in a peer-reviewed journal.[18] The manufacturer identified four conference abstracts presenting results from the PIX301 trial.[31-34] As conference abstracts, details of methodological processes and results are minimal. Of the

four abstracts identified by the manufacturer, two abstracts focused on the PIX301 trial,[31;32] which the ERG considers relevant to the decision problem. The remaining two conference abstracts provided an overview of clinical trials of pixantrone,[33;34] including the PIX301 study, in addition to trials in indolent NHL and evaluating pixantrone as a first-line treatment. The ERG does not consider the two abstracts providing an overview of pixantrone to be relevant to the decision problem as presented data are also reported elsewhere. Of the two remaining publications, one is the manufacturer's registration of the methodology of the PIX301 trial (first published in 2004 and updated in 2011),[28] and the second is a summary of the two conference abstracts presenting data from the PIX301 trial.[35]

No relevant non-RCTs were identified by the manufacturer.

The ERG considers it likely that all relevant studies have been included in the MS.

4.1.4 Quality assessment

The manufacturer assessed the PIX301 trial[18] against criteria adapted from guidance for undertaking reviews in health care issued by the Centre for Reviews and Dissemination,[36] as provided in NICE's template for manufacturer/sponsor submission of evidence to the Single Technology Appraisal (STA) process.[37] The ERG independently validated PIX301 and agrees with the manufacturer's assessment; the manufacturer's assessment, together with accompanying minor comments from the ERG, is presented in Appendix 3. Evidence on the clinical effectiveness of pixantrone is appropriately derived from the PIX301 trial. The ERG's critique of the design and conduct of PIX301 is discussed in more detail in Section 4.2.

4.2 Summary and critique of submitted clinical effectiveness evidence

The primary objective of the PIX301 trial was to compare the clinical effectiveness of pixantrone monotherapy against treatment of physician's choice (TPC) in terms of complete response (CR) and unconfirmed CR (CRu) at the end of treatment in the intention-to-treat (ITT) population. Included patients had multiply relapsed or refractory aggressive NHL (patients previously treated with ≥2 chemotherapy regimens).[28] Evaluation of CR and CRu was based on the International Workshop to Standardize Response Criteria for NHL and was determined by a blinded Independent Assessment Panel (IAP). Secondary objectives were to evaluate comparative clinical effectiveness of pixantrone on overall survival (OS), CR/CRu rate in histologically confirmed patients, overall response rate (ORR) lasting at least 4 months, and progression-free survival (PFS). Key characteristics of PIX301 are presented in Table 5 and definitions for outcomes evaluated are presented in Table 6.

Table 5. Key trial characteristics of PIX301[18]

Study: Design and patients	Intervention/comparator	Key inclusion criteria	Key exclusion criteria	Outcomes
140 patients with aggressive non-Hodgkin lymphoma and who had received two or more previous regimens of chemotherapy for relapsed or refractory aggressive non-Hodgkin lymphoma Open label, randomised trial (an independent assessment panel was blinded to treatment assignment) Two armed randomised trial with an active-control, evaluating single-agent pixantrone versus investigator's choice of an alternative single chemotherapeutic agent International multicentre Phase III trial: 66 hospitals in 17 countries (expanded to 189 sites in 24 countries) Patients randomised (block randomisation) 1:1 to pixantrone or treatment of physician's choice Randomisation stratified by:	***Intervention: pixantrone*** Pixantrone dimaleate was intravenously infused over 1 hour at a dose of 85 mg/m² (equivalent to 50 mg/m² of pixantrone in its base form) on days 1, 8, and 15 of a 28-day cycle, for up to six cycles. ***Comparator: physician's choice*** Treating physician's choice of single chemotherapeutic agent at prespecified standard doses and schedules. Treatment choice from: • Vinorelbine; • Oxaliplatin; • Ifosfamide; • Etoposide (intravenous); • Etoposide (oral); • Mitoxantrone; • Gemcitabine; • Rituximab.	Eligible patients were men or women: • aged 18 years and older; • aggressive *de novo* or transformed non-Hodgkin lymphoma (according to the Revised European–American Lymphoma and WHO classification); • relapse 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; • at least one objectively measurable lesion as demonstrated by CT, spiral CT, or MRI that could be followed for response as a target lesion; • life expectancy of at least 3 months; • Eastern Cooperative Oncology Group performance status of 2 or less; • measurable disease; • left-ventricular ejection fraction of ≥50% (measured by a	Main exclusion criteria were: • receipt of a cumulative dose of doxorubicin or equivalent of 450 mg/m²; • classification of New York Heart Association grade 3 or 4 cardiovascular abnormalities; • histological diagnosis of Burkitt's lymphoma, lymphoblastic lymphoma, or mantle-cell lymphoma; • active CNS lymphoma or HIV-related lymphoma; • receipt of chemotherapy, radiotherapy, or other anticancer treatment (including corticosteroids ≥10 mg/day of prednisone or equivalent) within the 2 weeks before randomisation	Patients were followed up for 18 months after last treatment for disease progression and survival. Primary endpoint: • proportion of patients who achieved a complete response or an unconfirmed complete response in the intention-to-treat population at end of treatment. Secondary endpoints: • proportion of patients who achieved an overall response (complete, unconfirmed complete, and partial response); • duration of progression-free survival; • duration of overall survival. Assessments were based on 1999 International Working Group criteria. Secondary analyses of response and survival endpoints was carried out that included prespecified analyses of

• region (North America vs Western Europe vs rest of world); • International Prognosis Index score (0 or 1 vs ≥2); • previous stem-cell transplantation (yes vs no). Due to poor accrual, recruitment stopped early. Study was designed to have at least 80% power to test the primary endpoint in the intention-to-treat population.		multiple-gated acquisition scan); • no persistent toxicities from previous therapy; • adequate bone marrow and organ function. Patients enrolled in countries where rituximab was given as standard of care and available at the patient's institution must have received rituximab in a prior regimen. Patients with non-Hodgkin lymphoma that had relapsed after stem-cell transplantation were eligible. Histology was assessed at each site's pathology laboratory. Central histological review before study entry was not carried out (deemed infeasible). Histology was retrospectively reviewed at a central laboratory, where a consensus from two of three pathologists was needed to verify aggressive non-Hodgkin lymphoma.		subgroup of patients with histologically confirmed disease (retrospectively confirmed by independent, central histological review).
Abbreviations used in table: CNS, central nervous system; HIV, human immunodeficiency virus; mg, milligram; vs, versus.				

Table 6. Summary of outcome definitions used in PIX301[18]

Outcome	Definition
Primary outcome	
CR/CRu	Proportion of patients with CR or CRu as assessed by the Independent Assessment Panel at the end of treatment Data on CR/CRu also reported at end of study (18 months' follow-up after end of treatment period)
	International Working Group criteria for CR (taken from Cheson et al.*[26])* • complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalisation of those biochemical abnormalities definitively assignable to NHL; • all lymph nodes and nodal masses must have regressed to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to <1 cm in their greatest transverse diameter after treatment, or by more than 75% in the SPD. • the spleen; if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size. • bone marrow; if positive at baseline, must be histologically negative for lymphoma.
	International Working Group criteria for CRu (taken from Cheson et al.*[26])* Those patients who fulfil criteria 1 and 3 for CR, but with one or more of the following features: • a residual lymph node mass >1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass; • indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypical).
Secondary outcomes	
OS	The time between the date of randomisation and the date of death due to any cause. Patients not known to have died at the time of analysis were 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
CR/CRu rate in histologically confirmed patients	As for CR/CRu but population is patients with diagnosis of aggressive NHL as determined retrospectively by a central laboratory
ORR 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

PFS	The time between the date of randomisation and the date of the initial documentation of progressive/relapsed disease or death due to any cause. The ERG notes that the full publication of PIX301 indicates that patients receiving a different treatment during follow-up were classified as having progressed, irrespective of whether disease progression had been confirmed radiologically. PFS for patients who were alive without disease progression at their date of last tumour assessment was censored at the date of last tumour assessment
Abbreviations used in table: CR, complete response; CRu, unconfirmed complete response; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SPD, sum of the products of the greatest diameters.	

4.2.1 Description of the PIX301 trial

Direct evidence on the clinical effectiveness of pixantrone in the treatment of multiply relapsed or refractory aggressive NHL is derived from a single RCT, the PIX301 trial. As highlighted in Section 3.1, although PIX301 enrolled patients with aggressive B-cell or T-cell NHLs, based on the conditional approval issued by the Committee for Medicinal Products for Human Use (CHMP),[17] the population of particular relevance to the decision problem is the subgroup of patients with aggressive B-cell NHLs.

Trial conduct

PIX301 was a multicentre (189 sites) parallel group, randomised Phase III trial carried out across 24 countries (initially 66 sites in 17 countries). Patients were randomised (1:1) to pixantrone or an active control of TPC. Randomisation occurred through a telephone interactive voice response system (IVRS) and was stratified by three factors: (i) region (North America vs Western Europe vs Rest of World); (ii) International Prognosis Index score at baseline (0 or 1 vs ≥2); and (iii) previous stem-cell transplantation (yes vs no). The ERG considers the method of randomisation to be robust.

Treating physicians and patients were not blinded to treatment allocation. However, final assessment of response was determined by an IAP comprising a radiologist, an oncologist, and a pathologist who were blinded to treatment allocation and to the PIX301 investigator's assessment of response. The PIX301 trial also incorporated an Independent Radiology Committee that reviewed computer tomography imaging of tumour response. The IAP subsequently reviewed all the assessments from the Independent Radiology Committee, together with relevant clinical, biochemical and pathological information, to determine response. If consensus among the IAP could not be reached on response assessment (i.e., 2 of 3 members did not agree), the lowest response was assigned.

Initially, it was planned that 320 patients would be recruited. Despite increasing the number of participating sites, slow accrual resulted in early closure of study enrolment, with only 140 patients randomised over a period of 4 years; the impact of lower than expected accrual on the power of the trial to detect a difference in CR/CRu is discussed in more detail in Section 4.2.2.

Patients were initially evaluated histologically for aggressive disease at the pathology laboratory of the individual participating sites. Subsequently, histology was retrospectively reviewed at a central laboratory, where consensus from two of three pathologists was required to confirm a diagnosis of aggressive NHL. Of the 140 patients randomised, 104 patients were subsequently confirmed to have aggressive NHL; it had been decided to cease enrolment once 100 patients with confirmed pathology had been randomised. Of the 36 patients without histological confirmation of disease, two patients were reviewed by only one pathologist, and six did not have a review because of shortage of specimen.[18] Reference pathologists agreed that 13 patients had low-grade histological features, and that five patients had a non-aggressive subtype other than NHL. The pathologists did not reach consensus on 10 patients. The manufacturer highlighted that a combination of the unstable nature of aggressive NHL and the urgent need for therapy in this patient group, together with the large number of participating sites, was judged to make it impractical to carry out central histological review before study entry. The ERG acknowledges the points raised by the manufacturer and considers retrospective histological review to be a pragmatic approach, but considers it important to evaluate data from the subgroup of patients with histologically confirmed disease. The ERG also considers it important to note that, as a subgroup analysis, the power of the study to detect a difference in CR/CRu between treatment groups in those with confirmed aggressive NHL will be diminished further, and results should be interpreted with a degree of caution. Moreover, patients with NHLs originating from T-cells were included in PIX301, albeit a small proportion (10%). Subtypes of NHL included in the classification of aggressive B-cell NHLs were DLBCL, transformed indolent lymphoma, and follicular lymphoma, grade III. The ERG's clinical expert commented that the grouping of the three subtypes of NHL as B-cell NHL was appropriate.

Pixantrone was administered intravenously at the recommended dose of 85 mg/m^2 (infused over an hour) on days 1, 8, and 15 of each 4-week cycle for up to 6 cycles.[18] In the TPC group, physicians had the choice of one agent from vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, or gemcitabine (only the USA) for up to 6 cycles. All treatments were given intravenously, with the additional option of administering etoposide orally. Treatments in the TPC group were administered using prespecified doses and schedules (summarised in Table 7), which were based on treatment regimens used in published studies. At sites in the USA, physicians could also choose to give rituximab to those patients who were identified as positive for expression of the CD20 protein; all mature B cells express the CD20 protein, as do cancerous B-cells. On completion of treatment, patients entered an 18-month follow-up period. In the ITT population, 18 patients in the pixantrone group and 27 patients in the TPC group did not enter the follow-up period. On request, the manufacturer clarified that most patients who did not continue into follow-up had died between the end of the last treatment visit and the first follow-up visit 2 months later (12/18 patients in the pixantrone group vs 20/27 patients in the TPC group).

Table 7. Treatment regimens of interventions available in the treatment of physician's choice group (adapted from MS; Table 13, pg 60)

Comparator	Dose	Cycle
Vinorelbine	30 mg/m²	Days 1, 8, 15, and 22 of each 4-week cycle
Oxaliplatin	100 mg/m²	Day 1 of each 3-week cycle
Ifosfamide	3,000 mg/m²	Days 1 and 2 of each 4-week cycle
Etoposide (intravenous)	100 mg/m²	Days 1, 2, 3, 4, and 5 of each 4-week cycle
Etoposide (oral)	50 mg/m²	Daily for 21 days of each 4-week cycle
Mitoxantrone	14 mg/m²	Day 1 of each 3-week cycle
Gemcitabine[a]	1,250 mg/m²	Days 1, 8, and 15 of each 4-week cycle
Rituximab (CD20+ patients only)[a]	375 mg/m²	Days 1, 8, and 15 of cycle 1 and day 1 of cycle 2, with a 3-week cycle length
[a] Available as a choice to physicians only in the USA. Abbreviations used in table: m, metre; mg, milligram; USA, United States of America.		

During the study period, patients were assessed on day 50 and day 106 ± 7 days after receipt of first study treatment and, where applicable, at discontinuation of treatment. During follow-up, patients who had a CR, CRu, PR or stable disease at the end of treatment were evaluated every 8 weeks ± 1 week until disease progression.

Of 140 patients randomised, 36 patients completed six cycles of protocol treatment, and 104 patients discontinued treatment early. The number of patients not completing the specified six cycles of treatment was similar in the two groups (32 patients in the pixantrone group vs 27 patients in the TPC group). In the histologically confirmed aggressive B-cell NHL subgroup, the median duration of treatment was 3.1 months in the pixantrone group compared with 1.9 months in the TPC group. A detailed breakdown of the proportion of people based on number of cycles received was provided by the manufacturer on request and is presented in Appendix 4. The most common reason for early discontinuation in both groups was disease progression or relapse. Of the 95 patients who entered the follow-up period at the end of treatment, 26 patients completed 18 months' follow-up (15 patients in the pixantrone group vs 11 patients in the TPC group).

Within the MS, the manufacturer highlights key amendments to the conduct of the trial and the planned analyses:[28]

- October 2004: inclusion criteria modified to state that patients must be sensitive to their last anthracycline/anthracenedione regimen;
- March 2005: gemcitabine and rituximab added as options for comparator treatments in the USA, and dosage specifications for oxaliplatin were removed. Follicular lymphoma grade III removed from eligible disease types;

- February 2006: statement 'with evidence of disease progression' added to inclusion criteria requiring relapse after two or more prior regimens and '(confirmed or unconfirmed PR or CR)' was added to inclusion criteria requiring prior response to anthracycline/anthracenedione;
- February 2006: expected accrual time extended from 12 months to 36 months to reflect lower than anticipated enrolment. In addition, 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;
- December 2006: secondary endpoint time to progression (TTP) changed to PFS;
- June 2007: follicular lymphoma (grade III) added to inclusion criteria.

In addition to the amendments highlighted by the manufacturer the ERG considers it important to highlight an additional revision that occurred in March 2005 "to clarify that eligible patients with CD20+ tumors had to have received rituximab in prior regimens if it was both available and the standard of care at their institution".[28] As the authors of the full publication of PIX301 identify, when the study was designed, rituximab was not available in all regions and was not the standard of care.[18] Thus, analyses based on prior rituximab treatment were not prespecified and as such are *post hoc* subgroup analyses.

Baseline characteristics for the full trial population are reasonably well balanced across the pixantrone and TPC groups in terms of age, subtypes of NHL, and key prognostic factors such as Ann Arbor Stage, International Prognostic Index (IPI) and Eastern Cooperative Oncology Group (ECOG) score (baseline characteristics provided in Appendix 5). As part of the clarification process, the ERG requested baseline characteristics for the subgroup of patients with histologically confirmed aggressive B-cell NHLs, which is the population the ERG considers to be of particular relevance to the decision problem. The manufacturer helpfully provided all data requested. Baseline characteristics in the specific subgroup of patients were also well balanced across treatment groups (Appendix 5).

The mean age of patients in the PIX301 trial was 58.2 years in the pixantrone group and 56.2 years in the TPC group; mean age was similar in the subgroup of patients with histologically confirmed aggressive B-cell NHL (59.6 years in the pixantrone group and 55.3 years in the TPC group). The population in the PIX301 trial is younger than patients with aggressive NHL typically seen in UK clinical practice. The ERG notes that a comparatively younger population than would be seen in clinical practice is characteristic of clinical trials. A larger proportion of patients was refractory (57% in the ITT population) to their last therapy and the mean time from last chemotherapy to randomisation was >13 months in the ITT population.

As noted earlier, DLBCL is the common subtype of aggressive B-cell NHL. Over 70% of patients randomised in PIX301 were diagnosed as having DLBCL (74%). As would be expected, the proportion of patients with DLBCL in the subgroup of patients with histologically confirmed B-cell

NHL was larger, increasing to 85%. Mean duration of NHL for patients in the PIX301 trial was 43.6 months in the pixantrone group and 46.6 months in the TPC group. In terms of prognostic factors in the full trial population, within the individual scoring systems, the largest proportion of patients had an: Ann Arbor Stage of III or IV (76%); IPI score of ≥2 (72%); and ECOG score of 1 (44%) or 0 (35%). About half of patients had undergone between 3 and 5 earlier rounds of chemotherapeutic treatment (55% of the full trial population and 51% of the histologically confirmed subgroup). All patients had previously been treated with an anthracycline/anthracenedione, whereas about only 50% of patients had prior treatment with a biologic (e.g., rituximab).

A key difference in patient baseline characteristics was highlighted by the manufacturer in that three patients in the pixantrone group had a history of congestive heart failure and two had continuing cardiomyopathy, whereas no patient in the TPC group had either disorder.

Blinding

As noted earlier, PIX301 is of an open-label design (i.e., patients and investigators were not blinded to treatment allocation). Given that physicians were able to choose from multiple treatments in the comparator group, which were of various doses and schedules, the ERG acknowledges that blinding of physicians would not have been possible. Evaluation of CR/CRu (the primary outcome) is dependent on subjective assessment of response according to set criteria, and, therefore, is open to bias. However, the ERG notes that the primary analysis of data is based on IAP review and that the IAP was blinded to treatment allocation. The ERG notes that the sponsor was blinded to treatment allocation until the end of treatment, when the database was locked for analysis.[18] PFS and OS were measured as secondary outcomes, both of which are less dependent on subjective assessment than CR/CRu.

Generalisability to UK clinical practice

Of the 140 patients randomised in PIX30l, only 7 (<0.1%) patients were recruited from the UK. Of the remaining 133 patients, 8 were recruited from North America, 31 from Western Europe and 94 from the Rest of World. As noted in Section 2, in UK clinical practice, rituximab added to a combination chemotherapeutic regimen is standard first-line treatment for aggressive B-cell NHL. To be eligible for enrolment in the PIX301 trial, patients living in a country where rituximab was available had to have received previous rituximab therapy (when their neoplastic cells expressed CD20). As a result of unequal enrolment across the three geographic regions, the largest proportion of patients was enrolled from the Rest of World (67%), and about only a third of those patients had received prior biologic therapy (37.2%); baseline characteristics of the Western Europe and Rest of World subgroups are presented in Appendix 6. Considering the baseline characteristics of the Western Europe subgroup, the CHMP highlighted that, compared with the Rest of World subgroup, patients

from Western Europe had more severe disease, being later stage patients with highly aggressive disease.[17] Patients in the Western Europe subgroup had been more heavily pretreated with multiple combination regimens (including rituximab), were more likely to have undergone autologous stem cell transplant (ASCT), had a shorter interval from the last treatment regimen, and have rapidly advancing disease (~50% of patients). The ERG's clinical expert indicated that the Western Europe subgroup could potentially have more severe disease than a patient who would typically be eligible for treatment with pixantrone in the UK. That is, compared with the Western Europe subgroup, patients in clinical practice in the UK might have received fewer lines of treatment before being considered eligible for treatment with pixantrone, with pixantrone given as a third-line treatment rather than fourth or fifth line treatment.

Considering the treatments given in the TPC group, the most common treatment chosen was oxaliplatin, followed by vinorelbine and ifosfamide (Table 8). The ERG notes that neither of the clinical experts consulted expressed a preference for use of oxaliplatin as a monotherapy for third and subsequent line treatment of aggressive NHL. However, as there is no consensus on treatment and no available data on comparative clinical effectiveness of treatments in this population, the ERG does not consider the choice of treatment in the TPC group to be a key issue. Moreover, the number of patients receiving each intervention in the TPC group is low, which would render the results of any subgroup analyses unreliable. For these reasons, the ERG did not request subgroup data based on pixantrone versus the individual treatments in the TPC group.

Table 8. Treatment received in the treatment of physician's choice group

Treatment	ITT	Histologically confirmed B-cell NHL subgroup[a]
	TPC (N = 67)	TPC (N = 47)
Vinorelbine	11 (16.4%)	10 (21.3%)
Oxaliplatin	30 (44.8%)	15 (31.9%)
Ifosfamide	12 (17.9%)	9 (19.1%)
Etoposide (intravenous)	4 (6.0%)	3 (6.4%)
Etoposide (oral)	5 (7.5%)	4 (8.5%)
Mitoxantrone	4 (6.0%)	3 (6.4%)
Gemcitabine	1 (1.5%)	1 (2.1%)
Rituximab	0	0
Not dosed	–	2 (4.3%)

[a] Data provided by manufacturer during clarification process.
Abbreviation used in table: TPC, treatment of physician's choice.

Based on the small proportion of patients receiving prior rituximab therapy, together with differences in baseline characteristics for Western Europe versus the Rest of World, the ERG has concerns around the generalisability of the results from the PIX301 trial to patients in the UK. As part of the

clarification process, the ERG requested data for the subgroup of patients who had histologically confirmed aggressive B-cell NHL and who had previously received rituximab as an element of their treatment. The potential influence of prior rituximab therapy on clinical effectiveness of pixantrone is discussed in more detail in Section 4.3.2. The ERG also requested data for the subgroup of patients from Western Europe, but, given the small number of events and patients in this subgroup, the ERG emphasises that these data are unlikely to provide a robust estimate of comparative clinical effectiveness.

4.2.2 Description and critique of manufacturer's outcome selection

The CHMP assessment report stated that evaluation of CR/CRu as a primary outcome in a single Phase III trial was deemed to be inappropriate, and that PFS or OS would have been more suitable primary measures of clinical effectiveness of pixantrone.[17] However, the CHMP report also stated that, because of the clinical benefit associated with pixantrone, the use of CR/CRu as the primary measure of effectiveness was not of major concern.

In the PIX301 trial, CR/CRu was determined as per response criteria outlined by the International Working Group (IWG) (summarised in Table 6).[26] The ERG notes that assignment of CR/CRu based on the original IWG criteria (implemented in the PIX301 trial) was dependent on physical examination. A marked variability across clinicians in interpretation of CR/CRu based on these criteria has been observed.[27] In addition, it has been acknowledged that CRu is open to misinterpretation, with partial responses (PRs) frequently designated as CRu.[27;38] Advances in available technology and recognition of the limitations of the original criteria prompted revision of the recommendations, with the revisions published in 2007.[27] As noted earlier, the updated response criteria introduced the use of positron emission tomography (PET), a technique that facilitates differentiation of CR from PR, thus rendering the outcome of CRu redundant.[27] PIX301 was initiated in 2004, before adoption of the revised criteria, and thus evaluation of CR/CRu was based on the original criteria.[26] After publication of the revised guidelines, the manufacturer provided additional clarification to radiologists on criteria for target and non-target lesions, which the manufacturer reports were in alignment with the revised IWG criteria.[18] Target lesions were required to be 1.5 cm or larger in both perpendicular directions. In agreement with the 1999 IWG criteria, lesions of 1.1–1.5 cm were classified as non-target lesions. To identify a new lesion as a sign of progressive disease, the new lesion had to be 1.5 cm or larger; no clear minimum requirement was cited in the 1999 IWG criteria, although the manufacturer indicates that a size of 1.5 cm or larger is inferred. The ERG has been advised by a clinical expert that not all clinical practices across the UK would have access to a PET scanner, and that the costs associated with this technology might prohibit its wide spread use. The ERG recognises that PIX301 was started before recommended use of PET in evaluating response in NHL, and that the manufacturer took steps to align evaluation of CR/CRu with the revised criteria.

However, because it is widely accepted that PR is frequently classified as CRu, the ERG considers that clinical effectiveness results based on this subjective outcome should be interpreted with caution.

As the manufacturer recognises, OS is widely accepted as the most robust outcome in cancer clinical trials.[29] The prognosis of patients with multiply relapsed or refractory aggressive NHL is poor, which is underscored by survival data from the PIX301 trial. Median OS in the full population of the PIX301 trial was 10.2 (95% Confidence Interval [CI] 6.4 to 15.7) months in the pixantrone group and 7.6 (95% CI 5.4 to 9.3) months in the TPC group. Given that median OS in both groups was less than 12 months, and it was planned that patients would enter an 18-month follow-up period after end of treatment, the ERG considers that it could have been more appropriate to evaluate OS or PFS as the primary outcome.

Within the MS, results are presented from an exploratory analysis carried out by the manufacturer to investigate the use of CR as a potential surrogate of OS. The manufacturer based their analysis on an analysis carried out by Lee *et al*.,[30] who evaluated correlation of the outcomes of CR, PFS, OS and other time to event outcomes in untreated aggressive and indolent NHL. In brief, the manufacturer reports that Lee *et al*.[30] analysed data from 38 RCTs in untreated aggressive NHL and identified a moderate correlation between CR and both 3-year and 5-year OS in NHL: correlation coefficient of 0.58 (95% CI 0.29 to 0.77) and 0.50 (95% CI 0.23 to 0.74) on 3-year and 5-year OS, respectively. The manufacturer goes on to highlight that 3-year PFS was strongly correlated with OS in aggressive NHL. Using a linear regression analysis, Lee *et al*.[30] observed that a 10% improvement in CR corresponded to a 9% ± 1% improvement in 3-year event free survival (EFS) (not PFS as reported by the manufacturer) and also that a 10% improvement in EFS or PFS (not solely PFS as reported by the manufacturer) predicted a 7% improvement in 5-year OS. The authors comment that there was no relationship between CR and 5-year OS in aggressive NHL, but that 3-year PFS as a potential surrogate warrants further investigation.[30] Based on the analysis by Lee *et al*.,[30] the manufacturer evaluated CR as a predictor of clinical benefit for OS in multiply relapsed or refractory aggressive NHL. Based on 3 RCTs and 9 single arm studies, the manufacturer carried out a correlation and linear regression analysis. Regression analysis of the 3 RCTs showed a trend towards a correlation (r^2 = 0.99, p = 0.07) between CR and 3-year OS. However, as the manufacturer acknowledges, this analysis was likely to be underpowered and is not statistically significant. The manufacturer states that evidence from the single arm studies identified a strong and statistically significant correlation between CR and OS (r^2 = 0.81, p <0.001). The ERG does not agree with the manufacturer's assertion that the results from the manufacturer's analysis in relapsed/refractory aggressive NHL, when taken with those of Lee *et al*.[30], "provide evidence for the relationship between CR and OS and the appropriate use of CR as a surrogate measure in aggressive NHL studies".

PFS, as defined in the PIX301 trial, includes treatment switch during follow-up as a progressive event; that is, patients who received an alternative treatment during follow-up were classified as having progressed, irrespective of whether disease progression had been confirmed radiologically. The ERG notes, as does the manufacturer, that PFS is typically defined as time from randomisation to first event of disease progression or death. Results of an analysis for the primary outcome of CR/CRu in the full trial population and censoring for patients who receive a different treatment during follow-up are provided in the CSR for the PIX301 trial (discussed in more detail in Section 4.3.1).[28]

Within the MS, the manufacturer presents results for the primary and secondary outcomes in the full trial population (ITT population) and the subgroup of patients with retrospectively histologically confirmed aggressive NHL (HITT). Only the analysis of CR/CRu in the HITT was prespecified. All other analyses in the HITT are *post hoc* analyses. Based on the conditional approval adopted by the CHMP, the ERG requested data in the subgroup of patients with histologically confirmed aggressive B-cell NHL, which are also *post hoc* analyses.

HRQoL data were not collected during PIX301.

4.2.3 Description and critique of statistical approach used

The MS presents a brief overview of the statistical approaches used in the PIX301 trial. Based on the description of the statistical analysis plan reported in the CSR, the ERG considers the manufacturer's statistical approach to be generally appropriate.[28] The primary endpoint was the proportion of patients achieving CR/CRu at the end of treatment in the ITT population. Database cut-off for the analysis at the end of treatment was after the last patient had completed the end-of-treatment visit. The sponsor was masked to the treatment assignment until the end of treatment, when the database was locked for analysis. The manufacturer also analysed data at the end of the study.

Two populations were prespecified:

- ITT: all randomised patients;
- histologically confirmed ITT; all randomised patients with histologically confirmed aggressive NHL as assigned by retrospective independent central pathology assessment.

The PIX301 trial was designed to have 80% power to detect a 10% difference in the proportion of patients achieving CR/CRu between pixantrone and TPC in the ITT population with a sample size of 160 patients in each group, and assuming CR/CRu response rates of 15% and 5% in the pixantrone and TPC groups, respectively.[28] Additionally, the study was designed to be powered for the evaluation of difference between groups in CR/CRu in the HITT population and for overall survival in the ITT population.[28] As discussed earlier, as a result of slow accrual, only 140 patients were randomised. Within the MS, the manufacturer states that, with inclusion 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". More detail is provided in the full publication of the PIX301 trial, where it is stated that "according to original sample size assumptions, a sample size of 70 in each group would have about 40% power. 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".[18]

Analyses of clinical efficacy endpoints were prespecified for the ITT and HITT populations. The ERG notes that the results of various *post hoc* subgroup analyses are reported in the MS, including analysis of data in the subgroup of patients classified as having aggressive B-cell NHL, previous treatment with rituximab versus no prior treatment, and ASCT versus no ASCT.

The submitted clinical evidence for pixantrone versus TPC is derived from a single trial, the PIX301 trial,[18] which was the sole study identified by the manufacturer evaluating the effects of pixantrone in the treatment of multiply relapsed or refractory aggressive NHL. Therefore, no meta-analysis or indirect comparison was carried out by the manufacturer.

4.2.4 Summary statement

The ERG considers that the manufacturer's systematic review of the literature followed recommended methodological practices. Although the ERG considers the submitted search to be out of date (over 12 months between the date of the search and submission of the manufacturer's report), the ERG considers it likely that the trial identified by the manufacturer is the only available direct evidence relevant to the decision problem. The submitted clinical evidence is derived from a single, multicentre open-label trial (PIX301[18]), the validity and quality of which was appropriately discussed by the manufacturer. The ERG noted that the manufacturer's search was carried out before full publication of results from the PIX301 trial.[18]

The primary objective of the PIX301 trial was to assess the comparative clinical effectiveness of pixantrone versus various single chemotherapeutic agents (TPC) as evaluated by the difference between groups in the proportion of patients achieving CR/CRu at the end of treatment in the ITT population. With the exception of HRQoL, which was not collected in PIX301, the outcomes assessed in the trial and presented in the MS are clinically relevant and address the decision problem as outlined in the final scope issued by NICE.[21] The internationally accepted criteria used to assign CR/CRu in NHL were updated after the initiation of PIX301. The revised criteria rendered the outcome of CRu redundant. The ERG appreciates that the manufacturer implemented additional guidance to radiologists to ensure consistency in measurement of the primary outcome, but considers that the outcome of CR/CRu has been identified to be an inconsistent measure of clinical effectiveness. Although the summary report issued by the CHMP states that use of CR/CRu was not a key concern, the CHMP deemed that PFS or OS would have been a more appropriate measure of

clinical benefit. In addition, as a result of slow accrual, fewer than intended patients were enrolled and randomised: 140 patients were randomised of a target sample size of 320 patients. The manufacturer calculated that, with 140 patients, the PIX301 trial was sufficiently powered (81%) to detect a difference between pixantrone and TPC in CR/CRu in the ITT population at the end of treatment. However, the full publication of the PIX301 trial indicates that "according to original sample size assumptions, a sample size of 70 in each group would have about 40% power".[18]

In PIX301, histology was initially evaluated at individual participating sites, followed by retrospective central histological review. Of the 140 patients randomised, only 104 patients were subsequently histologically confirmed to have aggressive NHL (HITT population). Analyses of the clinical endpoints in the HITT population were prespecified and the ERG considers that, of the ITT and HITT populations, results for the HITT population are more relevant to the decision problem. Moreover, the power of the study to identify a difference between treatments groups would be further diminished in subgroup analysis, and the ERG considers it likely that the study is underpowered to detect a difference between groups in CR/CRu in the HITT population.

Typical clinical practice in the UK and other Western European countries is to administer rituximab in combination with anthracycline-based chemotherapeutic regimens (typically CHOP) as a first-line treatment for aggressive NHL. Of the 140 patients enrolled, only 38 patients were from Western Europe, with only 7 patients enrolled from the UK. As noted earlier, a large proportion of patients (62.8%) enrolled from locations outside Western Europe had not received rituximab as part of a previous chemotherapeutic regimen. For these reasons, the ERG has concerns around the generalisability of the results from the ITT and HITT analyses to patients in the UK. As part of the clarification process, the ERG requested data for *post hoc* subgroup analyses based on prior rituximab treatment and for the Western Europe region for patients with histologically confirmed aggressive B-cell NHL. Despite randomisation being stratified by geographic location, the ERG stresses that, as *post hoc* subgroup analyses, results should be interpreted with caution.

4.3 Summary of submitted evidence

As discussed earlier, the primary efficacy outcome of the PIX301 trial was the proportion of patients achieving CR/CRu at the end of treatment in the ITT population as determined by an IAP and based on criteria set out by the IWG. Secondary outcomes analysed were PFS, OS, ORR lasting at least 4 months, and CR/CRu in the subgroup of patients with histologically confirmed aggressive NHL as determined retrospectively by a central panel (HITT population).

Within the MS, the manufacturer reported fully data and statistical analyses for the analysis of all outcomes in the ITT population. In addition, based on the conditional approval adopted by the CHMP,[17] the manufacturer provided results on clinical efficacy outcomes in the subgroup of patients

with aggressive B-cell NHL (defined as DLBCL, transformed indolent lymphoma, and follicular lymphoma, grade III) and the subgroup of patients with DLBCL, neither of which was prespecified in the protocol for PIX301.[28] The manufacturer did not present results for the HITT population. However, data on clinical effectiveness for the HITT population are available in the full publication,[18] the CSR,[28] and the CHMP summary report relating to PIX301 trial.[17] The ERG appreciates the manufacturer's rationale for presenting analyses for subgroups of patients with aggressive B-cell NHL, but considers that results for patients with histologically confirmed aggressive NHL, that is the HITT and the histologically confirmed aggressive B-cell NHL subgroups, to be more appropriate. The ERG recognises that only 10% of patients were classified as having T-cell-derived NHL at baseline, and, thus, the ERG anticipates similar results for the HITT and histologically confirmed aggressive B-cell NHL populations. On request, the manufacturer helpfully provided all data requested for the subgroup of patients with histologically confirmed aggressive B-cell NHL. The ERG emphasises that data for this population are from a *post hoc* subgroup that is likely to be underpowered to identify a difference between groups and as such should be interpreted with caution. For completeness, in the sections that follow, results from the ITT, HITT and histologically confirmed aggressive B-cell NHL populations are presented together.

4.3.1 Summary of clinical effectiveness results from the PIX301 trial

Primary outcome: complete response and unconfirmed complete response

In the subgroup of patients with histologically confirmed B-cell NHL, although a larger proportion of patients achieved CR/CRu at the end of treatment with pixantrone compared with TPC (16.0% with pixantrone vs 6.4% with TPC; Table 9), the difference between groups did not reach statistical significance ($p = 0.202$). The results for this *post hoc* subgroup analysis are supported by results for the prespecified analyses in the ITT and HITT populations (Table 9). In each analysis, a larger proportion of patients in the pixantrone group achieved CR/CRu at the end of treatment, but the difference between groups did not reach statistical significance. Given that the updated IWG criteria for definition of response no longer include CRu,[27] the ERG considers it noteworthy that no patients in the TPC group in either the ITT or the histologically confirmed B-cell NHL subgroup achieved CR. However, the revised guidelines also recommend the use of PET, which was not implemented in PIX301.

At the end of the study, results in the histologically confirmed B-cell NHL and HITT populations are consistent with those observed at end of treatment. By contrast, in the ITT population, the difference between pixantrone and TPC in the proportion of patients achieving CR/CRu at the end of the study was statistically significant in favour of pixantrone ($p = 0.009$). As noted earlier, the ITT population includes patients with indolent NHL and with non-specified aggressive NHL, and, therefore, the ERG considers the results from this analysis not to be the most relevant to the decision problem.

The primary analysis of CR/CRu was based on evaluation of response by an IAP. Sensitivity analysis included evaluation of response by PIX301 investigators. Results based on investigator response assessment were in agreement with the primary analysis, with a larger proportion of patients achieving CR/CRu at both end of treatment and end of study assessment points, but with no statistically significant difference between the groups in either analysis.

The ERG considers it important to reiterate guidance from the CHMP relating to evaluation of an intervention against a comparator such as TPC that "superior efficacy has to be shown versus the pooled results in the reference arm".[25] The difference between groups in most analyses of CR/CRu does not reach statistical significance, but results of the analyses in the histologically confirmed subgroups should be interpreted with caution as they are likely to be underpowered to detect a difference between treatment groups. As noted earlier, the manufacturer's revised power calculation indicated that, to achieve 81% power with 70 patients per group (the ITT population), the true proportion of patients with CR/CRu would have to have been 22% in the pixantrone group and 5% in the TPC group. The observed proportions of patients achieving CR/CRu in the ITT population were 20.0% and 5.7% in the pixantrone and TPC groups, respectively. Taken as whole, the ERG has reservations as to whether superior efficacy of pixantrone has been demonstrated.

As discussed in Section 4.2, the ERG has concerns around the generalisability of the results of the subgroups with retrospective histological confirmation of aggressive NHL, as well the ITT population, to UK patients. A considerable proportion of patients in PIX301 had not received rituximab as part of a previous chemotherapeutic regimen, which is standard care in the UK. Moreover, only a small proportion of patients was enrolled from Western Europe. Both of these factors were discussed by the CHMP in the evaluation of the PIX301 trial.[17] Subgroup analyses based on prior rituximab treatment and region (Western Europe) are described in Section 4.3.2.

Table 9. Results of pixantrone versus TPC for the proportion of patients achieving CR/CRu at the end of treatment and at the end of study

Outcome	ITT			HITT			Histologically confirmed aggressive B-cell NHL[a]		
	Pixantrone (N = 70)	TPC (N = 70)	p value	Pixantrone (N = 54)	TPC (N = 50)	p value	Pixantrone (N = 50)	TPC (N = 47)	p value
CR/CRu at end of treatment (primary outcome)									
CR/CRu	14 (20%) (11.4% to 31.3%)	4 (5.7%) (1.6% to 14.0%)	0.021	9 (16.7%) (7.9% to 29.3%)	3 (6.0%) (1.3% to 16.5%)	0.126	8 (16.0%)	3 (6.4%)	0.202
CR	8 (11.4%) (5.1% to 21.3%)	0 (0%) (0.0% to 5.1%)	0.006	–	–	–	6 (12.0%)	0 (0%)	0.027
CRu	6 (8.6%) (3.2% to 17.7%)	4 (5.7%) (1.6% to 14.0%)	0.075	–	–	–	2 (4.0%)	3 (6.4%)	0.671
CR/CRu at end of treatment (sensitivity analysis): PIX301 investigator assessment[17]									
CR/CRu	12 (17.1%) (9.2% to 28.0%)	4 (5.7%) (1.6% to 14.0%)	0.060	–	–	–	–	–	–
CR/CRu at end of study									
CR/CRu	17 (24.3%) (14.8% to 36.0%)	5 (7.1%) (2.4% to 15.9%)	0.009	10 (18.5%) (9.3% to 31.4%)	4 (8.0%) (2.2% to 19.2%)	0.154	9 (18.0%)	4 (8.5%)	0.236
CR	11 (15.7%) (8.1% to 26.4%)	0 (0%) (0% to 5.1%)	0.001	–	–	–	7 (14.0%)	0 (0%)	0.013
CRu	6 (8.6%) (3.2% to 17.7%)	5 (7.1%) (2.4% to 15.9%)	1.000	–	–	–	2 (4.0%)	4 (8.5%)	0.426
CR/CRu at end of study: (sensitivity analysis): PIX301 investigator assessment[17]									
CR/CRu	15 (21.4%) (12.5% to 32.9%)	6 (8.6%) (3.2% to 17.7%)	0.056	–	–	–	–	–	–

[a] Data provided by manufacturer during clarification process.

Abbreviations used in table: CR, complete response; CRu, unconfirmed complete response; HITT, patients in ITT population with retrospective histological confirmation of aggressive NHL; ITT, intention-to-treat; NHL, non-Hodgkin's lymphoma; TPC, treatment of physician's choice.

Secondary outcomes

Overall survival

In the subgroup of patients with histologically confirmed B-cell NHL, there was no statistically significant difference between pixantrone and TPC in median OS (HR 0.72: 95% Confidence Interval [CI]; 0.45 to 1.13; Table 10). Median OS in the pixantrone group was 8.1 months compared with 6.3 months in the TPC group. The results from the primary analysis in the ITT population and the analysis in the HITT population are analogous to those in the *post hoc* subgroup analysis of patients with histologically confirmed B-cell NHL (Table 10). On request, the manufacturer provided an estimate of the mean OS for the ITT population. The manufacturer reported that 14 patients from the pixantrone group and eight patients from the TPC group were censored as still alive at the end of the follow-up period of the PIX301 trial. To enable the estimation of the mean, it was necessary to extrapolate data beyond the trial period. The manufacturer fitted Kaplan–Meier data with parametric distributions. Of the distributions, the log-normal provided the best and the most clinically reasonable fit. Mean OS in the ITT population was 28.6 (SD 7.1) months and 20.0 (SD 4.7) months in the pixantrone and TPC groups, respectively. Estimates of mean OS in the subgroup of patients with histologically confirmed aggressive B-cell NHL were 11.3 (SD 8.80) months in the pixantrone group and 8.9 (SD 7.91) months in the TPC group (reported as "end of study"). The ERG notes that the estimated mean OS in the ITT population is considerably longer than the median OS. As noted earlier, the ITT population includes 36 patients who were subsequently identified by central histological review as not having aggressive NHL, and who, therefore, might have longer OS than patients in the HITT population and as a result mean OS may be overestimated in the ITT population. During clarification, the ERG also requested data on mean OS in the HITT population. In the response to the question, the manufacturer seemed to provide data for the histologically-confirmed aggressive B-cell NHL subgroup rather than the HITT (includes T-cell NHL). Extrapolation of data in patients with histologically confirmed aggressive B-cell NHL generated a mean OS gain of 7.2 (SD 7.4) months with pixantrone (mean OS [SD]: 22.6 [6.2] months with pixantrone vs 15.2 [4.1] months with TPC), but the ERG notes that the difference between treatment groups is not statistically significant.

It is widely accepted that OS data can be confounded by administration of post-progression treatments. On request, the manufacturer provided a breakdown of post-progression treatments given to the two groups of the PIX301 trial. The ERG notes that the proportion of patients receiving an antineoplastic agent (including etoposide, cisplatin, carboplatin) was similar across the pixantrone and TPC groups in both the histologically confirmed aggressive B-cell NHL and ITT populations. Kaplan–Meier plots for OS are presented in Appendix 7.

Table 10. Results of pixantrone versus TPC for overall survival

Overall survival	Pixantrone	TPC	HR (95% CI)
ITT			
	N = 70	**N = 70**	
Number of events	47 (67%)	52 (74%)	–
Median, months	10.2 (6.4 to 15.7)[b]	7.6 (5.4 to 9.3)[b]	0.79 (0.53 to 1.18)
Mean (SD), months[a]	28.6 (7.1)	20.0 (4.7)	–
HITT[18;28]			
	N = 54	**N = 50**	
Number of events	40 (74%)	42 (84%)	–
Median, months	7.5 (5.7 to 14.5)[b]	6.2 (4.1 to 8.2)[b]	0.74 (0.48 to 1.14)
Mean (SD), months[a]	–	–	–
Histologically confirmed aggressive B-cell NHL[a]			
	N = 50	**N = 47**	
Number of events	–	–	–
Median, months	8.1 (0.8 to 24.0)[c]	6.3 (0.1 to 24.0)[c]	0.72 (0.45 to 1.13)
Mean (SD), months (end of study)[a]	11.3 (8.80)	8.9 (7.91)	–
Mean (SD), months (extrapolated)[a]	22.6 (6.2)	15.2 (4.1)	–

[a] Data provided by manufacturer during clarification process.

[b] 95% CI.

[c] Range.

Abbreviations used in table: CI, confidence interval; HITT, patients in ITT population with retrospective histological confirmation of aggressive NHL; HR, hazard ratio; ITT, intention-to-treat; NHL, non-Hodgkin's lymphoma; SD, standard deviation; TPC, treatment of physician's choice.

Progression-free survival

In contrast to OS, analyses of median PFS based on IAP evaluation were statistically significant, with significantly longer PFS in the pixantrone group in all data sets (Table 11). In patients with histologically confirmed aggressive B-cell NHL, median PFS in the pixantrone group was 5.6 months compared with 2.5 months in the TPC group (HR 0.51; 95% CI: 0.33 to 0.78). On request, the manufacturer estimated mean PFS for this subgroup to be 7.7 (SD 7.75) months and 3.7 (SD 4.10) months in the pixantrone and TPC groups, respectively, at the end of the study. Based on extrapolation of data, the manufacturer estimated mean PFS in the ITT population to be 14.9 (SD 3.8) months and 6.6 (SD 1.4) months in the pixantrone and TPC groups, respectively. For the ITT population, mean PFS is substantially longer than median PFS (Table 11). Supporting analysis of PFS based on PIX301 investigator assessment in the ITT population (not reported by the manufacturer) was in accord with the analysis based on evaluation by the IAP (investigator analysis of median PFS:

4.2 months in the pixantrone group vs 2.6 months in the TPC group; HR 0.64; 95% CI: 0.45 to 0.92).[17;28]

As noted earlier, PFS in PIX301 included change in treatment without radiological confirmation of progression as a progressive event. The ERG notes that, as there is no radiological confirmation, these patients will not have undergone assessment by the Independent Radiological Committee. The CSR for the PIX301 trial presents two sensitivity analyses of PFS censoring for patients who changed treatment without radiological confirmation of disease progression. In the first sensitivity analysis (labelled in the CSR as "FU chemo ignored"), patients with no disease progression but who started additional treatment for NHL were censored.[28] In the second sensitivity analysis (labelled in the CSR as "FU chemo censored"), patients were censored who: did not have disease progression but who started additional NHL treatment; did not have disease progression, but commenced additional chemotherapy and died a month later; and started additional chemotherapy and had disease progression a month later.[28] The "ignored" and the "censored" sensitivity analyses support the findings from analysis of PFS for the ITT population (Table 12). The ERG does not consider inclusion of patients who initiate a different treatment during follow-up to have a considerable impact on PFS results. Kaplan–Meier plots for PFS are presented in Appendix 8.

Table 11. Results of pixantrone versus TPC for progression-free survival

PFS	**Pixantrone**	**TPC**	**HR (95% CI)**
ITT			
	N = 70	**N = 70**	
Number of events	58 (83%)	64 (91%)	–
Median, months	5.3 (2.3 to 6.2)[b]	2.6 (1.9 to 3.5)[b]	0.60 (0.42 to 0.82)
Mean (SD), months[a]	14.9 (3.8)	6.6 (1.4)	–
***HITT*[18;28]**			
	N = 54	**N = 50**	
Number of events	47 (87%)	48 (96%)	–
Median, months	5.0 (2.3 to 6.1)[b]	2.6 (1.9 to 3.4)[b]	0.54 (0.36 to 0.82)
Mean (SD), months[a]	–	–	–

Histologically confirmed aggressive B-cell NHL[a]			
	N = 50	**N = 47**	
Number of events	–	–	–
Median, months	5.6 (0.7 to 24.0)[c]	2.5 (0.0 to 24.0)[c]	0.51 (0.33 to 0.78)
Mean (SD), months (end of study)[a]	7.7 (7.75)	3.7 (4.10)	–
Mean (SD), months (extrapolated)[a]	14.3 (3.6)	5.2 (1.2)	–

[a] Data provided by manufacturer during clarification process.

[b] 95% CI.

[c] Range.

Abbreviations used in table: CI, confidence interval; HITT, patients in ITT population with retrospective histological confirmation of NHL; HR, hazard ratio; ITT, intention-to-treat; NHL, non-Hodgkin's lymphoma; SD, standard deviation; TPC, treatment of physician's choice.

Table 12. Results of sensitivity analyses for progression-free survival, censoring for patients who commenced a different treatment during the follow-up period

PFS	**Ignored**		**Censored**	
	Pixantrone (N = 70)	**TPC (N = 70)**	**Pixantrone (N = 70)**	**TPC (N = 70)**
Number of events, n (%)	55 (79%)	60 (86%)	45 (64%)	51 (73%)
Median PFS, months (95% CI)	5.7 (2.9 to 9.0)	3.4 (2.1 to 4.2)	5.8 (3.3 to 10.3)	3.4 (2.1 to 4.2)
HR (95% CI)	0.62 (0.43 to 0.90)		0.58 (0.39 to 0.88)	

Abbreviations used in table: CI, confidence interval; PFS, progression-free survival; TPC, treatment of physician's choice.

Overall response rate and duration of response

In the MS, the manufacturer presents various assessments of response to treatment (summarised in Table 13). In the subgroup of patients with histologically confirmed aggressive B-cell NHL, there was no statistically significant difference between pixantrone and TPC in the proportion of patients achieving an ORR at the end of treatment (34% in the pixantrone group vs 17.0% in the TPC group; p = 0.066; Table 13). However, at the end of the study, the difference between groups reached statistical significance and favoured pixantrone (36% in the pixantrone group vs 17.0% in the TPC group; p = 0.041). The ERG notes that the shift in statistical significance was based on one additional patient achieving CR in the pixantrone group by the end of the study, which the ERG considers underscores that the results of this *post hoc* subgroup analyses should be interpreted with caution. Guidance from the US Food and Drug Administration (FDA) states that, when complete and partial responses are combined, ORR is a direct measure of antitumor activity of a drug.[(29)] Based on this guidance, results for ORR suggest that pixantrone has greater antitumour activity than the various chemotherapeutic

agents available in the TPC group. The FDA guidance also stresses that clinical benefit in tumour response is not necessarily associated with benefit in OS.[29]

In the subgroup of patients with histologically confirmed aggressive B-cell NHL, analysis of duration of response (CR/CRu) found no statistically significant difference between pixantrone and TPC in the median duration of response (HR 0.64; 95% CI: 0.26 to 1.56), and no statistically significant difference in the proportion of patients who achieved a response that lasted 4 months or longer (p = 0.526). Moreover, there was no statistically significant difference between groups in the median time to response, based on analysis of CR plus CRu (HR 3.15; 95% CI: 0.82 to 12.1) or of the combination of CR, CRu, and PR (HR 0.56; 95% CI: 0.23 to 1.36). Median time to response was shorter for pixantrone than for TPC in the analysis of CR/CRu but longer than that for TPC when time to PR was included (Table 13). The ERG notes that the number of patients achieving any type of response in the TPC group at end of treatment and end of study in all data sets was low (8–10), and, therefore, the results of the analyses of duration of and time to response should be interpreted with caution.

Analyses of outcomes of response to treatment in the ITT population and HITT population are predominantly in accord with those for the histologically confirmed aggressive B-cell NHL subgroup. The key difference noted by the ERG is that, in both the ITT and HITT populations, the difference between pixantrone and TPC in ORR at the end of treatment is statistically significant and favours pixantrone. In all analyses of ORR, the key driver of clinical effectiveness is the number of patients achieving CR in the pixantrone group as no patient achieved CR in the TPC group.

Table 13. Results of pixantrone versus TPC for overall response rate, time to response, and duration of response

Outcome	ITT			HITT[18;28]			Histologically confirmed aggressive B-cell NHL[a]		
	Pixantrone (N = 70)	TPC (N = 70)	p value or HR (95% CI)	Pixantrone (N = 54)	TPC (N = 50)	p value or HR (95% CI)	Pixantrone (N = 50)	TPC (N = 47)	p value or HR (95% CI)
ORR (end of treatment)									
ORR	26 (37.1%)	10 (14.3%)	0.003	18 (33.3%)	8 (16.0%)	0.045	17 (34.0%)	8 (17.0%)	0.066
CR	8 (11.4%)	0 (0%)	0.006	6 (11.1%)	0 (0%)	0.027	6 (12.0%)	0 (0%)	0.027
CRu	6 (8.6%)	4 (5.7%)	0.745	3 (5.6%)	3 (6.0%)	1.000	2 (4.0%)	3 (6.3%)	0.671
PR	12 (20.0%)	6 (8.6%)	0.206	9 (16.7%)	5 (10.0%)	0.395	9 (18%)	5 (10.6%)	0.391
ORR (end of study)									
ORR	28 (40.0%)	10 (14.3%)	0.001	19 (35.2%)	8 (16.0%)	0.043	18 (36.0%)	8 (17.0%)	0.041
CR	11 (15.7%)	0 (0%)	<0.001	7 (13.0%)	0 (0%)	0.013	7 (14.0%)	0	0.013
CRu	6 (8.6%)	5 (7.1%)	1.000	3 (5.6%)	4 (8.0%)	0.708	2 (4.0%)	4 (8.5%)	0.426
PR	11 (15.7%)	5 (7.1%)	0.183	9 (16.7%)	4 (8.0%)	0.240	9 (18.0%)	4 (8.5%)	0.236
Proportion of patients achieving a response (CR/CRu/PR) lasting ≥4 months (end of study)									
CR/CRu/PR	12 (17.1%)	6 (8.6%)	0.206	–	–	–	7 (14.0%)	4 (8.5%)	0.526
Time to response									
Median time to CR/CRu/PR, months	1.9 (1.8 to 2.3)[b]	1.9 (1.6 to 2.3)[b]	0.68 (0.32 to 1.43)	–	–	–	2.0 (1.6 to 8.2)[c]	1.9 (1.6 to 2.8)[c]	0.56 (0.23 to 1.36)
Median time to CR/CRu, months	2.0 (1.7 to 3.7)[b]	3.6 (2.3 to 19.0)[b]	1.92 (0.64 to 5.77)	–	–	–	2.0 (1.6 to 8.2)[c]	3.7 (2.3 to 19.0)[c]	3.15 (0.82 to 12.1)
Duration of CR/CRu									
Median duration of response, months	9.6 (4.0 to 20.8)[b]	4.0 (1.0 to 5.1)[b]	0.32 (0.09 to 1.23)	–	–	–	5.2 (2.1 to 22.5)[c]	3.3 (0.0 to 22.2)[c]	0.64 (0.26 to 1.56)

[a] Data provided by manufacturer during clarification process. [b] 95% CI. [c] Range.

Abbreviations used in table: CI, confidence interval; CR, complete response, CRu, unconfirmed complete response; HITT, patients in ITT population with retrospective histological confirmation of NHL; HR, hazard ratio; ITT, intention-to-treat; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; PR, partial response; SD, standard deviation; TPC, treatment of physician's choice.

4.3.2 Subgroup analysis

The final scope issued by NICE specified no subgroups of interest.[21] In the MS, the manufacturer presents results for the subgroup of patients with aggressive B-cell NHL (defined as DLBCL, transformed indolent lymphoma, and follicular lymphoma, grade III) and of patients with DLBCL. The two subgroups presented by the manufacturer were not prespecified in the protocol and include patients without retrospective histological confirmation of aggressive NHL. As discussed earlier, the ERG considers data from the *post hoc* subgroup of patients with histologically confirmed aggressive B-cell NHL to be more relevant to the decision problem and, therefore, the ERG decided against presenting the results of the manufacturer's subgroup analyses in full. In brief, 91.4% of patients (64 patients) in the pixantrone group and 88.6% (62 patients) in the TPC group had aggressive B-cell NHL. For the primary outcome of proportion of patients achieving CR/CRu at the end of treatment, the difference between groups was statistically significant and favoured pixantrone (15/64 [23.4%] in the pixantrone group vs 5/62 [8.1%] in the TPC group; p = 0.027). Median PFS was significantly prolonged in the pixantrone group (5.7 months in the pixantrone group vs 2.5 months in the TPC group; HR 056; 95% CI: 0.38 to 0.81). However, as in other analyses, the difference in median OS was not statistically significant (10.2 months in the pixantrone group vs 7.6 months in the TPC group; HR 0.79; 95% CI: 0.53 to 1.18).

Considering other subgroups of potential relevance to the decision problem, in the MS (pg 56), the manufacturer states that various *post hoc* subgroup analyses were carried out:

- effect of rituximab on the efficacy of pixantrone;
- efficacy in patients with prior stem cell transplantation;
- efficacy in European patients;
- efficacy in older adults and women.

Of the listed *post hoc* subgroups, the ERG considers analyses based on prior rituximab and enrolment in Europe, and specifically Western Europe, to be of relevance to the decision problem. As discussed in Section 2.2, rituximab forms part of initial standard care for the treatment of aggressive NHL in UK clinical practice, and only 7 patients were enrolled from the UK. The largest proportion of patients was enrolled from the Rest of World and only a third (37.2%) of those received prior rituximab. In addition, it has been identified that patients enrolled from Western Europe had rapidly advancing disease (~50% of patients) and had been more heavily pretreated with multiple combination regimens (including rituximab) compared with the Rest of World subgroup.[17] The CHMP summary report discussed the generalisability of results from the PIX301 trial to patients in Europe. The ERG notes that the conditional approval adopted for the use of pixantrone in multiply relapsed or refractory

aggressive B-cell NHL was based on a majority decision.[17] CHMP members commented that (labelled as "divergent positions" in the CHMP report):[17]

- "the benefit in terms of CR and PFS is driven by patients treated in 'rest of the world'";
- "no benefit has been demonstrated for target population relevant for the clinical practice in Western Europe: No clear benefit for pixantrone over comparator is demonstrated for patients with previous treatment with anti-CD20 or stem cell transplant and most importantly, patients in treated in North America or Western Europe";
- "the study results observed in patients treated in "rest of the world" cannot be extrapolated to the Western European population because the population differed clearly in baseline characteristics, e.g. age, performance status, histology, relevant prior treatments, including rituximab use and stem cell transplantation, and refractoriness to prior treatments".

In addition, the CHMP condition approval stated that "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".[17] On the basis of this finding, the ERG also requested subgroup data for patients receiving pixantrone and TPC as third or fourth line treatment.

On request, the manufacturer helpfully provided all data on clinical efficacy outcomes for the subgroups of interest in the histologically confirmed aggressive B-cell NHL data set. The ERG considers it important to stress that the data presented are derived from *post hoc* subgroups of a subgroup and as such are likely to be underpowered to identify a difference between groups. Moreover, some subgroups comprise a small number of patients, which increases the uncertainty of results and the possibility of chance findings. For these reasons, the ERG considers that the results should be interpreted with caution.

Prior rituximab treatment

In patients with retrospective histological confirmation of aggressive B-cell NHL, the proportion of patients achieving CR/CRu (primary outcome) in the individual treatment groups is comparable across the subgroups of previously treated with rituximab versus no prior treatment with rituximab (prior treatment: 16.7% [pixantrone] vs 7.7% [TPC]; no prior treatment: 15.0% [pixantrone] vs 4.8% [TPC]; Table 14). Moreover, the comparative clinical effectiveness results are analogous to those observed in the overall population of patients with histologically confirmed aggressive B-cell NHL (Table 9). For example, considering the primary outcome, in the overall population, the proportion of patients achieving CR/CRu was 16.0% and 6.4% in the pixantrone and TPC groups, respectively (Table 9).

For most clinical outcomes, the difference between pixantrone and TPC did not reach statistical significance in either of the subgroups analysed (Table 14); additional secondary outcomes for this subgroup are presented in Appendix 9. The ERG considers the key difference between the analyses to be the disparity in PFS, in that, in patients not having received previous treatment with rituximab, PFS

is significantly prolonged in the pixantrone group, a result which is analogous to the result observed for the overall population (Table 11). By contrast, in patients previously treated with rituximab, the difference between treatment groups in PFS was not statistically significant, although the direction of effect favoured pixantrone (Table 14). The ERG notes that median PFS and OS are considerably shorter in patients who have received prior rituximab compared with those who have not. There is evidence that the routine use of rituximab as part of initial treatment chemotherapeutic strategies is altering the nature of relapsed disease.[39] The CORAL trial evaluated the effect of R-ICE versus R-DHAP in patients with DLBCL and who were experiencing a first relapse or who were refractory to first-line treatment. The authors of the trial reported that 3-year OS was affected by prior rituximab treatment compared with no prior rituximab (40% with rituximab vs 66% with no rituximab; p <0.01).[39] In addition, patients receiving prior rituximab are likely to be predominantly from Western Europe, and it has been noted that this subgroup of patients in the PIX301 trial has more advanced disease.[17]

Table 14. Clinical effectiveness results for subgroup analyses based on prior rituximab treatment in patients with histologically confirmed aggressive B-cell NHL

	Prior rituximab treatment			**No prior rituximab treatment**		
Outcome	**Pixantrone (N = 30)**	**TPC (N = 26)**	**p value or HR (95% CI)**	**Pixantrone (N = 20)**	**TPC (N = 21)**	**p value or HR (95% CI)**
CR/CRu (end of treatment)						
CR/CRu	5 (16.7%)	2 (7.7%)	0.431	3 (15.0%)	1 (4.8%)	0.343
CR	4 (13.3%)	0 (0%)	0.115	2 (10.0%)	0 (0%)	0.232
CRu	1 (3.3%)	2 (7.7%)	0.592	1 (5.0%)	1 (4.8%)	1.000
CR/CRu (end of study)						
CR/CRu	6 (20.0%)	3 (11.5%)	0.481	3 (15.0%)	1 (4.8%)	0.343
CR	5 (16.7%)	0 (0%)	0.055	2 (10.0%)	0 (0%)	0.232
CRu	1 (3.3%)	3 (11.5%)	0.328	1 (5.0%)	1 (4.8%)	1.000
OS						
Median (range), months	6.0 (0.8 to 24.0)	4.6 (0.1 to 24.0)	0.85 (0.48 to 1.50)	16.1 (1.8 to 24.0)	7.8 (1.2 to 24.0)	0.52 (0.24 to 1.11)
Mean (SD), months	8.9 (7.9)	7.7 (7.8)	–	14.8 (9.07)	10.4 (7.98)	–
PFS						
Median (range), months	3.5 (0.7 to 24.0)	2.3 (0.0 to 24.0)	0.66 (0.38 to 1.14)	6.3 (1.3 to 24.0)	3.5 (0.3 to 13.5)	0.35 (0.17 to 0.70)
Mean (SD), months	5.9 (6.2)	3.6 (4.78)	–	10.4 (9.13)	3.7 (3.17)	–
ORR (end of treatment)						
CR/CRu/PR	9 (30.0%)	5 (19.2%)	0.537	8 (40.0%)	3 (14.3%)	0.085
CR	4 (13.3%)	0	0.115	2 (10.0%)	0 (0%)	0.232
CRu	1 (3.3%)	2 (7.7%)	0.592	1 (5.0%)	1 (4.8%)	1.000
PR	4 (13.3%)	3 (11.5%)	1.000	5 (25.0%)	2 (9.5%)	0.238

ORR (end of study)						
CR/CRu/PR	9 (30.0%)	5 (19.2%)	0.537	9 (45.0%)	3 (14.3%)	0.043
CR	5 (16.7%)	0 (0%)	0.055	2 (10.0%)	0 (0%)	0.232
CRu	1 (13.3%)	3 (11.5%)	0.328	1 (5.0%)	1 (4.8%)	1.000
PR	3 (10.0%)	2 (7.7%)	1.000	6 (30.0%)	2 (9.5%)	0.130
Abbreviations used in table; CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; HR, hazard ratio; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, standard deviation; TPC, treatment of physician's choice.						

The CHMP highlighted that increasing number of prior chemotherapeutic regimens was associated with a decrease in the response rate to pixantrone, a relationship that was clearest in patients for whom pixantrone was at least the fifth line of treatment (i.e., patients had received 4 or more prior regimens).[17] Most patients receiving pixantrone as a fifth-line treatment had also received prior rituximab (27/28; ITT population of the PIX301 trial), and, therefore, it was not possible to evaluate the effect of prior treatment with rituximab on response rate in this group of patients. The CHMP presented results by the number of regimens patients had received prior to study entry. The ERG requested analogous data in the subgroup of patients with retrospective histological confirmation of aggressive B-cell NHL limited to patients receiving pixantrone as a third or fourth line treatment. Although not requested, the manufacturer also helpfully provided analyses based on prior rituximab versus no prior rituximab treatment in this patient population.

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 NHL, with most results not reaching statistical significance but the direction of effect favouring pixantrone (Table 15). The ERG notes that prior treatment with rituximab had little effect on comparative clinical effectiveness in this group of patients, although the clinical benefit of pixantrone was reduced in patients who had previously received rituximab (Table 16), a trend also highlighted by the CHMP for results from the ITT population of PIX301.[17] The CHMP commented that the reduction in clinical benefit was not as marked in patients receiving pixantrone as a third-line treatment and concluded that the results "support the efficacy of pixantrone in patients that have received prior rituximab and up to 3 prior treatment regimens". The CHMP issued a condition approval for pixantrone in multiply relapsed or refractory B-cell NHL, but stated that, in the context of the marketing authorisation, additional clinical effectiveness data are required to confirm the benefit of pixantrone in patients who have received prior treatment with rituximab. At this time, a clinical trial is ongoing that is evaluating the addition of pixantrone versus addition of gemcitabine to rituximab in patients with multiply relapsed or refractory B-cell NHL and who have previously been treated with at least one rituximab-containing combination chemotherapeutic regimen.[40] Results from this trial are anticipated to be available by 30 June 2015, and should help to inform on the effect of prior treatment with rituximab on clinical benefit of pixantrone.

Table 15. Clinical effectiveness results for subgroup analyses based on number of previous chemotherapeutic treatments in patients with histologically confirmed aggressive B-cell NHL

	Third or fourth line of treatment		
Outcome	**Pixantrone (N = 39)**	**TPC (N = 39)**	**p value or HR (95% CI)**
CR/CRu (end of treatment)			
CR/CRu	8 (20.5%)	2 (5.1%)	0.087
CR	6 (15.4%)	0 (0%)	0.025
CRu	2 (5.1%)	2 (5.1%)	1.000
CR/CRu (end of study)			
CR/CRu	9 (23.1%)	2 (5.1%)	0.047
CR	7 (17.9%)	0 (0%)	0.012
CRu	2 (5.1%)	2 (5.1%)	1.000
OS			
Median (range), months	11.9 (1.1 to 24.0)	7.0 (0.2 to 24.0)	0.67 (0.40 to 1.12)
Mean (SD), months	12.1 (8.78)	9.3 (7.92)	–
PFS			
Median (range), months	5.7 (0.7 to 24.0)	2.8 (0.0 to 13.5)	0.44 (0.27 to 0.71)
Mean (SD), months	8.3 (8.07)	3.4 (2.94)	–
ORR (end of treatment)			
CR/CRu/PR	17 (43.6%)	5 (12.8%)	0.005
CR	6 (15.4%)	0 (0%)	0.025
CRu	2 (5.1%)	2 (5.1%)	1.000
PR	9 (23.1%)	3 (7.7%)	0.114
ORR (end of study)			
CR/CRu/PR	17 (43.6%)	5 (12.8%)	0.005
CR	7 (17.9%)	0 (0%)	0.012
CRu	2 (5.1%)	2 (5.1%)	1.000
PR	8 (20.5%)	3 (7.7%)	0.192

Abbreviations used in table: CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; HR, hazard ratio; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, standard deviation; TPC, treatment of physician's choice.

Table 16. Clinical effectiveness results for subgroup analyses based on patients receiving third or fourth line treatment and prior rituximab treatment in patients with histologically confirmed aggressive B-cell NHL

	Prior rituximab treatment			No prior rituximab treatment		
Outcome	**Pixantrone (N = 20)**	**TPC (N = 18)**	**p value or HR (95% CI)**	**Pixantrone (N = 19)**	**TPC (N = 21)**	**p value or HR (95% CI)**
CR/CRu						
End of treatment	5 (25.0%)	1 (5.6%)	0.184	3 (15.8%)	1 (4.8%)	0.331
End of study	6 (30.0%)	1 (5.6%)	0.093	3 (15.8%)	1 (4.8%)	0.331
OS						
Median (range), months	7.5 (1.1 to 24.0)	5.4 (0.2 to 22.5)	0.76 (0.38 to 1.55)	14.5 (1.8 to 24.0)	7.8 (1.2 to 24.0)	0.56 (0.26 to 1.20)
Mean (SD), months	9.9 (8.15)	7.9 (7.85)	–	14.3 (9.05)	10.4 (7.98)	–
PFS						
Median (range), months	5.4 (0.7 to 24.0)	2.8 (0.0 to 10.3)	0.52 (0.26 to 1.04)	6.1 (1.3 to 24.0)	3.5 (0.3 to 13.5)	0.36 (0.18 to 0.73)
Mean (SD), months	6.4 (6.19)	3.2 (2.71)	–	10.4 (9.38)	3.7 (3.17)	–
ORR (end of treatment)						
CR/CRu/PR	9 (45.0%)	2 (11.1%)	0.033	8 (42.1%)	3 (14.3%)	0.078
CR	4 (20.0%)	0 (0%)	0.107	2 (10.5%)	0 (0%)	0.219
CRu	1 (5.0%)	1 (5.6%)	1.000	1 (5.3%)	1 (4.8%)	1.000
PR	4 (20.0%)	1 (5.6%)	0.344	5 (26.3%)	2 (9.5%)	0.226
ORR (end of study)						
CR/CRu/PR	9 (45.0%)	2 (11.1%)	0.033	8 (42.1%)	3 (14.3%)	0.078
CR	5 (25.0%)	0 (0%)	0.048	2 (10.5%)	0 (0%)	0.219
CRu	1 (5.0%)	1 (5.6%)	1.000	1 (5.3%)	1 (4.8%)	1.000
PR	3 (10.0%)	1 (5.6%)	0.606	5 (26.3%)	2 (9.5%)	0.226

Abbreviations used in table: CI, confidence interval; CR, complete response; CRu, unconfirmed complete response; HR, hazard ratio; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, standard deviation; TPC, treatment of physician's choice.

Western Europe subgroup

As noted earlier, compared with other patients enrolled in the PIX301 trial, patients from Western Europe had highly aggressive disease, with nearly 50% of patients having rapidly advancing disease. Most patients from Europe had also received multiple prior combination chemotherapeutic regimens, including rituximab, and had a short interval from their last regimen. In the full publication of the PIX301 trial, the authors note that subgroup analyses of response by region are confounded because a substantially larger proportion of patients in Western Europe and North America had received four or more previous chemotherapy regimens than patients from the Rest of World group (41.3% in Western Europe vs 9.7% in Rest of World).[18] As discussed earlier, the ERG's clinical expert indicated that the Western Europe subgroup could potentially have more severe disease than a patient who would typically be eligible for treatment with pixantrone in the UK. The ERG agrees that there is a disparity

among subgroups in terms of number of previous chemotherapy regimens but considers that this does not preclude evaluation of the results for the Western Europe subgroup.

Data provided by the manufacturer on request indicate that the response rate in the primary outcome of CR/CRu was considerably lower in the Western Europe subgroup than in the Rest of World subgroup, and the contrast between subgroups was particularly marked at the assessment of results at the end of study (Table 17). Notably, the results for PFS and OS in the Western Europe subgroup are in direct contrast with those of the Rest of World subgroup, with the direction of effect favouring TPC, albeit a statistically non-significant difference (Table 17). In the Rest of World subgroup, pixantrone is associated with a significantly longer PFS and OS. The ERG stresses that the TPC group for Western Europe comprises only 10 patients, which renders the results of the analyses unreliable. The uncertainty around the effect size is indicated by the wide confidence intervals.

Table 17. Clinical effectiveness results for subgroup analyses based on geographic strata in patients with histologically confirmed aggressive B-cell NHL

	Patient location		
Outcome	**Pixantrone (n/N [%])**	**TPC (n/N [%])**	**Measure of effect (95% CI)**
CR/CRu (end of treatment)			
North America	0/3 (0%)	0/4 (0%)	–
Western Europe	1/16 (6.3%)	0/10 (0%)	% difference: 6.3% (–5.6% to 18.1%)
Rest of World	7/31 (22.6%)	3/33 (9.1%)	% difference: 13.5% (–4.2% to 31.2%)
CR/CRu (end of study)			
North America	0/3 (0%)	0/4 (0%)	–
Western Europe	1/16 (6.3%)	1/10 (10.0%)	% difference: –3.8% (95% CI: –25.8% to 18.3%)
Rest of World	8/31 (25.8%)	3/33 (9.1%)	% difference: 16.7% (–1.5% to 35.0%)
OS			
North America	–	–	HR 0.00 (0.00 to NE)
Western Europe	–	–	HR 1.73 (0.70 to 4.32)
Rest of World	–	–	HR 0.47 (0.26 to 0.85)
PFS			
North America	–	–	HR 0.00 (0.00 to NE)
Western Europe	–	–	HR 1.23 (0.54 to 2.81)
Rest of the World	–	–	HR 0.35 (0.20 to 0.61)

ORR (end of treatment)			
North America	1/3 (33.3%)	0/4 (0%)	% difference: 33.3% (95% CI: –20.0% to 86.7%)
Western Europe	2/16 (12.5%)	3/10 (30.0%)	% difference: –17.5% (95% CI: –50.2% to 15.2%)
Rest of World	14/31 (45.2%)	5/33 (15.2%)	% difference: 30.0% (95% CI: 8.6% to 51.4%)
ORR (end of study)			
North America	1/3 (33.3%)	0/4 (0%)	% difference: 33.3% (95% CI: –20.0% to 86.7%)
Western Europe	2/16 (12.5%)	3/10 (30.0%)	% difference: –17.5% (95% CI: –50.2% to 15.2%)
Rest of World	15/31 (48.4%)	5/33 (15.2%)	% difference: 33.2% (95% CI: 11.8% to 54.7%)
Abbreviations used in table: CI, confidence interval; CR, complete response, CRu, unconfirmed complete response; HR, hazard ratio; NE, not estimable; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation; TPC, treatment of physician's choice.			

4.3.3 Adverse effects

The Summary of Product Characteristics (SmPC) for pixantrone reports that the overall safety profile of pixantrone is based on data from 407 patients (12 clinical studies) with cancer,[19] of which 345 patients had NHL.[17] The SmPC states that some of the most frequent toxicities observed with pixantrone treatment are haematologic toxicities (e.g., lymphopaenia, anaemia, and thrombocytopaenia). In general, haematologic toxicities associated with pixantrone have been easily managed with immunostimulants and transfusion support as needed. Adverse effects of treatment that would be anticipated in patients receiving chemotherapeutic agents include nausea, vomiting, and diarrhoea. In patients receiving pixantrone, such adverse effects were reported to be "generally infrequent, mild, reversible, and manageable".[17] Pixantrone safety has not been established in patients with hepatic or renal failure, or those with a poor performance status (ECOG score >2). Treatment with pixantrone has been associated with changes in cardiac function, including decreased left-ventricular ejection fraction or fatal congestive heart failure. It is recommended that cardiac function be monitored before initiation of pixantrone treatment and at regular intervals subsequent to treatment initiation. Moreover, should cardiac toxicity during treatment with pixantrone be identified, it is necessary to re-evaluate the risk versus benefit of continued treatment with pixantrone.

The manufacturer presented adverse event data from the "safety-evaluable" population of the PIX301 trial, which comprised patients who received any amount of protocol therapy.[28] Information provided in the patient flow diagram (MS; Figure 5, pg 57), indicates that two patients in the pixantrone group and three patients in the TPC group did not receive a dose of protocol therapy. Thus, the safety-evaluable population comprised 68 patients in the pixantrone group and 67 patients in the TPC group.

The mean and median doses intensities of pixantrone and TPC were similar across the two groups in the safety evaluable population. Median dose intensity in the pixantrone group was 55 mg/m^2 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 TPC group, with the exception of those patients who received vinorelbine. Patients received a median of 4 cycles (range 2–6) and 3 cycles (range 2–6) of pixantrone and TPC, respectively. Median duration of treatment was 3.8 months (range 0.5–8.1 months) in the pixantrone group compared with 2.8 months (range 0.0–6.1 months) in the TPC group. The longer median duration of treatment with pixantrone is explained by the greater length of the pixantrone treatment cycle (28 days) compared with the TPC group, the cycle length of which varied with individual intervention and was either 21 or 28 days. Dose reductions were infrequent in both treatment groups (18% with pixantrone vs 15% with TPC). The manufacturer reports that more patients in the pixantrone group required a dose delay (40% in the pixantrone group vs 22% in the TPC group), but indicates that most of the delays affected only one dose.

In the MS, the manufacturer presented adverse event data derived from PIX301 based on any grade of adverse event and Grade 3 or 4 adverse events. At clarification, the manufacturer reported that adverse events were defined and Graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. Adverse event data in the MS predominantly related to the most common adverse events, with results presented for any grade of event occurring in ≥10% of patients and for Grade 3 or 4 events occurring in >2% of patients in either group (Table 18). Most patients in PIX301 experienced an adverse event, but the incidence of Grade 3 or 4 adverse events was higher in the pixantrone group than the TPC group. In the pixantrone group, the most frequent adverse effects (any grade) were haematological, gastrointestinal, and respiratory system disorders. In line with the common adverse effects reported in the SmPC for pixantrone, the most frequently occurring Grade 3 or 4 adverse effects in the pixantrone group were neutropaenia, and leukopaenia (Table 18). By contrast, patients in the TPC group had higher rates of vomiting, diarrhoea, renal failure, and neoplasm progression. The manufacturer commented that the higher incidence of respiratory system adverse effects (predominantly Grade 1–2 cough and dyspnoea) might have been associated with pixantrone or the administration of pixantrone. In PIX301, pixantrone was infused in 500 mL of saline over 1 hour, whereas it is recommended that the total volume of saline infused should be 250 mL administered intravenously over 1 hour.

Table 18. Common adverse events in PIX301 (reproduced from MS; Table 22, pg 95)

Preferred term	Common adverse event (any Grade)		Grade 3 or 4 adverse event	
	Pixantrone (N = 68)	TPC (N = 67)	Pixantrone (N = 68)	TPC (N = 67)
Any adverse event				
Adverse event	66 (97.1%)	61 (91.0%)	52 (76.5%)	35 (52.2%)
Blood and lymphatic disorders				
Anaemia	21 (30.9%)	22 (32.8%)	4 (5.9%)	9 (13.4%)
Neutropaenia	34 (50.0%)	16 (23.9%)	28 (41.2%)	13 (19.4%)
Leukopaenia	17 (25.0%)	7 (10.4%)	16 (23.5%)	5 (7.5%)
Thrombocytopaenia	14 (20.6%)	13 (19.4%)	8 (11.8%)	7 (10.4%)
Febrile neutropaenia	6 (8.8%)	2 (3.0%)	5 (7.4%)	2 (3.0%)
Lymphopaenia	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%)
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%)
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%)
Abbreviation used in table: TPC, treatment of physician's choice.				

Treatment-related adverse events were experienced by a larger proportion of patients in the pixantrone group compared with the TPC group (55/68 [81%] with pixantrone vs 38/67 [57%] with TPC). The key differences between groups in treatment-related adverse effects were reported to be line with the overall adverse effects reported in PIX301:[17]

- neutropaenia (33/68 [48.5%] with pixantrone vs 15/67 [22.4%] with TPC);
- leukopaenia (17/68 [25%] with pixantrone vs 7/67 [10.4%] with TPC);
- ejection fraction decreased (13/68 [19.1%] with pixantrone vs 3/67 [4.5%] with TPC);
- skin discolouration (7/68 [10.3%] with pixantrone vs 0/67 [0%] with TPC).

The manufacturer highlighted that the higher frequency of treatment-related adverse events is consistent with the higher rate of neutropaenia observed in the pixantrone group and could be related to number of blood counts recorded. As per the PIX301 protocol, blood counts were carried out on days 1, 8, and 15 of the treatment cycle in the pixantrone group compared with on only day 1 of 52% of patients in the TPC group. The lower frequency of blood count in the TPC group could potentially have resulted in under-reporting of haematopoietic adverse events in these patients.

In the MS, the manufacturer reports that serious adverse events occurred in 51.5% (35/68) and 44.8% (30/67) of patients in the pixantrone and TPC groups, respectively. The most common serious adverse events (occurring in ≥5% of patients) were:

- neutropaenia (9/68 [13.2%] with pixantrone vs 6/67 [9.0%] with TPC);
- pyrexia (7/68 [10.3%] with pixantrone vs 7/67 [10.4%] with TPC);
- malignant neoplasm progression (1/68 [1.5%] with pixantrone vs 9/67 [13.4%] with TPC);
- pneumonia (5/68 [7.4%] with pixantrone vs 4/67 [6.0%] with TPC);
- anaemia (2/68 [2.9%] with pixantrone vs 5/67 [7.5%] with TPC);
- thrombocytopaenia (1/68 [1.5%] with pixantrone vs 6/67 [9.0%] with TPC).

In summary, the adverse events reported to occur more frequently in the pixantrone group than in the TPC group were consistent with the common adverse effects associated with pixantrone as reported in the SmPC.[19]

Cardiotoxic adverse effects

As discussed in Section 3, pixantrone was designed to reduce the cardiotoxicity associated with anthracyclines and anthracenediones while maintaining clinical effectiveness. All patients in the PIX301 trial had received previous anthracyclines or anthracenediones at equivalent doses. At baseline, approximately 40% of patients in each treatment group were identified as having any cardiac history at enrolment (MS; Table 23, pg 98); cardiac risk factors (e.g., diabetes or hypertension) were balanced between the groups. Considering left-ventricular ejection fraction abnormalities, 55% of patients had Grade 1, 3% had Grade 2 and no patient had Grade 3 abnormality. A key difference between the groups was that three patients in the pixantrone group had a history of congestive heart failure and two had continuing cardiomyopathy, whereas no patient in the TPC group had either disorder. More patients in the TPC group had a history of arrhythmia.

The mean cumulative prior anthracycline dose for patients in the pixantrone group was 285 mg/m^2 and the mean normalised pixantrone dose administered during PIX301 was 822 mg/m^2 (242 mg/m^2 doxorubicin equivalent).[18] In the pixantrone group, 13 patients (19.1%) experienced a decrease in ejection fraction that was determined to be an adverse event (defined as a >10% decrease irrespective of absolute value), with 11 events (16.2%) classified as Grade 1/2 events and 2 (2.9%) events categorised as Grade 3 (Table 19). In the TPC group, seven patients (10.4%) had a decrease in ejection fraction, all of which were categorised as Grade 1 or 2 (Table 19). Cardiac failure (MedDRA terms cardiac failure and cardiac failure congestive) was reported in six patients (8.8%) in the pixantrone group compared with one patient (1.5%) in the TPC group. In addition, one patient (1.5%) in the TPC group had a decline in left-ventricular ejection fraction that was considered to be related to the chosen intervention.

Table 19. Cardiac adverse events by toxicity grade and preferred term in PIX301 (reproduced from MS; Table 24, pg 99)

Adverse event	Pixantrone (N= 68)			TPC (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. Abbreviation used in table: TPC, treatment of physician's choice.						

The manufacturer reports that an independent cardiology review identified that, in the pixantrone group, 14 events occurred in 13 patients (19.1%) that were considered likely (9 events in nine patients) or possibly (5 events in four patients) to be associated with pixantrone therapy, including two putative cases of congestive heart failure.

In the MS, the manufacturer provides a detailed description of additional data on the safety profile of pixantrone from the PIX203 trial, which evaluated the substitution of pixantrone for doxorubicin in the CHOP-rituximab regimen in the first-line treatment in patients with DLBCL.[41] Enrolment into the trial was stopped early because of resource constraints. The proportion of patients experiencing an adverse event was similar across the groups, and the types of adverse event were evenly distributed across groups. However, a larger proportion of patients in the CHOP-rituximab group had congestive heart failure, >20% declines in left-ventricular ejection fraction, and increases in troponin T levels.

Discontinuation due to adverse effect

The most reported reason for discontinuation from PIX301 was disease progression or relapse (28/70 [40.0%] with pixantrone vs 39/70 [55.7%] with TPC). Considering discontinuation due to an adverse effect, a slightly larger proportion of patients in the pixantrone group experienced a treatment-related adverse event that led to discontinuation compared with the TPC group (Table 20). The most frequent treatment-related adverse effect leading to discontinuation in the pixantrone group was neutropaenia

(9 patients [3.6%]) and was respiratory, thoracic and mediastinal disorders in the TPC group (7 patients [10.4%]).

Table 20. Discontinuation from PIX301 due to an adverse effect[17]

Adverse event	Pixantrone (N = 68)	TPC (N = 67)
Any adverse event leading to withdrawal	29 (42.6%)	25 (37.3%)
Neutropaenia	7 (10.3%)	1 (1.5%)
Thrombocytopaenia	0 (0%)	3 (4.5%)
Febrile neutropaenia	2 (2.9%)	0 (0%)
Anaemia	0 (0%)	2 (3.0%)
Cardiac disorders	5 (7.4%	1 (1.5%)
Cardiac failure	2 (2.9%)	1 (1.5%)
Asthenia	5 (7.4%)	0 (0%)
Hepatobiliary disorders	2 (2.9%)	0 (0%)
Infections and infestations	3 (4.4%)	4 (6.0%)
Ejection fraction decreased	2 (2.9%)	0 (0%)
Neoplasms, benign, malignant and unspecified	2 (2.9%)	6 (9.0%)
Renal failure	0 (0%)	2 (3.0%)
Respiratory, thoracic and mediastinal disorders	4 (5.9%)	7 (10.4%)
Abbreviations used in table: NHL, non-Hodgkin's lymphoma; TPC, treatment of physician's choice.		

4.4 Conclusions of the clinical effectiveness section

4.4.1 Clinical results

- The submitted evidence is derived from the PIX301 trial (140 patients randomised).[18]
- PIX301 was an open-label trial designed to evaluate the clinical effectiveness of pixantrone monotherapy versus various other single chemotherapy agents (treatment of physician's choice [TPC]) in patients with multiply relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL). To be eligible for enrolment in PIX301, patients had to have received at least two prior chemotherapeutic regimens for NHL.
- Pixantrone has been granted a conditional marketing authorisation by the European Medicines Agency (EMA) for treatment of patients with multiply relapsed or refractory aggressive B-cell NHL as monotherapy.[17] The Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of pixantrone outweigh the associated risks but that the data are not yet comprehensive, particularly in patients who have received prior treatment with rituximab.
- The primary outcome of the PIX301 trial was the proportion of patients achieving complete response (CR) or unconfirmed CR (CRu) in the intention-to-treat (ITT) population at the end of treatment, as evaluated by an Independent Assessment Panel (IAP) who were blinded to treatment allocation. In the ITT population, a statistically significantly larger proportion of patients in the pixantrone group achieved CR/CRu compared with the TPC group (20.0% with pixantrone vs 5.7% with TPC; p = 0.021).

- Analysis of the proportion of patients achieving CR/CRu at the end of treatment in patients retrospectively confirmed by central histological review to have aggressive NHL (104 patients; HITT population) was a prespecified secondary outcome. The HITT population comprises a small number of patients with NHL subtype originating from T-cells (7 patients). In the HITT population, there was no statistically significant difference between pixantrone and TPC in the proportion of patients achieving CR/CRu (16.7% with pixantrone vs 6.0% with TPC; p = 0.126).
- Based on the conditional approval adopted by the CHMP, the ERG requested data on all clinical outcomes in the subgroup of patients with histologically confirmed aggressive B-cell NHL. For the primary outcome of proportion of patients achieving CR/CRu at the end of treatment, there was no statistically significant difference between pixantrone and TPC in the proportion of patients achieving CR/CRu at the end of treatment (16.0% with pixantrone vs 6.4% with TPC; p = 0.202).
- Additional prespecified secondary outcomes analysed were PFS, OS, and ORR lasting at least 4 months. In the three patient populations evaluated, median progression-free survival (PFS) was significantly longer in the pixantrone group compared with the TPC group.
- Median overall survival (OS) was longer in the pixantrone group compared with the TPC group in all data sets evaluated but the difference between groups did not reach statistical significance in the prespecified ITT and HITT populations, or in the requested subgroup of patients with histologically confirmed aggressive B-cell NHL.
- Overall response rates (ORR) at the end of treatment were higher in the pixantrone group compared with the TPC group in the ITT, HITT and histologically confirmed aggressive B-cell populations. The difference between groups reached statistical significance in the ITT and HITT populations but not in the subgroup of patients with histologically confirmed aggressive B-cell NHL.
- In the UK, addition of rituximab to a combination chemotherapy regimen is standard of care for the first-line treatment of NHL. In the subgroup of patients who had received prior treatment with rituximab and who had histologically confirmed aggressive B-cell NHL, there was no significant difference between pixantrone and TPC in the proportion of patients achieving CR/CRu at the end of treatment. Although median PFS and OS were longer in the pixantrone group for this subgroup of patients, the difference between groups did not reach statistical significance for either outcome.
- The most frequently occurring Grade 3 or 4 adverse effects in the pixantrone group were neutropaenia and leukopaenia, both of which are recognised adverse effects of treatment. An independent cardiology review identified that there were 14 events (in 13 patients) considered likely (9 events in nine patients) or possibly (5 events in four patients) to be associated with pixantrone treatment, including two putative cases of congestive heart failure. The most frequent treatment-related adverse effect leading to discontinuation from pixantrone treatment was neutropaenia.

4.4.2 Clinical issues

- Only one small RCT (140 patients randomised) is available for the comparison of pixantrone monotherapy various other single chemotherapy agents. The ERG considers it important to acknowledge that there is a paucity of clinical trials evaluating treatments for multiply relapsed or refractory aggressive NHL.
- The PIX301 trial is likely to be underpowered to detect a difference between pixantrone and TPC for the primary outcome assessed of proportion of patients achieving CR/CRu at the end of treatment as evaluated by an IAP.
    - PIX301 was designed with 80% power to detect a 10% difference in the ITT population with a sample size of 320 patients (160 patients per group).

- As a result of slow accrual, only 140 patients were recruited and randomised. The revised power calculation indicated that, to achieve 81% power with 70 patients per group, the true proportion of patients with CR/CRu would have to be 22% in the pixantrone group and 5% in the TPC group. In the ITT analysis, the proportion of patients achieving CR/CRu was 20.0% and 5.7% in the pixantrone and TPC groups, respectively.
- Diagnosis of aggressive NHL was initially carried out at the individual participating sites, with subsequent review by a central panel. Of the 140 patients randomised, only 104 were subsequently histologically confirmed as having aggressive NHL. Therefore, the ITT population comprises patients without aggressive NHL and results in the full trial population might not reflect benefit of pixantrone in patients with aggressive B-cell NHL.
- Power to detect a difference between pixantrone and TPC is reduced further in analyses based on data from subgroups of patients with histological confirmation of disease.

- Primary outcome evaluated was CR/CRu, which is not considered to be as appropriate as OS or PFS in trials evaluating treatments for cancer.
- Of 140 patients randomised, only 36 patients completed six cycles of protocol treatment. In addition, only 95 (67.9%) patients entered the follow-up period at the end of treatment, with 26 patients completing 18 months' follow-up.
- The ERG has reservations about the generalisability of the results of the PIX301 trial to patients with multiply relapsed or refractory aggressive NHL in the UK. As noted by the CHMP[17] and the authors of the full publication of the PIX301 trial,[18] based on data from PIX301, there is uncertainty around the clinical benefit associated with pixantrone in patients who have previously been treated with rituximab. In the UK, patients with multiply relapsed or refractory aggressive NHL will have received rituximab as a component of their standard care.
- A small proportion of patients in the PIX301 trial were recruited from Western Europe (38/140), which included seven patients from the UK. Compared with the Rest of World subgroup, patients from Western Europe had more severe disease, being later stage patients with highly aggressive disease.
- Comparative clinical effectiveness results for most subgroups presented (e.g., histologically confirmed aggressive B-cell NHL, prior treatment with rituximab, and geographic region) are based on *post hoc* subgroup analyses. Moreover, as subgroups, the power to detect a difference is reduced further, the number of patients in the analysis is generally small, and there is increased uncertainty around the robustness of the result. In the case of subgroups based on retrospective histological confirmation of disease and prior rituximab treatment, because randomisation was not stratified by these factors, there is the potential for unbalanced groups. For these reasons, results of subgroup analyses should be interpreted with caution.

5 COST EFFECTIVENESS

This section provides a structured description and critique of the systematic cost-effectiveness literature review and *de novo* economic analyses submitted by the manufacturer in support of this Single Technology Appraisal (STA). The manufacturer provided a written submission of the economic evidence together with an electronic version of the Microsoft© EXCEL-based economic model.

To summarise, the manufacturer did not identify any published economic evaluations or costing studies that were relevant to the decision problem. Consequently, the manufacturer developed a *de novo* cost-utility model to evaluate the cost-effectiveness of pixantrone versus treatment of physician's choice (TPC), from monotherapy drugs used in third line or later (TPC group). The manufacturer's base case model considered a population of patients with multiply relapsed or refractory, aggressive, B-cell non-Hodgkin's lymphoma (NHL), who had received at least two prior therapies. The manufacturer estimated the deterministic incremental cost-effectiveness ratio (ICER) for pixantrone versus TPC to be £28,503 per quality adjusted life year (QALY); a probabilistic ICER of £34,416 was obtained from the manufacturer's model (Section 5.2.10). The location of the key economic information within the manufacturer's submission (MS) is summarised in Table 21.

Table 21. Summary of key information within the manufacturer's submission

Information	Section (MS)
Details of the systematic review of the economic literature	7.1
Population	7.2.1
Model structure	7.2.2–7.2.6
Technology	7.2.7
Clinical parameters and variables	7.3
Measurement and valuation of health effects and adverse events	7.4
Resource identification, valuation and measurement	7.5
Sensitivity analysis	7.6
Results	7.7
Validation	7.8
Subgroup analysis	7.9
Interpretation of economic evidence	7.10
Abbreviation used in table: MS, manufacturer's submission.	

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

The manufacturer carried out a systematic review of the literature to identify full economic evaluations and/or resource use or cost studies in patients who had relapsed or refractory aggressive NHL after at least two prior therapies. The following databases were searched: MEDLINE; EMBASE; MEDLINE (R) In-Process, EconLIT and NHS Economic Evaluation Database (NHS EED). The searches were carried out between 16th December 2011 and 2nd February 2012 and were

restricted by date (from year 2000) and language (English language). No country restrictions were applied; however, the manufacturer stated that UK-based studies were preferred (MS; pg 116). The manufacturer's rationale for applying publication date and language limits was to "select those studies relevant to the decision problem and the current clinical practice in the UK" (MS; pg 116).

In addition, the websites of manufacturers of treatments currently used in multiply relapsed or refractory aggressive NHL were also searched (between 2nd and 20th February 2012) , as were the websites of the following organisations:

- American Society of Clinical Oncology (ASCO);
- European Association for Cancer Research (EACR);
- European Society for Medical Oncology (ESMO);
- National Cancer Research Institute (NCRI);
- National Comprehensive Cancer Network (NCCN);
- Health Technology Assessments via the Cochrane Library (HTAs).

After consideration of 4,345 records retrieved by the review, no relevant economic evaluations or costing studies were identified by the manufacturer. The Evidence Review Group (ERG) considers that the search terms (Appendix 10) and inclusion/exclusion criteria used in the review were reasonable, and, therefore, the ERG considers it unlikely that relevant publications were excluded.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

The manufacturer developed a *de novo* economic model which considered pixantrone versus TPC in a population of patients with multiply relapsed or refractory aggressive B-cell NHL, who had received at least two prior therapies. The model was constructed in Microsoft© EXCEL over a life-time (23 year) time horizon and captured costs and QALYs associated with an average patient treated with either pixantrone or TPC. Individual patient level data from the PIX301 trial were used to populate the model. In addition, as part of the manufacturer's clarification response, a corrected list price for pixantrone was provided. Unless otherwise stated all results presented within this report are based on the corrected list price for pixantrone.

Overall, the ERG considers the manufacturer's model to be well constructed and largely transparent. However, the ERG considers it important to note that the manufacturer's base case economic evaluation included data from patients whose disease had not been histologically confirmed as aggressive. The ERG considers this to be an important limitation of the manufacturer's base case analysis. Furthermore, the ERG notes that the results of the subgroup analysis (requested at

clarification) in patients with B-cell NHL that has been histologically confirmed as aggressive is more informative to the decision problem that is the focus of this STA.[21]

5.2.1 NICE reference case checklist

Table 22 and Table 23 summarise the ERG's quality assessment of the manufacturer's economic evaluation. Table 22 summarises the ERG's appraisal of the manufacturer's economic evaluation against the requirements set out in the National Institute of Health and Clinical Excellence (NICE) reference case checklist[42] for a base case analysis. The ERG's assessment of the quality of the manufacturer's economic evaluation using the Philips checklist[43] is summarised in Table 23.

Table 22. NICE reference case[42]

Attribute	**Reference case**	**Does the *de novo* economic evaluation match the reference case?**
Decision problem	The scope developed by the National Institute for Health and Clinical Excellence	Broadly yes, however, the ERG considers that the subgroup analysis in the histologically confirmed aggressive B-cell population, submitted by the manufacturer as part of the clarification response, adheres to the scope of the decision problem more closely than the manufacturer's original base case.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	IPD data were used to inform treatment discontinuation and efficacy and outcomes. Systematic reviews were carried out to inform HRQoL and costs
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, taken from literature
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes

Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes. However, the manufacturer asserts that the submission is to be considered under end-of-life criteria
Sensitivity analysis	Probabilistic sensitivity analysis	Yes. The manufacturer carried out sensitivity analysis, scenario analysis and probabilistic sensitivity analysis
Abbreviations used in table: ERG, evidence review group; HRQoL, health-related quality of life; IPD, individual patient data; NHS, National Health Service; QALY, quality adjusted life year; NHS, National Health Service.		

Table 23. Philips checklist[43]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2:Statement of scope/perspective	The scope and perspective of the model were clearly stated; the manufacturer adhered to the NICE scope.
S3: Rationale for structure	Clearly stated.
S4: Structural assumptions	Appropriate. The structural assumptions were transparent. In addition, a number of scenario and sensitivity analyses were undertaken to test the robustness of the different assumptions.
S5: Strategies/comparators	All relevant comparators currently used in the NHS were evaluated.
S6: Model type	Appropriate; Markov model.
S7: Time horizon	Appropriate: lifetime time horizon (i.e., 23 years) is considered sufficient to capture the lifetime cost and consequences of pixantrone in this patient population.
S8: Disease states/pathways	Appropriate and in line with related oncology models.
S9: Cycle length	Appropriate; the ERG considers 1 week to be a reasonable cycle length to capture the consequences of model events.
Data	
D1: Data identification	The manufacturer's literature searches for cost-effectiveness analyses, resource use and cost studies, and studies reporting relevant utility data were clearly described. Effectiveness data were taken from IPD data of the PIX301 trial.
D2: Premodel data analysis	The manufacturer developed parametric approximations of OS and PFS based on patient level data from PIX301. After inspection of data provided by the manufacturer, the ERG considers these to be correctly formulated.
D2a: Baseline data	IPD from PIX301 were used in the economic model.
D2b: Treatment effects	Treatment effects were taken from analyses carried out on IPD from PIX301. The ERG has concerns about the population included in the original submission, which included about 23% of patients who did not have histologically confirmed aggressive B-cell NHL. However, on request, the manufacturer provided an analysis which focused on patients with histologically confirmed aggressive B-cell NHL.
D2d: Quality of life weights (utilities)	The ERG is of the opinion that inappropriate utility weights were used. The manufacturer used utility weights from a population of patients receiving first-line treatment for aggressive NHL.

D3: Data incorporation	The manufacturer has not always given a detailed description of how data were incorporated in the model. For example, the calculation of adverse event rates and health state costs was not clearly described. However, sources were referenced and copies of referenced papers were provided. In addition, the manufacturer provided full justification of the choice of distributions used for the PFS and OS parameters.
D4: Assessment of uncertainty	The assessment of uncertainty was very detailed. Both probabilistic and one-way sensitivity analyses including various scenario analyses were satisfactorily reported.
D4a: Methodological	Appropriate analytical methods were used and justified by the manufacturer.
D4b: Structural	The manufacturer considered multiple alternative parametric extrapolations of the PFS and OS data as recommended by the NICE DSU report.[44]
D4c: Heterogeneity	Heterogeneity was addressed by the analysis of different subgroups of patients that were pre-specified in the protocol. In addition, the ERG requested that the manufacturer consider the subgroup of patients with histologically confirmed aggressive B-cell NHL.
D4d: Parameter	Parameter uncertainty was assessed through deterministic and probabilistic sensitivity analyses.
Consistency	
C1: Internal consistency	The model seems to be mathematically sound. The model was subjected to rigorous stress testing by two modelling experts. In addition, the model was reviewed by an independent health economics consultancy (BresMed Health Solutions Limited) that was not involved in the PIX301 study.
C2: External consistency	Expert clinical 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. In addition, model results for the base case and subgroup (histologically confirmed B-cell aggressive) analysis appear to be biased towards pixantrone by the overestimation of PFS benefit with pixantrone.
Abbreviations used in table: DSU, Decision Support Unit; ERG, Evidence Review Group; IPD; individual patient level data, NHL, non-Hodgkin's lymphoma; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; OS; overall survival; PFS; progression-free survival..	

5.2.2 Population

The manufacturer's base case economic analysis considered a population of patients with multiply relapsed or refractory aggressive B-cell NHL, with disease that was sensitive to treatment with anthracyclines and who had received at least two prior therapies. The manufacturer states that this population was chosen for the base case analysis "as this most closely resembles the licensed indication of pixantrone" (MS; pg 8). The ERG notes that the full population of the pivotal PIX301 trial (intention-to-treat [ITT] population) included both aggressive B-cell and T-cell NHLs. The manufacturer defined aggressive B-cell NHL as including the following subtypes of NHL:

- diffuse large B-cell lymphoma (DLBCL);
- transformed indolent lymphoma;
- follicular lymphoma, grade 3.

In addition, the manufacturer carried out economic analyses in the ITT patient population and the subgroup of patients with DLBCL (representing ~74% of the ITT population). Based on expert clinical advice, the ERG considers the disease types included in the manufacturer's defined subgroup

of aggressive B-cell NHL to be representative of an aggressive B-cell NHL patient population. In addition, the ERG notes that patients with aggressive B-cell NHL formed a large proportion of the ITT population, representing 91.4% (64 out of 70 patients) and 88.6% (62 out of 70 patients) of patients in the pixantrone and TPC groups, respectively.

However, as discussed in Section 4.2.1, the ERG notes that histological confirmation of aggressive disease by central independent pathological review was carried out retrospectively. Moreover, retrospective analysis revealed that, in the ITT patient population, 23% of patients in the pixantrone group and 29% of patients in the TPC group had disease that was subsequently determined not to be aggressive. The ERG notes that the severity of disease is an important factor in determining the treatment strategy used patients without aggressive disease are likely to have a more favourable response than those whose disease is histologically confirmed as aggressive. On request, the manufacturer provided an updated model which considered patients with histologically confirmed (retrospectively by central independent pathological review) aggressive B-cell NHL. The base case deterministic ICER increased by 15% from £28,503 to £32,830 per QALY, see Section 5.2.11 on subgroup analysis for details.

Overall, the ERG considers the analysis carried out in the population of patients with histologically confirmed aggressive B-cell NHL to be a more appropriate base case than that originally presented by the manufacturer. However, the ERG notes that this analysis is based on second level subgroup data (i.e., data from a subgroup of a subgroup) and should therefore be interpreted with caution. In addition, as discussed in Section 4.2.1, the ERG notes that 42% of the population included in this analysis had not received prior rituximab therapy. The ERG notes that rituximab is a standard component of first-line treatment of aggressive NHL in the UK; therefore, the results of this analysis may not be generalisable to a UK patient population. Furthermore, the ERG notes that the treatment effect of pixantrone in patients previously treated with rituximab was observed to diminish (see Section 4.3.2) compared with the treatment effect observed in the histologically confirmed aggressive B-cell NHL patient population. However, the ERG notes that data for the effect of pixantrone in a population of patients previously treated with rituximab is highly unreliable as a result of small patient numbers and observed effects. Therefore, it is possible that any observations may be as a result of random chance rather than actual treatment effect.

5.2.3 Intervention and comparators

The treatment comparison considered in the manufacturer's economic model is that between pixantrone (dose of 85 mg/m^2 intravenously, which is equivalent to 50 mg/m^2 pixantrone base) and TPC. In the TPC group, physicians could choose from six monotherapy agents that had been approved for cancer indications other than aggressive NHL but with demonstrated activity in aggressive NHL.

The therapies used and the proportion of patients reported to receive each therapy in PIX301 was used to inform the TPC group of the manufacturer's economic model, as follows:

- ifosfamide 3,000 mg/m^2 (17.9%);
- vinorelbine 30 mg/m^2 (16.4%);
- etoposide (intravenous) 100 mg/m^2 (6.0%);
- etoposide (oral) 50 mg/m^2 (7.5%);
- gemcitabine 1,250 mg/m^2 (1.5%);
- oxaliplatin 100 mg/m^2 (44.8%);
- mitoxantrone 14 mg/m^2 (6.0%).

All drugs were assumed to be used in accordance with the respective Summary of Product Characteristics (SmPCs).

As discussed in Section 3.3, clinical advice received by the ERG suggests that, at third-line (and beyond), treatment preference would most likely be for chemotherapeutic agents that can be used as a monotherapy. However, expert advice also indicated that combination regimens may be considered in patients with a previous response to treatment of longer than 12 months. Therefore, the ERG accepts the composition of the TPC group proposed by the manufacturer, but considers it important to highlight that treatment in this patient population is likely to vary across practices in the UK. In addition, the ERG notes that, although not listed in the final scope for this STA issued by NICE,[21] rituximab is included as a potential therapy option for patients receiving TPC; however, on inspection of the economic model, it appears that no patients received therapy with rituximab.

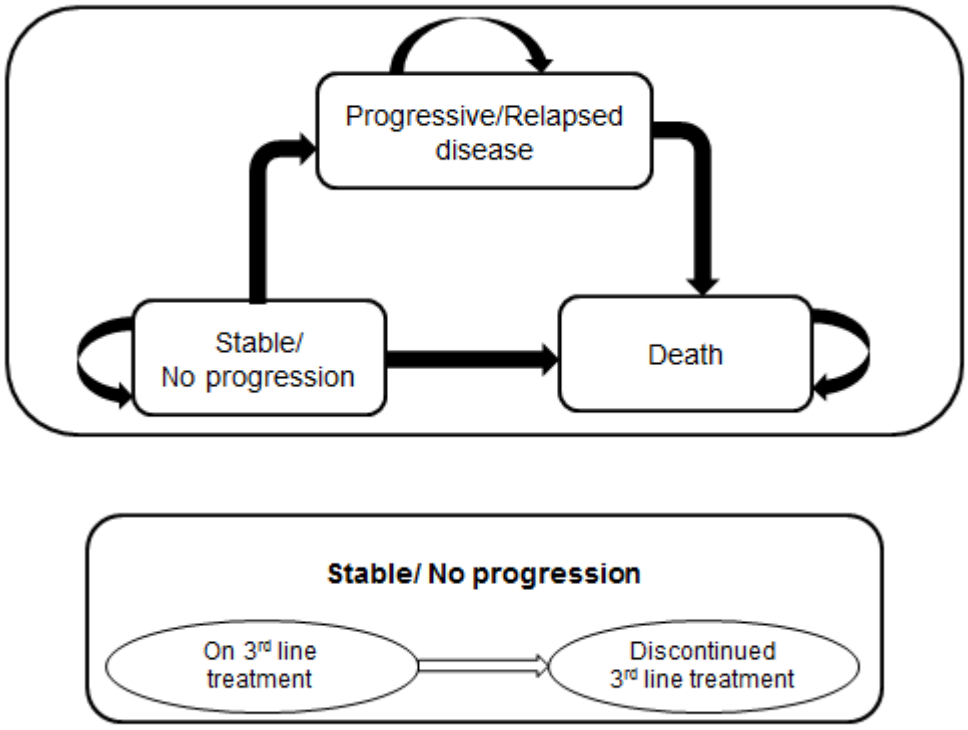
5.2.4 Model structure

The manufacturer developed a *de novo* semi-Markov cost-utility model, in which, at any given time, patients were assumed to be in one of four possible discrete health states:

- stable/no progression (progression-free survival [PFS]), on 3rd (or 4th) line treatment;
- stable/no progression (PFS), discontinued 3rd (or 4th) line treatment;
- progressive/relapsed disease (PD);
- death (absorbing state).

The structure of the model is summarised in Figure 2.

Figure 2. Model structure (reproduced from MS; Figure 16, pg 124)



All patients enter the model in the "PFS, on 3rd (or 4th) line treatment" health state; following which, during each cycle (cycle length 1 week), patients may:

- remain within the "PFS, on 3rd (or 4th) line treatment" health state;
- discontinue 3rd (or 4th) line treatment and move into the "PFS, discontinued 3rd (or 4th) line treatment" health state;
- progress and move into the "PD" health state;
- die and transition to the absorbing state of death.

Patients, who discontinue 3rd (or 4th) line treatment prior to progression remain at risk of progression or death, they are unable to re-initiate 3rd (or 4th) line therapy. Following progression, patients are solely at risk of death and are unable to return to either of the PFS health states. Furthermore, it is assumed that following disease progression, patients cease receiving original therapy and instead receive further lines of treatment or palliative care (see Section 5.2.7). In addition, adverse events, whilst not explicitly modelled as health states, were captured as events within the model (see Section 5.2.8).

In each weekly cycle, the proportion of patients located in the PFS, PD and death health states was estimated from parametric models fitted to PFS and overall survival (OS) data from PIX301. Patients in the PFS health states include responders (i.e., patients with complete response [CR], unconfirmed complete response [CRu] or partial response [PR]) and patients who have not progressed (i.e., patients

with stable disease [SD]). However, “a significant number of patients (71.4% and 77.1% in the pixantrone and comparator arm, respectively) discontinued treatment before progression” (MS; pg 132). Therefore, the manufacturer divided PFS into two health states to capture differences between patients who remain on original therapy and those who discontinue. Kaplan–Meier data on treatment discontinuation were used to establish the proportion of patients in each PFS health state (see Section 5.2.7).

Each health state is associated with a specific cost and utility. Costs captured within the manufacturer’s model include drug, administration, health state and disease management (including adverse events) costs (Section 5.2.9). Baseline utility values for each health state (except death) were based on self-reported quality of life values from elderly patients with aggressive NHL[45] (Section 5.2.8). In addition, the model applied utility decrements (disutilities) related to adverse events experienced by patients on original therapy. Based on expert clinical opinion, the manufacturer assumed no difference between the two PFS health states with respect to baseline health-related quality of life (HRQoL); however, utility decrements were not applied to patients on further lines of treatment or palliative care resulting in an overall lower utility associated with patients on original therapy (see Section 5.2.8). In addition, differences in cost (Section 5.2.9) and OS (Section 5.2.7) between patients on original or subsequent therapy were taken into account.

Within the MS, the manufacturer provides a rationale for the model structure used. The manufacturer states that a weekly cycle length was required to capture the frequency of disease monitoring and the different cycle lengths of considered therapies. In addition, the manufacturer highlights that “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” (MS; pg 125). The ERG considers the manufacturer’s use of a short (1 week) cycle length to be appropriate.

Furthermore, the manufacturer states that the modelling approach (semi-Markov) and model structure chosen are used “extensively” in oncology. However, the manufacturer highlights that “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” (MS; pg 124). The manufacturer asserts that these simplifying assumptions (i.e., no distinction between patients by level of response) are conservative (i.e., likely to bias the model against pixantrone) as the larger proportion of patients achieving CR with pixantrone versus those achieving CR with TPC are not exposed to the potential benefits of stem cell transplantation (MS; pg 124).

The ERG notes that the use of a semi-Markov model is consistent with previous NICE oncology submissions[46;47] and considers the modelling approach used to be appropriate for the decision problem that is the focus of this STA. However, based on expert clinical opinion, the ERG notes that, in transplant eligible patients, stem cell transplant is likely to be used at second-line rather than third-line. Therefore, the ERG considers the exclusion of stem cell transplantation to be an accurate rather than conservative assumption.

5.2.5 Perspective, time horizon and discounting

The economic evaluation was undertaken from the perspective of the NHS and PSS in accordance with NICE guidelines.[42] A lifetime (23 years) time horizon, incorporating a half-cycle correction applied to each weekly cycle, was used. Both costs and benefits were discounted at 3.5% per annum.

The ERG considers that a lifetime time horizon was appropriate to capture differences in costs and consequences associated with the interventions and is in accordance with NICE guidelines. In addition, the ERG notes that both costs and benefits were subject to discounting from model initiation, rather than after 1 year. The ERG considers this to be a reasonable approach. Furthermore, the ERG carried out a sensitivity analysis which delayed discounting for 1 year and resulted in a £17 decrease in the ICER (from £28,503 to £28,486 per QALY).

5.2.6 Model parameters

Parameters used within the manufacturer's model are summarised in Table 24.

Table 24. Summary of the manufacturer's model parameters

Parameter type	Parameter	Mean value (SE)	PSA distribution	Source
General parameters	Discount rate (costs)	3.50%	–	NICE guide to the methods of technology appraisal (2008)[48]
	Discount rate (benefits)	3.50%		
	Time horizon	Lifetime		
	Cycle length	1 week		Assumption
	Median FU pixantrone	915 weeks		PIX301[18]
	Median FU TPC	639 weeks		PIX301[18]
Patient demographics	Average BSA males	1.86 m^2 (0.02m^2)	Normal (μ, σ) (1.86, 0.02)	PIX301[18]
	Average BSA females	1.67 m^2 (0.03 m^2)	Normal (μ, σ) (1.67, 0.3)	PIX301[18]
	Proportions of males	61.4% (0.04)	Beta (α, ß) (86, 54)	PIX301[18]

Drug cost	Pixantrone 50mg	£553.50	N/A	British National Formulary 62[49]
	Etoposide (oral) 50 mg	£4.99		
	Etoposide (oral) 100 mg	£8.72		
	Etoposide IV 20 mg/mL (5mL)	£12.15		
	Etoposide IV 20 mg/mL (10 mL)	£29.00		
	Etoposide IV 20 mg/mL (25 mL)	£60.75		
	Gemcitabine 200 mg	£32.00		
	Gemcitabine 100 mg	£162.00		
	Gemcitabine 1,500 mg	£213.93		
	Gemcitabine 2,000 mg	£324.00		
	Ifosfamide 1,000 mg	£43.53		
	Ifosfamide 2,000 mg	£88.62		
	Mitoxantrone 2 mg/mL (10 mL)	£100.00		
	Mitoxantrone 2 mg/mL (13 mL)	£152.33		
	Mitoxantrone 2 mg/mL (15 mL)	£203.04		
	Oxaliplatin 50 mg	£150.00		
	Oxaliplatin 100 mg	£299.50		
	Oxaliplatin 5 mg/mL (40 mL)	£622.38		
	Rituximab 10 mg/mL (10 mL)	£174.63		
	Rituximab 10 mg/mL (50 mL)	£873.15		
	Vinorelbine 10 mg/mL (1 mL)	£29.00		
	Vinorelbine 10 mg/mL (5 mL)	£139.00		

Administration cost	Oral chemotherapy	£163(£16.63)	Gamma (α, ß) (96.04, 1.70)	National reference costs (2010/11)[50]
	Simple parenteral chemotherapy at first attendance	£231 (£23.57)	Gamma (α, ß) (96.04, 2.41)	
	More complex parenteral chemotherapy at first attendance	£252 (£25.71)	Gamma (α, ß) (96.04, 2.62)	
	Complex chemotherapy including prolonged infusion treatment at first attendance	£302 (£30.82)	Gamma (α, ß) (96.04, 3.14)	
	Deliver subsequent elements of a Chemotherapy cycle	£206 (£21.02)	Gamma (α, ß) (96.04, 2.14)	
Outcomes pixantrone	PFS	Log-normal distribution: Intercept 3.5423, scale 1.3397	Variance-covariance tables for the lognormal parametric fitting (using Cholesky decomposition)	PIX301[18]
	OS	Log-normal distribution: Intercept 4.0486, scale 1.4910		
Outcomes TPC	PFS	Log-normal distribution: Intercept 2.6811, scale 1.0624		
	OS	Log-normal distribution: Intercept 3.6986, scale 1.4051		
Utilities	PFS	0.81 (0.08)	Beta (α,ß) (17.44,4.09)	Groot *et al.*[45]
	OS	0.6 (0.06)	Beta (α,ß) (37.82,25.21)	
Adverse events rate pixantrone	Grade 2	0.014 (95% CI 0.004 to 0.033)	Calculated from weighted average of adverse events that were each sampled from Gamma distributions	PIX301[18]
	Grade 3–4	0.122 (95% CI 0.064 to 0.221)		
Adverse events rate TPC	Grade 2	0.025 (95% CI 0.007 to 0.055)		
	Grade 3–4	0.099 (95% CI 0.033 to 0.218)		
Adverse events rate costs pixantrone	Grade 2	£39.65 (95% CI £32.86 to £47.32)	Calculated from number of and costs of adverse events that were each sampled from Gamma distributions	PIX301[18] and Ref costs[50]
	Grade 3–4	£254.26 (95% CI £170.70 to £341.95)		

Adverse events rate costs TPC	Grade 2	£43.18 (95% CI £37.03 to £50.40)		
	Grade 3–4	385.78 (95% CI £279.54 to 472.30)		
Adverse events disutilities pixantrone	Grade 2	0.008 (95% CI 0.002 to 0.018)	Calculated from number of and duration of adverse events that were each sampled from Gamma distributions and utility decrements that were each sampled from beta distributions	PIX301[18]
	Grade 3–4	0.008 (95% CI 0.003 to 0.019)		
Adverse events disutilities TPC	Grade 2	0.007 (95% CI 0.003 to 0.015)		
	Grade 3–4	0.008 (95% CI 0.002 to 0.019)		
Cost of resource use whilst on treatment		£383.33	Calculated from a weighted average of professional and social services, health care professional, treatment follow-up and hospital costs that were each sampled from Gamma distributions using assumed 20% variation	PIX301[18] and ref costs[50] Clinical experts
Cost of resource use post treatment		£202.67		
Cost of resource use post progression		£798.00		
Cost at progression active therapy (one off)		£1,454.73 (£148.44)	Gamma (α, ß) (96.04, 15.15)	
Cost at progression palliative therapy (one off)		£47.99 (£4.90)	Gamma (α, ß) (96.04, 0.50)	
Cost at progression total (one off)		£798.20 (£81.45)	Gamma (α, ß) (96.04, 8.31)	
Abbreviations used in the table; BSA, body surface area; CI, confidence interval; FU, follow up; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PSA; probabilistic sensitivity analysis; SE, standard error; TPC, treatment of physician's choice.				

5.2.7 Treatment effectiveness and extrapolation

All parameters used to determine the effectiveness of original treatment (pixantrone or TPC) within the manufacturer's model were informed by data from PIX301, including the:

- parameters of predictive equations used to inform OS;
- parameters of predictive equations used to inform PFS;
- cycle-specific probability of treatment discontinuation.

As discussed in Section 5.2.4, the proportions of patients in the PFS, PD and death health states, per cycle, were estimated from parametric models based on OS and PFS data from PIX301. The partition method was used to estimate the proportions of patients in these health states. In particular, the proportion of patients in the PFS health states (either on or discontinued from 3rd or 4th line treatment) was estimated based on the area under the PFS curve. The number of patients in the death state was

estimated by 1 – OS and the number of patients in the "PD" health state was estimated by OS – PFS. In addition, patients with PFS were exposed to the risk of treatment discontinuation, based on Kaplan–Meier treatment discontinuation data.

Overall and progression-free survival

OS and PFS (defined as "time to progression or death" [MS; pg 142]) data from PIX301 were fitted with parametric distributions to enable the extrapolation of treatment effectiveness (with respect to OS and PFS) beyond the trial duration (~ 2 years). The method used by the manufacturer to select the parametric distributions applied in the estimation of model OS and PFS is displayed in Box 1.

Box 1. Method employed by the manufacturer to select parametric distributions used in manufacturer's model (reproduced from MS; pg 131)

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.

Abbreviations used in Box: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria.

Based on the method described in Box 1, the manufacturer selected separately fitted log-normal distributions to estimate both OS and PFS in the base case model. Generalised gamma and log-logistic distributions were also used in sensitivity analyses (see Section 5.2.12). The following points formed the basis of the manufacturer's rationale for selecting separately fitted log-normal distributions:

- the shape of the hazard functions differed by treatment arm;
- the hazard curves were non-monotonic, prohibiting the use of a Weibull distribution;
- following assessment of visual and statistical goodness-of-fit across the two-year trial period the generalised gamma, log-normal and log-logistic distributions provided the best fit (Figures 3 and 4 and Appendix 11);

- piecemeal fittings were not considered as a result of identifying distributions of sufficiently good fit;
- UK clinical experts suggested that the log-normal distributions provided realistic estimations of OS and PFS consistent with observations made in clinical practice (Figures 5 and 6 and Appendix 11).

Figure 3. Plot of log-normal parametric distributions and Kaplan–Meier data for OS (trial period)

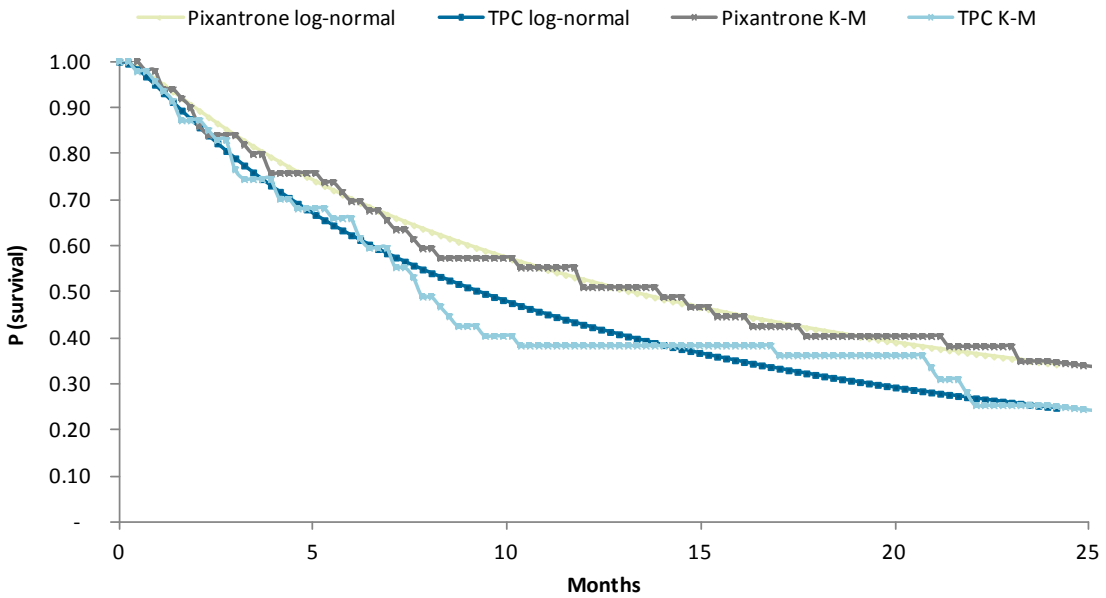


Figure 4. Plot of log-normal parametric distributions and Kaplan–Meier data for PFS (trial period)

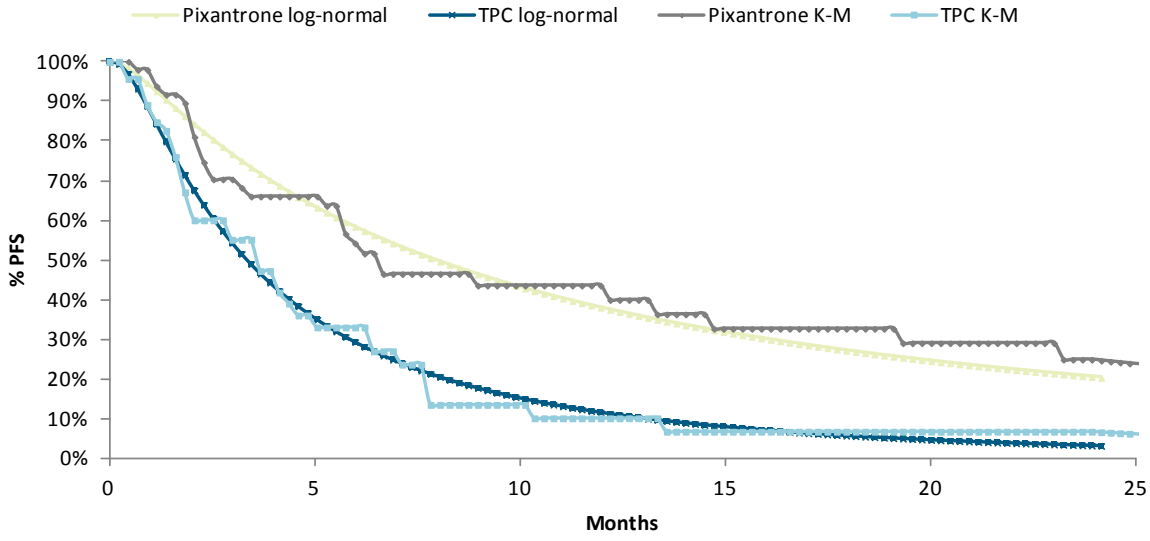


Figure 5. Plot of log-normal parametric distributions and Kaplan–Meier data for OS (long-term projection)

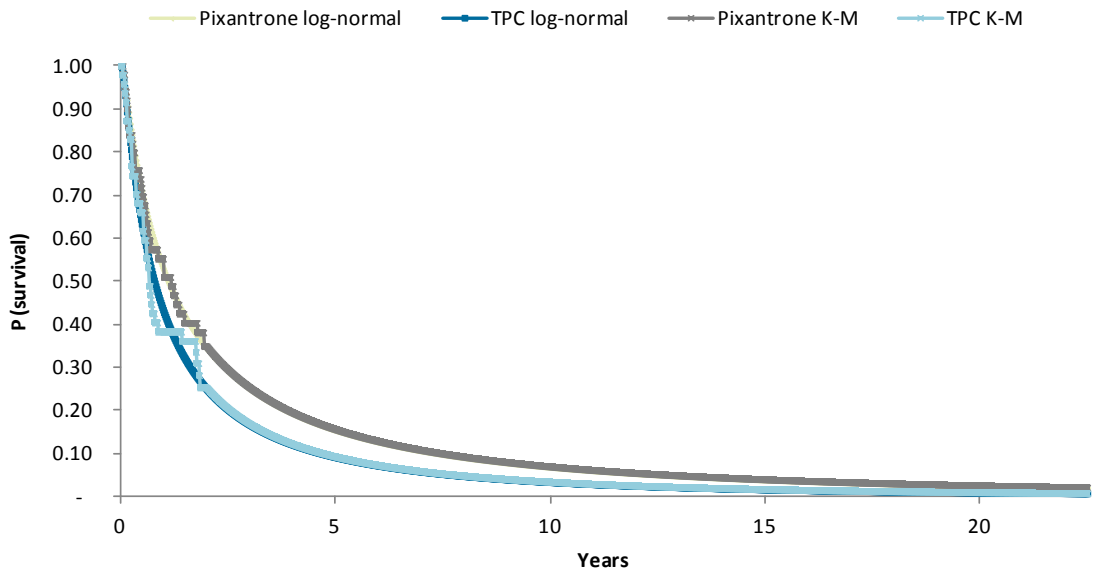
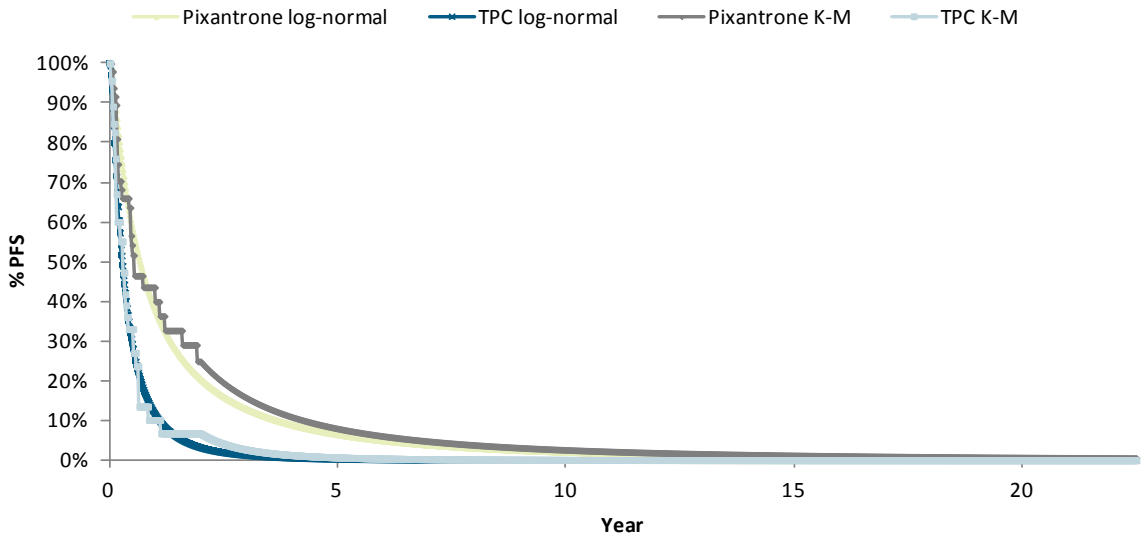


Figure 6. Plot of log-normal parametric distributions and Kaplan–Meier data for PFS (long-term projection)



The ERG notes that the manufacturer has adhered to the recommendations of the NICE DSU technical report in the development and implementation of the predictive equations used to estimate OS and PFS in the model.[44] In addition, based on the evidence provided by the manufacturer, the ERG considers the selection of separate log-normal distributions to inform OS and PFS by treatment to be appropriate.

Treatment discontinuation

As highlighted earlier in this Section, all patients experiencing disease progression discontinued original (3rd [or 4th] line) treatment upon entry into the "PD" health state. In addition, patients

experiencing PFS could remain on or discontinue from original therapy. Patients who discontinued original therapy were assumed to do so as a result of CR, adverse event (AE), completion of six months treatment duration, or non-clinical reason" (MS; pg 122). Within the economic model, the manufacturer applied a per cycle risk of treatment discontinuation to patients in "PFS, on 3rd (or 4th) line treatment" that was derived from Kaplan–Meier data on time to treatment discontinuation (TTD) observed in PIX301 (Table 25). Discontinuation within PIX301 occurred as a result of any of the following events (CSR; pg 47):

- completion of treatment;
- progressive disease/relapsed disease;
- the development of toxicity which, in the investigator's judgment, precluded further therapy;
- cardiac toxicity;
- patient refusal to continue;
- patient lost to follow-up or noncompliance;
- intercurrent illness precluding further therapy, in the investigator's opinion;
- pregnancy.

The ERG notes that the most common reason for discontinuation was disease progression; however, it is unclear whether, ahead of implementing these data into the economic model, the manufacturer has censored patients who discontinued as a result of disease progression. In the absence of censoring patients, the ERG notes that discontinuation, within the economic model, may be over-estimated. However, disease progression was higher in the TPC group (56% [39/70]) than in the pixantrone group (40% [28/70]). Furthermore, patients in the "PFS, discontinued 3rd (or 4th) line treatment" health state had a higher overall utility and lower costs; therefore, the potential double counting of discontinuation as a result of disease progression in the manufacturer's model is likely to bias against pixantrone.

The per cycle risk of treatment discontinuation was estimated from Kaplan–Meier data used in the manufacturer's base case model are presented in Table 25. These data were used to calculate the per cycle probability of treatment discontinuation as follows:

$$P_d = \frac{n_{t-1} - n_t}{n_t}$$

Where, P_d is the per cycle probability of discontinuation, n_{t-1} is the number of patients not reported to have discontinued in the previous cycle, n_t is the number of patients not reported to have discontinued in the present cycle. These probabilities were then used to estimate the per cycle incidence of treatment discontinuation as follows:

$$I_d = P_d . N_t^{PFS}$$

Where, I_d is the per cycle incidence of treatment discontinuation, P_d is the per cycle probability of discontinuation and N_t^{PFS} is the number of patients currently in the "PFS, on 3rd (or 4th) line treatment" health state. The per cycle incident treatment discontinuation is then used to determine the number of patients in the "PFS, on 3rd (or 4th) line treatment" health state as follows:

$$N_t^{PFS} = \frac{N_t^{PFS}}{N_{t-1}^{PFS}} . N_{t-1}^{PFS} . I_{d_{t-1}}$$

Where N_t^{PFS} is the number of patients in the "PFS, on 3rd (or 4th) line treatment" health state in the present cycle, N_{t-1}^{PFS} is the number of patients in the "PFS, on 3rd (or 4th) line treatment" health state in the previous cycle, $I_{d_{t-1}}$ is the per cycle incidence of treatment discontinuation in the previous cycle.

Table 25. Kaplan–Meier data on treatment discontinuation used in the manufacturer's base case model

Cycle	Treatment			
	Pixantrone		TPC	
	K–M data	Per cycle probability (%)	K–M data	Per cycle probability (%)
0	100.00%	0.00%	100.00%	0.00%
1	100.00%	0.00%	85.11%	17.78%
2	89.80%	0.00%	85.11%	0.00%
3	83.67%	10.00%	85.11%	0.00%
4	83.67%	11.11%	76.60%	8.10%
5	83.67%	0.00%	68.09%	14.72%
6	81.63%	0.00%	63.83%	6.89%
7	77.55%	0.00%	63.83%	7.40%
8	71.43%	5.00%	59.57%	4.01%
9	63.27%	10.53%	51.06%	16.67%
10	57.14%	11.76%	40.43%	14.99%
11	57.14%	6.67%	38.30%	0.00%
12	57.14%	0.00%	36.17%	5.88%
13	57.14%	3.57%	29.79%	25.00%
14	51.02%	0.00%	29.79%	0.00%
15	46.94%	11.11%	29.79%	8.36%

16	44.90%	12.50%	19.15%	36.33%
17	44.90%	4.76%	17.02%	14.33%
18	42.86%	5.00%	17.02%	0.00%
19	42.86%	5.26%	14.89%	0.00%
20	40.82%	0.00%	10.64%	33.31%
21	40.82%	5.56%	8.51%	0.00%
22	38.78%	0.00%	0.00%	100.00%
23	20.41%	0.00%	0.00%	100.00%
24	12.24%	47.06%	0.00%	100.00%
25	12.24%	55.56%	0.00%	100.00%
26	10.20%	0.00%	0.00%	100.00%
27	2.04%	25.00%	0.00%	100.00%
28	2.04%	66.67%	0.00%	100.00%
29	2.04%	0.00%	0.00%	100.00%
30	2.04%	0.00%	0.00%	100.00%
31	2.04%	0.00%	0.00%	100.00%
32	2.04%	0.00%	0.00%	100.00%
33	2.04%	0.00%	0.00%	100.00%
34	0.00%	100.00%	0.00%	100.00%
Abbreviations used in table: K–M, Kaplan–Meier; TPC, treatment of physician's choice.				

Following treatment discontinuation (pre- or post-progression), patients were eligible for subsequent therapies or palliative care. Table 26 summarises the proportions of patients receiving subsequent treatments or palliative care in the "PFS, discontinued 3rd (or 4th) line therapy" and "PD" health states.

Table 26. Proportion of patients receiving subsequent therapies or palliative care following discontinuation of original therapy, with respect to progression status

Health state		**Proportion of patients receiving each therapy**	
		PFS, discontinued 3rd (or 4th) line therapy[a]	**PD[a]**
Treatment	**Gemcitabine monotherapy (administered over 4 weeks)**	2%	8%
	Gemcitabine monotherapy (administered over 3 weeks)	8%	–
	Rituximab monotherapy	5%	–
	CVP	15%	–
	IVE	8%	–
	RVIG	–	–
	DHAP	–	12%
	CHOP	–	2%
	IVAC	2%	3%

	Weekly therapy[b]	10%	8%
	GEM-P	20%	–
	Palliative care[c]	23%	47%
	Clinical trial	7%	3%

[a] Based on the opinions of three clinical experts.

[b] Weekly therapy includes prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine and methotrexate.

[c] Palliative care consisted of the following medications as provided by the clinical experts; co-trimoxazole, aciclovir, red blood cell, dexamethasone, morphine, metoclopramide.

Abbreviations used in table: CHOP, cyclophosphamide, prednisolone, doxorubicin and vincristine; CVP, cyclophosphamide, vincristine and prednisolone; DHAP, dexamethasone, cytarabine and cisplatin; GEM-P, gemcitabine, cisplatin and prednisolone; IVAC, etoposide, cytarabine, mesna and ifosfamide; IVE, ifosfamide, etoposide, mesna and epirubicin; PD, progressive disease; PFS, progression-free survival; RVIG, rituximab, vinorelbine, ifosfamide and gemcitabine.

The ERG notes that the impact of subsequent therapy or palliative care on PFS and OS was assumed to be captured within the data from PIX301. The ERG considers this to be a pragmatic assumption that is reasonable in the context of this submission. However, the ERG considers it important to highlight that many of the subsequent therapies considered in the manufacturer's model are combination therapies, whereas, the subsequent treatment used in patients from PIX301 following progression were monotherapies (Manufacturer's Appendix Z; Table 2.4.7 and 2.4.8). Therefore, the ERG considers that data from PIX301 may not accurately capture the impact of subsequent therapies on PFS and OS in the economic model. However, the ERG notes that expert clinical opinion is that the survival benefit of subsequent treatments is likely to be negligible. Moreover, given that the cost of subsequent treatment is applied as a one-off cost and is the same for both arms, the ERG considers it unlikely that the disparity between treatments received in PIX301 and treatments included in the model would bias the model results.

5.2.8 Health-related quality of life

No HRQoL data were collected in the PIX301 trial; therefore, the manufacturer carried out a systematic review to identify utility value studies relevant to the health states and adverse events considered in the model. The following databases were searched:

- MEDLINE;
- EMBASE;
- NHS EED;
- EconLIT;
- Health Economics Evaluations Database (HEED).

Searches were carried out in December 2011 and were restricted by date (January 1995) and language (English language). The manufacturer reports that a similar search strategy (including supplementary searches of relevant manufacturers' and organisations' websites) to that used to identify studies for

the clinical and cost-effectiveness reviews (see Sections 4.1.1 and 5.1) was used in the HRQoL review; however, broader inclusion criteria were applied. In particular, "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" (MS; pg 153). The manufacturer's rationale for including a broader population in the HRQoL review was that "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" (MS; p153). The ERG considers the manufacturer's approach to be reasonable, particularly given the paucity of quality of life studies available in the patient population considered in the economic model. In addition, the ERG notes that reasonable search terms (Appendix 12) were used and considers it unlikely that any relevant studies have been missed.

Health state utilities

The manufacturer's model consisted of the following four health states:

- PFS, on 3rd (or 4th) line treatment;
- PFS, discontinued 3rd (or 4th) line treatment;
- PD;
- death (absorbing state).

Based on expert clinical opinion, the manufacturer assumed equal baseline utility (i.e., notwithstanding adverse event disutilities) for the two PFS health states. In addition, the manufacturer assumed zero utility for patients in the death state. Therefore, the manufacturer's HRQoL review focussed, in part, on the identification of utility values for the PFS and PD health states.

However, despite the broader population inclusion criteria applied in the HRQoL review, the manufacturer reports that no health state utility data were identified for patients with aggressive NHL. Furthermore, the manufacturer states that, consequently, "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. The identified utilities included those for patients with DLBCL, chronic myelogeneous leukaemia, chronic lymphocytic leukaemia, follicular lymphoma, renal cell carcinoma and melanoma" (MS; pg 156); no further details regarding the identification of utility data were provided. The health state utility values used in the manufacturer's base case and sensitivity analyses are summarised in Table 27.

Table 27. Summary of health state utility values identified by the manufacturer (adapted from MS; Table 33; pg 158)

Description of data sources	Pre-progression utility	Post-progression utility	Reference in submission
Utility values used in the base case analysis			
Self-reported quality of life during first-line chemotherapy in elderly patients with aggressive NHL	0.81	0.60	Doorduijn *et al*.[51], 2005 in Groot *et al*.[45] 2005
Utility values used in sensitivity analysis			
Second-line treatment in patients with chronic myelogeneous leukaemia	0.85	0.73	NICE 2011 (FAD from TA 241)[52]
Third-line treatment in patients with chronic lymphocytic leukaemia	0.65	0.47	Ferguson *et al*.[53], 2008
First-line maintenance treatment in patients with follicular lymphoma	0.78	0.62	Wild *et al*.[54], 2006 Pettengell *et al*.[55], 2008 NICE TA226, 2011[56]
First-line treatment in patients with metastatic renal cell carcinoma	0.70	0.59	Kilonzo *et al*., 2010 (NICE TA215)[57]
Second-line treatment in patients with renal cell carcinoma	0.76	0.68	NICE 2009 (FAD from NICE TA178)[58]
Second-line treatment in patients with malignant melanoma	0.80	0.76	Dickson *et al*.[59], 2011 (NICE ERG report ID73)
Abbreviations used in table; ERG, Evidence Review Group; FAD, Final Appraisal Determination; NICE, National Institute of Health and Clinical Excellence; TA, technology appraisal.			

The ERG notes that despite stating that no health state utility data were identified for patients with aggressive NHL, the manufacturer has used utility values from elderly patients with aggressive NHL[51] to inform the base case model (Table 27). In addition, the ERG notes that these values were indirectly derived from a study by Doorduijn *et al*.[51] which was identified and rejected in the manufacturer's original HRQoL review. These values were used in a cost-effectiveness analysis of rituximab in a DLBCL population[45] (identified in the manufacturer's supplementary search). Groot *et al*. stated that the utility values used in their cost-effectiveness analysis were derived from a "weighted average of utilities found on different time points after initial treatment" cited as a personal communication of the study by Doorduijn *et al*.[45] The study by Doorduijn *et al*.[51] considered the self-reported quality of life in elderly patients with aggressive NHL and was originally rejected by the manufacturer as "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" (MS; pg 155). In addition, the ERG considers it important to note that the utility values reported in Doorduijn *et al*. are higher than UK time trade off values for healthy elderly patients.[60]

Consequently, the ERG notes that the utility data selected to inform the manufacturer's base case model may not be appropriate. Therefore, the ERG sought expert clinical opinion regarding alternative utility data identified by the manufacturer (and used in sensitivity analyses Table 27), to

determine which patient population was most analogous to the modelled population with respect to quality of life. Based on expert clinical advice, the ERG considers the population of patients on third-line treatment for chronic lymphocytic leukaemia (reported in Ferguson *et al*.[53]) to be most representative of the population of patients considered in the manufacturer's model. In addition, the ERG notes that the study by Ferguson *et al*. reports PFS and PD utility values for patients on first, second and "final" line treatment (Table 28).

Table 28. Utility data for patients with chronic lymphocytic leukaemia reported by Ferguson *et al*.[53]

Patient population	Health state	
	PFS	PD
First-line CLL	0.777	0.540
Second-line CLL	0.650	0.470
Final-line CLL	**0.428**	**0.279**
Abbreviations used in table: CLL, chronic lymphocytic leukaemia; PD, progressive disease; PFS, progression-free survival.		

The ERG notes that the manufacturer has selected, for use in sensitivity analysis, utility values reported for patients on second-line therapy; however, the ERG considers that the utility values reported for patients on "final line therapy" may be more representative of the patient population that is the focus of this STA. Therefore, the ERG carried out a sensitivity analysis using the final line utility values (PFS: 0.428, PD: 0.279) reported in Ferguson *et al*.[53] to inform the model. This analysis resulted in an increase in the ICER of £24,126 (from £28,503 to £52,629 per QALY).

Disutilities

As discussed in Section 5.2.4, adverse events were modelled as events rather than as health states. That is, costs and disutilities related to the occurrence of an adverse event were applied to the proportion of patients, within a health state, assumed to experience the adverse event. Based on a combination of a paucity of data and expert clinical opinion that "the impact of subsequent treatments on health related quality of life (HRQoL) is negligible" (MS; pg 124); the manufacturer's model limited the consideration of adverse events to patients on original therapy (pixantrone or TPC). The ERG notes that this may bias the model towards the treatment arm with a higher discontinuation rate and/or a longer duration of PD (i.e., TPC); however, the ERG notes that the impact of this bias is likely to be minimal.

The adverse event profile of each treatment arm was obtained from *post-hoc* analysis of data from PIX301. The manufacturer highlights that the adverse events considered in the model were events of Grade 3 and 4, occurring in at least 5% of the total patient population. In addition, some Grade 2 and rarer Grade 3 and 4 events, considered important by UK clinical experts, were included. The treatment-related adverse events accounted for in the manufacturer's model, together with the

disutility and duration assumed to be associated with each event, is displayed in Table 29. The manufacturer states that as a consequence of the paucity of data identified in the manufacturer's HRQoL review, "a targeted review of relevant literature from other oncology indications for which similar AEs occur" was carried out to identify adverse event-related disutilities (MS; pg 155). The ERG notes that no further details were provided regarding the methods or results of the targeted search for utility decrements. In addition, the ERG noted several inconsistencies between the utility decrement values reported in the MS and those used in the manufacturer's model. However, as part of the clarification process, the manufacturer provided an updated list of the disutilities used.

Table 29. Adverse events, considered in the manufacturer's model, by treatment arm (adapted from MS; Tables 29 and 30, pgs 134-35 and manufacturer's clarification response; Table B2-1; pg 20)

Adverse event	Number of events observed (N)		Duration[a]	Disutility	Reference for disutility value
	Pixantrone	TPC			
Grade 2					
Neuropathy	–	–	35.33	–0.12	Assumed to be the same as for fatigue and asthenia
Abdominal pain	3	3	17.00	–0.07	Assumption[b]
Vomiting	2	4	2.33	–0.10	Lloyd *et al*.[(61)], 2006, 683–690. Table 3
Asthenia	6	3	35.33	–0.12	Assumption[b]
Pain	–	–	18.00	–0.07	
Fatigue	2	6	31.50	–0.12	
Grade 3–4					
Abdominal pain	3	1	17.00	–0.07	Doyle *et al*.[(62)], 2008 374–380. Table 2
Anaemia	2	8	16.07	–0.25	Swinburn *et al*.[(63)], 2010, 1091–1096 Table 1
Anorexia	3	1	35.00	–0.37	Assumption[c]
Asthenia	3	2	35.33	–0.12	Lloyd *et al*.[(61)], 2006, 683–690. Table 3
Back pain	–	–	18.00	–0.07	Doyle *et al*.[(62)], 2008 374–380. Table 2
Bronchitis	1	–	24.00	–0.37	Assumed to be the maximum disutility of all the other Grade 3–4 adverse events

Cellulitis	1	4	12.50	–0.37	Assumed to be the maximum disutility of all the other Grade 3-4 adverse events
Dehydration	2	–	8.00	–0.10	Lloyd *et al*.[61], 2006, 683–690. Table 3
Dyspnoea	2	2	12.72	–0.05	Doyle *et al*.[62], 2008 374 – 380. Table 2
Ejection fraction decreased	2	–	11.50	–0.37	Assumed to be the maximum disutility of all the other Grade 3–4 adverse events
Fatigue	1	–	31.50	–0.12	Lloyd *et al*.[61], 2006, 683–690. Table 3
Febrile neutropaenia	4	2	7.14	–0.15	Lloyd *et al*.[61], 2006, 683–690. Table 3
Hypotension	2	1	8.00	–0.37	Assumed to be the maximum disutility of all the other Grade 3–4 adverse events
Leukopaenia	19	3	13.96	–0.37	Assumed to be the maximum disutility of all the other Grade 3–4 adverse events
Lymphopaenia	2	–	34.00	–0.37	Assumed to be the maximum disutility of all the other Grade 3–4 adverse events
Malignant neoplasm progression	–	–	11.00	–0.37	Assumed to be the maximum disutility of all the other Grade 3–4 adverse events
Mucosal inflammation	–	1	4.00	–0.37	Assumed to be the maximum disutility of all the other Grade 3–4 adverse events
Nausea	–	–	6.00	–0.05	Nafees *et al*.[64], 2008. Table 2
Neutropaenia	52	16	15.09	–0.09	Nafees *et al*.[64], 2008. Table 2

Pain in extremity	–	1	3.00	–0.07	Doyle *et al*.[62], 2008 374–380. Table 2
Platelet count decreased	1	1	16.50	–0.11	Tolley 2010 (A273–A274)[65]
Pleural effusion	1	–	3.00	–0.37	Swinburn *et al*.[63], 2010. 1091–1096. Table 1
Pneumonia	1	1	14.00	–0.20	Beusterien 2010. p50. Table 1[66]
Pyrexia	3	6	12.30	–0.11	Beusterien 2010. p50. Table 1[66]
Renal failure	–	4	29.75	–0.27	Poole *et al*.[67], 2009 (A203)
Thrombocytopaenia	7	5	23.23	–0.11	Tolley 2010 (A273–A274)[65]
Vomiting	–	3	2.33	–0.05	Nafees *et al*.[64], 2008. Table 2
Weight decreased	–	1	55.33	–0.117	Sinno *et al*.[68], 2011

[a] Duration of adverse events taken from secondary analysis of PIX301.

[b] Assumed to be the same as The same disutility used for this event at Grade 3 or 4 is used (pain and pain in extremity are assumed to be equivalent events).

[c] Disutility of this event was assumed to be equal to the maximum disutility of Grade 3–4 adverse events identified in the manufacturer's HRQoL review.

Abbreviations used in table: HRQoL, health-related quality of life; TPC, treatment of physician's choice.

For Grade 3 and 4 adverse events, in which no disutility data were identified by the targeted review, the manufacturer applied "the maximum value of the range identified" (MS; pg 156). The ERG notes that the "maximum value of the range identified" was –0.371, cited as being obtained from a study by Swinburn *et al*.[63] Swinburn *et al.*[63] reported health state utility values for patients with metastatic renal cell carcinoma. It is unclear which data from Swinburn *et al.* have been used to inform this disutility. In response to the ERG's clarification question regarding which data had been used, the manufacturer responded that the correct disutilities had been used in the model; therefore, it remains unclear which data were used. Moreover, the ERG notes, that, as asserted by the manufacturer, the use of this "maximum" value to inform the disutility associated with adverse events for which no data were identified, is a conservative assumption (i.e., likely to bias against pixantrone). The ERG notes that, of the adverse events to which the "maximum" disutility value is applied, patients treated with pixantrone experienced a higher occurrence of all but two (mucosal inflammation and cellulitis).

In addition to the uncertainty around the derivation of the maximum disutility value used in the manufacturer's model, the ERG notes that two of the studies[67;68] identified to provide disutility data were in disease areas other than cancer. In particular, the study by Poole *et al*.[67] provided utility decrements associated with "transition from a remitting to relapsing states in adults with established

ulcerative colitis". These data were used to inform the disutility associated with renal failure, which the ERG notes may be applicable across cancer and non-cancer disease areas. However, the ERG notes that the disutility associated with weight loss was obtained from a study by Sinno *et al*.[68] which quantified the utility of patients with substantial weight loss following surgical procedures carried out to manage obesity. The ERG notes that the utility change experienced by obese patients with substantial weight loss may not be representative of patients experiencing weight loss as a result of lymphatic cancer or the associated treatments.

Furthermore, the ERG was unable to verify the disutility values used for anaemia and renal failure. The ERG considers that based on the data presented in the relevant papers, the disutility associated with anaemia could be assumed to be –0.119 (stable with no adverse event utility [0.795] minus the utility of patient with Grade 3 anaemia [0.676]) and disutility with renal failure assumed to be –0.159 (utility of renal failure [0.651] subtracted from the utility of PFS used in the manufacturer's model [0.81]). In addition, the ERG notes that the disutility of Grade 2 vomiting was higher than the disutility applied to Grade 3 or 4 vomiting. Therefore, the ERG carried out a sensitivity analysis using revised disutility estimates for the adverse events over which there was concern over the propriety of the values used in the manufacturer's analysis. Values used in the ERG's analysis are presented in Table 30; implementing these values increased the ICER by £3 (from £28,503 to £28,506 per QALY).

Table 30. ERG's revised disutility values

Adverse event	Disutility used in MS	ERG's revised disutility	ERG's rationale for adjustment
Anaemia (Grade 3 or 4)	–0.25	–0.119	Unclear how the value used by the manufacturer was calculated. The ERG calculated disutility based on the utility values reported in the paper[63] for stable disease with no adverse event (0.795) and utility for patients with anaemia (0.676)
Renal failure (Grade 3 or 4)	–0.27	–0.159	Unclear how the value used by the manufacturer was calculated. The ERG calculated disutility based on the utility values reported in the paper for renal failure (0.651), and subtracted from the manufacturer's baseline utility for PFS (0.81)
Vomiting (Grade 3)	–0.05	–0.10	To address the issue of face validity regarding the disutility associated with a Grade 3 or 4 adverse event being less than that of a Grade 2 adverse event
Weight decreased	–0.117	–0.37	In the absence of a reliable source for the disutility associated with weight decrease as a result of disease or treatment, the ERG has assumed the maximum disutility in line with the manufacturer's approach
Abbreviations used in table: ERG, Evidence Review Group; MS, manufacturer's submission; PFS, progression-free survival.			

Implementation of disutility associated with adverse events

The disutilities associated with the adverse events considered in the manufacturer's model were applied as weighted average disutilities. That is, for each treatment the manufacturer calculated a weighted average of Grade-specific disutilities; weighted by the number of events of that particular Grade experienced by patients (Table 29). In addition, the disutility associated with each adverse event was applied for the duration specific to that adverse event (Table 29). This gave the annual utility decrement expected per treatment arm; therefore, the manufacturer converted these annual decrements into weekly disutilities for use in the model engine (Table 31).

Table 31. Annual and per cycle utility decrement per treatment arm, applied in the manufacturer's model

Adverse event Grade	Pixantrone		TPC	
	Annual	Weekly	Annual	Weekly
Grade 2	–0.0075	–0.0010	–0.0066	–0.0009
Grade 3 or 4	–0.0079	–0.0011	–0.0080	–0.0011
Abbreviation used in table: TPC, treatment of physician's choice.				

These average weekly disutilities were then applied, per cycle, to all patients experiencing adverse events on original treatment. The number of patients experiencing Grade 2 or Grade 3 or 4 adverse events was in turn calculated by the application of a per cycle probability. The calculations used to estimate these probabilities are summarised in Table 32.

Table 32. Treatment-specific probability of adverse events used in the manufacturer's model

Treatment	Risk per week[a]	Per cycle probability[b]
Grade 2		
Pixantrone	0.0142	0.0141
TPC	0.0250	0.0247
Grade 3 and 4		
Pixantrone	0.1224	0.1152
TPC	0.0986	0.0939
[a] Calculated as the sum of Grade 2 adverse events experienced divided by the total patient exposure in weeks (915 weeks and 639 weeks for pixantrone and TPC, respectively). [b] Calculated as 1-EXP(-risk per week). Abbreviation used in table: TPC, treatment of physician's choice.		

As highlighted by the manufacturer, the overall frequency of adverse events was similar between treatment groups; however, more Grade 3 or 4 adverse events occurred in the pixantrone group (MS; pg 217). The ERG notes that the probabilities of adverse events used in the manufacturer's model were assumed to be independent of time; that is, the probability of experiencing an adverse event did not vary by time on treatment. The manufacturer asserts that this is a conservative assumption, as "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" (MS; pg 136). However, the ERG notes that the consideration of adverse events is limited to patients on original therapy and that, while the weighted average approach used to calculate the adverse events rates may not accurately reflect the rate in each cycle (i.e., underestimate the rate in the earlier cycles and overestimate the rate in later cycles), any inaccuracy is unlikely to greatly affect the ICER.

Finally, the ERG notes that utility data were not adjusted for age; however, as highlighted by the manufacturer, the patient population considered in this STA is expected to have a very short life expectancy. Therefore, the ERG considers that the exclusion of age adjustment is unlikely to substantially impact on the cost-effectiveness results.

5.2.9 Resources and costs

As discussed in Section 5.1, the manufacturer carried out a systematic literature review to identify economic evaluations and costing studies relevant to the use of third or subsequent line treatment in a population of patients with aggressive NHL. The systematic review did not identify any relevant costing studies. Consequently, the manufacturer obtained data on resource use from a survey of clinical experts (see Appendix 13), who were consulted as part of the development of the economic model. Clinical experts were asked to complete a questionnaire designed to gather data on the aspects of resource use as outlined in Box 2.

Box 2. Aspects of resource use collected in survey of clinical experts (reproduced from MS; pg 169)

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)
Abbreviation used in box: AEs, adverse events.

In addition, unit cost data from the following UK-specific sources were used to inform the cost profile used in the manufacturer's model:

- British National Formulary (BNF) Volume 62;[49]
- Unit Costs of Health and Social Care 2011;[69]
- NHS Reference Costs (2010–2011);[50]
- National Audit Office, End of Life Care.[70]

Within the economic evaluation, the manufacturer identified four key types of cost: intervention and comparator; health state, subsequent treatment/palliative care; and adverse event. The calculation and application of each of the costs covered within these categories are detailed in the following sections.

Intervention and comparator costs

This section describes the calculation and implementation of the costs associated with drug (pixantrone [intervention] and TPC [comparator]) procurement and administration.

The manufacturer's model was constructed to allow the calculation of drug costs including or excluding the assumption of wastage (i.e., no vial sharing); the base case analysis assumes that wastage occurs. The manufacturer's method of calculating drug costs, assuming wastage, is displayed in Box 3.

Box 3. Method used in the manufacturer's model to account for wastage in the cost of drugs

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.
Abbreviation used in Box: BSA, body surface area.

For example, based on a required dose of oxaliplatin of 90 mg per m^2, 24% of the male and 59% of the female population of PIX301 would require three 50 mg packs. Whereas, four 50mg packs would be required by 72% and 41% of the male and female PIX301 population respectively (obtained from the manufacturer's model). For each drug used in the TPC group, the proportions of administrations from each pack size available per drug were calculated to inform the overall drug procurement cost of TPC. The ERG notes that the calculation of drug costs to include wastage was partially hard coded within the manufacturer's model and therefore unable to be fully validated. However, the ERG notes that, compared with the costs obtained under the assumption of vial sharing (i.e., no wastage), the costs obtained under the assumption of wastage were reasonable; when vial sharing was assumed the manufacturer simply applied the lowest unit cost (per mg) to the average body surface area (BSA) (1.79 m^2) of patients in PIX301. The costs of each drug used in the TPC group calculated assuming wastage and calculated assuming vial sharing are summarised in Table 33.

Table 33. Drug procurement costs associated with treatments used in the TPC group

Treatment	Dose requirement per m^2	Average unit requirement[a]	Cost no wastage (£)	Proportion of administrations per pack/vial (pack/vial type)		Cost with wastage (£)
Ifosfamide	2,614	4,670	203	5.13 (1,000 mg)		223
Vinorelbine	14	25	68	2.97 (1 mg/mL)		86
Etoposide (intravenous)	100	179	22	2.15 (5 mg/mL)		26
Etoposide (oral)	30	53	5	0.40 (50 mg)	0.60 (100 mg)	7
Gemcitabine	985	1,759	251	2.18 (200 mg)	0.99 (1,500 mg)	282
Oxaliplatin	90	160	480	0.40 (50 mg)	1.62 (100 mg)	546

[a] Equals dose requirement per m^2/average BSA from PIX301.

Abbreviations used in table: mg, milligram; mL, millilitre.

Following the calculation of drug cost per administration, the cost per cycle of pixantrone and TPC is determined, taking into account the administration schedule for each drug. Table 34 summarises the drug costs and administration schedule associated with pixantrone and TPC. The weekly cost to patients in the pixantrone and TPC arms is summarised in Table 35.

Table 34. Drug cost and administration schedule used in the manufacturer's model (adapted from MS; Table 36, pg 172)

Intervention or comparator	Distribution of TPC drugs[a]	Average dose (mg/m^2) per administration	Treatment cycle (weeks)	Week				Drug cost per administration (£)[b]
				1	2	3	4	
Pixantrone	–	71.7	4	1	1	1	–	1,665
TPC								
Vinorelbine	16.40%	14.0	4	1	1	1	1	86
Oxaliplatin	44.80%	89.8	3	1	–	–	–	546
Ifosfamide	17.90%	2,614.0	4	2	–	–	–	223
Etoposide 100 mg	6.00%	100.0	4	5	–	–	–	26
Etoposide 50 mg	7.50%	30.0	4	7	7	7	–	7
Mitoxantrone	6.00%	13.0	3	1	–	–	–	185
Gemcitabine	1.50%	984.6	4	1	1	1	–	282

[a] Based on data from PIX301.

[b] Including wastage.

Table 35. Drug cost per cycle used in manufacturer's model

Treatment arm	Drugs administered in cycles of	Week[a]			
		1	2	3	4
Pixantrone	4 weeks	£1,665.18	£1,665.18	£1,665.18	£0
	3 weeks	N/A	N/A	N/A	N/A
TPC[b]	4 weeks	£109.94	£22.11	£22.11	£14.12
	3 weeks	£255.66	£0	£0	N/A

[a] For treatments given in cycles of 4 weeks the costs of treatment in weeks 1, 2, 3 and 4 are reapplied in weeks 5, 6, 7 and 8, and then again in weeks 9, 10, 11 and 12 and so on until patients discontinue from treatment or progress. Similarly, for treatments given in cycles of 3 weeks, the costs of treatment in weeks 1, 2 and 3 are reapplied in weeks 4, 5 and 6, and then again in weeks 7, 8 and 9, *etc*.

[b] The cost of TPC per week is derived from a weighted average of TPC treatments; weighted by the proportion of patients receiving each therapy (reported in Table 34).

Abbreviation used in table: TPC, treatment of physician's choice.

The ERG notes that in response to clarification, the manufacturer highlighted that the price of pixantrone used in the original submission was calculated in error. The price per vial used in the original submission was £343.80 per 29 mg, rather than £553.50 per 50 mg, which was confirmed by the manufacturer to be the correct price. The ERG notes that this correction results in an increase of £5 (from £1,660.27 to £1,665.18) in the drug cost per administration (based on approximately 5 and 3 vials per administration, respectively). The impact of using the correct price (of £553.50 per 50 mg), increased the ICER by £80 (from £28,423 to £28,503 per QALY).

In addition, the ERG notes that the manufacturer used drug costs from BNF 62 (published in 2010),[49] rather than the current BNF 64[71] to inform the model. Therefore, as part of the clarification process, the ERG requested an updated model using prices from the BNF 64. In the clarification response, the manufacturer asserts that only the price of epirubicin at a concentration of 2 mg/mL and vial size of 100 mL differed between the two versions of the BNF; the price decreased from £386.16 in BNF 62 to £306.20 in BNF 64. The ERG notes that, in addition to the change in price of epirubicin, there was a change in price of cisplatin 50 mg, increasing from £17 (BNF 62) to £25 (BNF 64). However, updating the model to use drug costs from BNF 64 had minimal impact on the ICER (increased by £2, from £28,503 to £28,505).

Furthermore, the ERG notes that the trial population of PIX301 may not be entirely representative of the UK population. In particular, the ERG notes that many of the patients in PIX301 were from regions outside Western Europe (72.9%) and that these patients may have different BSA to the UK patient population; therefore, the drug costs used in the manufacturer's model may not be entirely representative of the cost incurred by the NHS. However, the ERG accepts that in the absence of UK-specific NHL patient BSA data, trial data may provide a reasonable approximation.

Cost of drug administration

In the absence of Payment by Results (PbR) tariffs for chemotherapy delivery, the manufacturer used 2010–2011 NHS reference costs[50] to inform the cost of administration associated with pixantrone and TPC. With the exception of etoposide 50 mg, which is given orally, all treatments were delivered intravenously. For complex regimens (oxaliplatin and ifosfamide), the cost of initial administration was assumed to be represented by HRG code: SB14Z (deliver complex chemotherapy, including prolonged infusion treatment at first attendance). For pixantrone, vinorelbine, etoposide 100 mg, mitoxantrone and gemcitabine, HRG code SB12Z (deliver simple parenteral chemotherapy at first attendance) was used to inform the cost of initial administration. The cost of subsequent administration of therapies administered intravenously was assumed to be equal to the cost associated with HRG code SB15Z (deliver subsequent elements of a chemotherapy cycle). The administration costs applied within the model are summarised in Table 36.

Table 36. Costs of drug administration used in the manufacturer's model

Cost component	HRG code	Unit cost in the model
First cycle administration	(SB12Z): Deliver simple parenteral chemotherapy at first attendance	**£231**
First cycle administration	(SB14Z): Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	**£302**
First cycle and subsequent cycles administration	(SB11Z): Deliver exclusively oral chemotherapy	**£163**
Subsequent cycles administration	(SB15Z): Deliver subsequent elements of a chemotherapy cycle	**£206**
Abbreviation used in table: HRG, healthcare resource group.		

The ERG considers that the manufacturer has used the correct HRG codes to inform the administration of the considered interventions.

Health state costs

The cost of care associated with patients was assumed to differ by health state; that is, with respect to the progression (PFS or PD) and treatment (active treatment versus palliative care) status of a patient. Within the manufacturer's model the cost of care included the costs of:

- professional and social services (residential care, day care, home care and hospice care);
- health care professionals (oncologist visit, haematologist visit, radiologist visit, nurse visit, palliative care specialist visit, specialist nurse visit, GP, district nurse and CT scan);
- treatment follow-up (full blood cell counts, lactate dehydrogenase [LDH], liver function, renal function, immunoglobin and calcium phosphate);
- hospital resource use (number of inpatient days, junior haematologist visits, senior haematologist visits, radiologist, specialist nurse, oncologist and GP visits).

The constitution of each health state, with respect to the elements of patient care outlined above, were estimated from a survey of three key opinion leaders, commissioned by the manufacturer. The unit costs of each element of patient care were sourced from NHS reference costs 2010–2011, the Unit Costs of Health and Social Care 2011 or National Audit Office, End of Life Care.[69;70] Overall, the manufacturer estimated the per cycle cost of patient care to be £383.33, £202.67 and £798.00 for patients in the "PFS, on 3rd (or 4th) line treatment", "PFS, discontinued 3rd (or 4th) line treatment" and "PD", respectively. Tables 37 to 40 summarise the unit costs and resource use assumed in the calculation of each component of health state costs.

Table 37. Resource use and costs associated with professional and social services used in the manufacturer's model

Resource	Resource use (days)[a]			Unit costs of resource (£)	Duration	Source
	PFS on 3rd (or 4th) line treatment	PFS, discontinued 3rd (or 4th) line treatment	PD			
Residential care	2.99	0.75	–	71.00	28 days	Unit costs of health and social care[69]
Day care	1.12	0.28	1.87	36.00	28 days	
Home care	4.67	1.17	9.33	28.89	28 days	National Audit Office, End of Life Care.[70]
Hospice	0.65	0.16	12.13	136.57	Annual	
Total per cycle costs (£)[b]	**119.10**	**29.78**	**498.47**	–		

[a] Estimated from expert clinical opinion.

[b] Calculated as a weighted average of unit costs per week (i.e., unit cost/duration*7 days); weighted by resource use.

Abbreviations used in table: PD, progressive disease; PFS, progression-free survival.

Table 38. Resource use and costs associated with health care professionals, used in the manufacturer's model

Resource	Resource use (number of visits)[a]			Unit costs (per 28 days) of resources (£)	Source
	PFS on 3rd (or 4th) line treatment	PFS, discontinued 3rd (or 4th) line treatment	PD		
Hospital-based health care					
Oncologist	1.67	0.42	0.33	119.99	National Schedule of Reference Costs Year: 2010–2011. NHS Trusts and PCTs combined[50]
Haematologist	0.78	0.19	1.00	148.00	
Radiologist	1.33	0.33	0.00	17.00	
Nurse	4.00	1.00	0.00	50.00	Unit costs of health and social care[69]

Palliative care team	0.00	0.00	1.33	207.00	National Schedule of Reference Costs Year: 2010–2011. NHS Trusts and PCTs combined[50]
Specialist nurse	0.67	0.17	2.50	59.00	Unit costs of health and social care[69]
Community-based health care					
GP	2.00	0.50	3.33	53.00	Unit costs of health and social care[69]
District nurse	1.50	0.38	4.00	50.00	
CT scan	0.31	0.31	0.03	100.65	National Schedule of Reference Costs Year: 2010–2011. - NHS Trusts and PCTs combined[50]
Total costs per health state (£)[b]	**197.24**	**55.10**	**247.68**	–	

[a] Estimated from expert clinical opinion.

[b] Calculated as a weighted average of unit costs; weighted by resource use, divided by 4 (to give weekly rather than 28 day cost).

Abbreviations used in table: CT, computerised tomography; GP, general practitioner; PCT, Primary Care Trust; PD, progressive disease; PFS, progression-free survival.

Table 39. Resource use and costs associated with treatment follow-up used in the manufacturer's model

Resource	**Resource use (visits)[a]**			**Unit costs (per 28 days) of resources**	**Source**
	PFS on 3rd (or 4th) line treatment	**PFS, discontinued 3rd (or 4th) line treatment**	**PD**		
Full blood cell counts	3.33	3.33	1.00	3.36	National Schedule of Reference Costs Year: 2010–2011. NHS Trusts and PCTs combined[50]
LDH	2.00	2.00	0.33	1.26	
Liver function	3.33	3.33	1.00	8.80	
Renal function	3.33	3.33	0.33	12.57	
Immunoglobulin	0.67	0.67	0.33	1.26	
Calcium phosphate	0.67	0.67	1.00	1.26	
Total costs per health state (£)[b]	**21.66**	**21.66**	**4.61**	**–**	

[a] Estimated from expert clinical opinion.

[b] Calculated as a weighted average of unit costs; weighted by resource use, divided by 4 (to give weekly rather than 28 day cost).

Abbreviations used in table: LDH, Lactate dehydrogenase; PCT, Primary Care Trust; PD, progressive disease; PFS, progression-free survival.

Table 40. Hospital-related resource use and costs used in the manufacturer's model

Resource	Resource use[a]			Unit costs (per annum) of resources	Source
	PFS on 3rd (or 4th) line treatment	PFS, discontinued 3rd (or 4th) line treatment	PD		
Number of inpatient days	3.17	3.17	2.70	490.91	National Schedule of Reference Costs Year: 2010–2011. NHS Trusts and PCTs combined[50]
Junior haematologist visits	2.00	2.00	2.00	148.00	
Senior haematologist visits	1.07	1.07	0.67	148.00	
Radiologist visits	0.03	0.03	0.03	17.00	
Specialist nurse visits	2.53	2.53	2.07	59.00	Unit costs of health and social care[69]
Nurse visits	2.40	2.40	2.00	50.00	
Oncologist visits	0.60	0.60	0.30	119.99	National Schedule of Reference Costs Year: 2010–2011. NHS Trusts and PCTs combined[50]
GP visits	0.13	0.13	0.07	50.00	Unit costs of health and social care[69]
Total costs per health state (£)[b]	**45.33**	**45.33**	**38.12**	–	

[a] Estimated from expert clinical opinion.

[b] Calculated as a weighted average of unit costs; weighted by resource use, divided by 52 (to provide weekly rather than annual costs).

Abbreviations used in table: GP; general practitioner; PCT, Primary Care Trust; PD, progressive disease; PFS, progression-free survival.

In addition to the weekly cost of patient care detailed in Tables 37 to 40, patients in the "PD" health state also incur a one-off cost of disease follow up. Table 41 summarises the resource use and unit cost of disease follow up applied in the manufacturer's model.

Table 41. Resource use and unit cost of disease follow up for patients with progressive disease applied in the manufacturer's model

Resource	Resource use[a]		Unit costs (£)	Source
	Subsequent therapy	Palliative care		
ECG	67%	–	31.00	National Schedule of Reference Costs Year: 2010–2011. NHS Trusts and PCTs combined[50]
MUGA	33%	–	179.22	
CT	17%	33%	100.65	

MRI	7%	7%	215.99	
PET-CT	57%[b]	–	842.90	
Bone marrow biopsy	70%[b]	–	273.00	
Total costs (£)[c]	**1,454.73**	**47.99**	**798.20**	

[a] Based on expert clinical opinion

[b] PET-CT and bone marrow biopsy were performed twice and so the percentages used in the model were (57%*2) = 114% and (70%*2) = 140%, respectively.

[c] Calculated as the weighted cost of disease follow up for patients receiving subsequent treatment and palliative care (£1454.73*0.53 + £47.99*0.47) = **£798.20.**

Abbreviations used in table: CT, computerised tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; PCT, Primary Care Trust; PET-CT, positron emission tomography-computerised tomography.

The ERG notes that expert clinical opinion was used extensively to inform the resource use associated with health state-specific costs; therefore, the ERG considers that this aspect of the manufacturer's model is likely to be subject to a higher level of uncertainty. However, based on clinical advice received, the ERG notes that the manufacturer has identified and used appropriate unit costs.

Subsequent treatment/palliative care costs

The costs of subsequent treatment and palliative care, including drug procurement and administration are applied as one-off costs on the advent of treatment discontinuation (i.e., when patients enter the "PFS, discontinued 3rd (or 4th) line treatment" health state) or progression (i.e., on transition into the "PD" health state). Drug procurement costs are calculated using the method previously described for intervention and comparator procurement costs. The cost of administration for each subsequent treatment was derived from NHS reference costs 2010–2011,[50] based on administration details provided in the Summary of Product Characteristics (SmPC) or publications by Marcus *et al*.[72] and ASWCS Haematology Chemotherapy Protocols.[73] Administration cost per subsequent therapy used in the manufacturer's model is presented in Table 42. The total cost of subsequent treatment and palliative care applied to patients entering the "PFS, discontinued on 3rd (or 4th) line treatment" and "PD" health states is summarised in Table 43.

Table 42. Cost of administration associated with subsequent therapies included in the manufacturer's model

Subsequent therapy[a]	Administration cost (£)[b]	Administration schedule	Source
Gemcitabine monotherapy (administered over 4 weeks)	643.00	Infused over 0.4 to 1.2 hours; simple administration (£231) used for first attendance, subsequent (£206) for two following administrations	Gemcitabine SmPC page 11
Gemcitabine monotherapy (administered over 3 weeks)	437.00	Infused over 0.4 to 1.2 hours; simple administration (£231) used for first attendance, subsequent (£206) for following administration	
Rituximab monotherapy	302.00	First administration at 50 mg/per hour. Therefore, administration of 375 mg would require approx 8 hours (simple administration [£231] plus subsequent [£206])	Rituximab SmPC page 5
CVP	231.00	Simple administration cost assumed for first attendance (£231) as combination infusion time is below 60. Prednisolone is assumed not to have an administration cost.	Marcus *et al*.[72], 2005
IVE	920.00	Complex chemotherapy for first attendance (£302) given infusion time; subsequent (£206) chemotherapy administration cost for three further administrations	ASWCS Haematology Chemotherapy Protocols[73]
RVIG			
DHAP	508.00	Complex chemotherapy for first attendance (£302) given infusion time; subsequent (£206) chemotherapy administration cost for further administration	
CHOP	231.00	Simple administration cost assumed for first attendance (£231) as combination infusion time is below 60; no subsequent chemotherapy administration cost. Prednisolone is assumed not to have an administration cost.	
IVAC	1,126.00	Complex chemotherapy for first attendance (£302) given infusion time; subsequent (£206) chemotherapy administration cost for four further administrations	
Weekly therapy[c]	437.00	Infused over 0.4 to 1.2 hours; simple administration (£231) used for first attendance, subsequent (£206) for following administration	

GEM-P	643.00	Complex chemotherapy for first attendance (£302) given infusion time; subsequent (£206) chemotherapy administration cost for two further administrations	

[a] Palliative care and clinical trial are assumed to be associated with zero cost.

[b] Source: NHS reference costs 2010–2011.[50]

[c] Weekly therapy includes: prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine and methotrexate.

Abbreviations used in table: CHOP, cyclophosphamide, prednisolone, doxorubicin and vincristine; CVP, cyclophosphamide, vincristine and prednisolone; DHAP, dexamethasone, cytarabine and cisplatin; GEM-P, gemcitabine, cisplatin and prednisolone; IVAC, etoposide, cytarabine, mesna and ifosfamide; IVE, ifosfamide, etoposide, mesna and epirubicin; RVIG, rituximab, vinorelbine, ifosfamide and gemcitabine; SmPC, Summary of Product Characteristics.

Table 43. Total costs associated with subsequent therapy and palliative care used in the manufacturer's model

Therapy	**Distribution of patients across therapies (%)[a]**		**Number of cycles**	**Drug cost per administration (£)[b]**	**Administration cost (£)**
	PFS, discontinued on 3rd (or 4th) line treatment	**PD**			
Gemcitabine monotherapy (administered over 4 weeks)	1.67	8.33	4.00	860.71	643.00
Gemcitabine monotherapy (administered over 3 weeks)	8.33	0.00	3.50	573.81	437.00
Rituximab monotherapy	5.00	0.00	8.00	1,249.83	302.00
CVP	15.00	0.00	6.00	61.05	231.00
IVE	8.33	0.00	5.00	1,226.25	920.00
RVIG	0.00	16.67	4.50	2,531.67	920.00
DHAP	0.00	11.67	6.00	204.15	508.00
CHOP	0.00	1.67	6.00	234.46	231.00
IVAC	1.67	3.33	3.50	1,115.52	1,126.00
Weekly therapy[c]	10.00	8.33	7.00	238.32	437.00
GEM-P	20.00	0.00	3.50	1,003.11	643.00
Palliative care	23.33	46.67	–		
Clinical trial	6.67	3.33			
Total cost (£)[d]	**3,928.42**	**4,290.63**			

[a] Based on expert clinical opinion.

[b] Including wastage.

[c] Weekly therapy includes prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine and methotrexate.

[d] Calculated as the sum of the weighted average of treatment costs and the weighted average of administration costs; weighted by proportion of patients receiving each treatment regimen.

Abbreviations used in table: CHOP, cyclophosphamide, prednisolone, doxorubicin and vincristine; CVP, cyclophosphamide, vincristine and prednisolone; DHAP, dexamethasone, cytarabine and cisplatin; GEM-P, gemcitabine, cisplatin and prednisolone; IVAC, etoposide, cytarabine, mesna and ifosfamide; IVE, ifosfamide, etoposide, mesna and epirubicin; PD, progressive disease; PFS, progression-free survival; RVIG, rituximab, vinorelbine, ifosfamide and gemcitabine.

The post-progression treatments used and the distribution of patients across considered therapies were based on expert clinical opinion. However, the ERG notes that the questionnaire used to obtain expert clinical opinion requested the distribution of drugs used at third line, rather than at fourth line or later. In response to clarification, the manufacturer stated that "we were interested in current treatment practice, so pixantrone was not incorporated in the treatment pathway. The assumption is that pixantrone, used as third-line, would push these current third-line therapies into fourth-line treatment. However, as mentioned, participants in the interview were informed that we were interested in third-line and subsequent therapy, so their answers should be valid for the purposes of the model". The ERG considers the manufacturer's approach to be reasonable. However, the ERG considers it important to note that as the cost of subsequent treatment is applied as a one-off cost at the advent of treatment discontinuation or disease progression, the cost of subsequent treatment will not be subject to appropriate discounting. However, the ERG notes that the life expectancy of patients receiving subsequent treatment is likely to be short and, therefore, the impact of discounting likely to be minimal.

Cost of adverse events

As highlighted in Section 5.2.8, consideration of the impact of adverse events with respect to cost (and quality of life) is restricted to patients on original therapy. Resource use data for each considered adverse event were obtained from a survey of three clinical experts. Expert clinical opinion was gauged on the following areas:

- percentage of patients treated in hospital or managed as outpatients;
- medication received (dosage, frequency and number of days on treatment);
- estimated percentage of people receiving medication;
- tests performed (e.g., routine tests, scans).

Each set of resource use values were used to calculate a set of adverse event costs, which were then averaged to provide mean estimates of cost for each adverse event; medication costs were obtained from the BNF 62[(49)] and NHS reference costs 2010–2011[(50)] and unit costs of health and social care[(69)] were used to inform the cost of hospital, outpatient care and laboratory tests. However, the ERG notes that the manufacturer may have used missing data to inform the calculation of mean adverse event costs. That is, the cost associated with each resource use profile provided by clinical experts was used to inform the average cost associated with that adverse event. However, it is not clear whether all experts provided a resource use profile for each adverse event considered; that is, there are some blank resource use profiles in the manufacturer's cost calculation file and it is unclear whether they are blank because the clinical expert considered there to be zero cost associated with that adverse event. Consequently, it is possible that the manufacturer has assumed that an absence of a resource use profile equates to zero cost for that particular adverse event. Therefore, the ERG has carried out a

sensitivity analysis which excludes potentially missing data in the calculation of adverse event costs. The impact of this sensitivity analysis was to increase the ICER by approximately £300 to (from £28,503 to £28,804 per QALY). The adverse event costs used by the manufacturer and the ERG are summarised in Table 44. The cost of Grade 2 and Grade 3 or 4 adverse events were calculated as weighted averages of the events listed in Table 44; weighted by the occurrence per treatment arm.

Table 44. Summary of adverse event costs used by the manufacturer and the ERG (adapted from MS; Table 38; pg 174)

Adverse event		Costs used in the manufacturer's analysis (£)	Costs used in ERG sensitivity analysis (£)
Grade 2 adverse events			
Neuropathy		6	17
Abdominal pain		4	11
Vomiting		49	49
Asthenia		49	147
Pain in extremity		4	11
Fatigue		56	84
Total cost	Pixantrone	39.65	90.76
	TPC	43.18	73.31
Grade 3–4 adverse events			
Abdominal pain		4	11
Anaemia		129	194
Anorexia		–	–
Asthenia		49	147
Back pain		4	11
Bronchitis		–	–
Cellulitis		953	1,430
Dehydration		869	1,303
Dyspnoea		265	794
Ejection fraction decreased		–	–
Fatigue		56	84
Febrile neutropaenia		1,627	1,627
Hypotension		653	1,958
Leukopaenia		–	–
Lymphopaenia		–	–
Malignant neoplasm progression		–	–
Mucosal inflammation		–	–
Nausea		–	–
Neutropaenia		245	736
Pain in extremity		4	11
Platelet count decreased		573	1,718

Pleural effusion		–	–
Pneumonia		889	889
Pyrexia		915	1,373
Renal failure		590	1,771
Thrombocytopaenia		–	–
Vomiting		558	558
Weight decreased		–	–
Total cost	Pixantrone	254.26	550.86
	TPC	385.78	723.33
Abbreviations used in table: ERG, Evidence Review Group; TPC, treatment of physician's choice.			

The ERG notes that not all adverse events (e.g., leukopaenia and thrombocytopaenia) were associated with a cost. Therefore, as part of the clarification procedure, the ERG requested further information on the manufacturer's rationale for excluding the cost of specific adverse events. The manufacturer stated that expert clinical opinion was that adverse events such as leukopaenia and thrombocytopaenia are often asymptomatic. However, for completeness, the manufacturer supplied scenario analyses which considered different cost assumptions for leukopaenia and thrombocytopaenia. The cost inputs and results of the scenario analyses are presented in Table 45. The ERG considers the exclusion of the cost of asymptomatic adverse events to be reasonable. In addition, the ERG notes that the scenario analyses carried out by the manufacturer demonstrate that the inclusion or exclusion of these adverse event costs has little impact on the manufacturer's base case ICER.

Table 45. Scenario analyses carried out by the manufacturer to investigate the impact of including costs for leukopaenia and thrombocytopaenia

Scenario	Cost of leukopaenia and thrombocytopaenia	ICER (£/QALY)
Base case	£0	28,503.33
Scenario 1	• Cost of leukopaenia £0 • Cost of thrombocytopaenia £227.45 (cost of platelet transfusion)	28,515.30
Scenario 2	• Cost of leukopaenia £1,626.79 (same as febrile neutropaenia) • Cost of thrombocytopaenia £227.45 (cost of platelet transfusion)	29,063.19
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.		

5.2.10 Cost-effectiveness results

The manufacturer's base case incremental cost-effectiveness results were generated deterministically rather than probabilistically; that is, mean values rather than distributions were used to inform the value of each parameter. However, the manufacturer's model, submitted as part of this STA, enabled an assessment of the manufacturer's probabilistic cost-effectiveness results. The results from the

manufacturer's deterministic and probabilistic incremental analyses (using the correct price for pixantrone, as submitted at clarification) are presented in Table 46.

Table 46. Base case deterministic and probabilistic results (adapted from MS; Table 46; pg 186)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Deterministic results							
TPC	68,650	1.71	1.13				
Pixantrone	86,337	2.42	1.75	17,688	0.71	0.62	28,503
Probabilistic results (based on 5,000 simulations)							
TPC Mean (95% CI)	69,484 (37,763 to 108,848)	1.74 (1.00 to 2.67)	1.15 (0.66 to 1.76)				
Pixantrone Mean (95% CI)	87,384 (45,831 to 143,143)	2.45 (1.38 to 3.69)	1.77 (1.02 to 2.64)	17,900 (-42,254 to 83,944)	0.71 (-0.70 to 2.19)	0.62 (-0.26 to 1.58)	£28,846 (Dominant to £308,681)
Abbreviations used in table: CI, confidence interval; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; QALYs, quality adjusted life years.							

The manufacturer's deterministic cost-effectiveness results estimated that the ICER for pixantrone compared with TPC is £28,503 per QALY. The ERG notes that this is highly consistent with the probabilistic ICER of £28,846. However, the ERG considers it important to note that, as indicated by the 95% CI in which the mean probabilistic ICER falls, there is a substantial amount of uncertainty in the manufacturer's cost-effectiveness results, with ICERs ranging from dominance of pixantrone over TPC to £308,681 per additional QALY. Furthermore, as indicated in Table 47, pixantrone is either less costly and less effective than or dominated by TPC in approximately 9% of simulations.

Table 47. Proportion of probabilistic iterations in each quadrant of the cost-effectiveness plane (estimated from the manufacturer's model)

Concept	Definition of concept with reference to pixantrone	Proportions of iterations
Dominant	Better outcomes and fewer costs than the comparator	20.86%
Needs evaluation	Costs and outcomes higher than comparator	70.22%
	Less effective and less expensive than comparator	8.70%
Dominated	Less effective and more expensive than comparator	0.22%

In addition to the deterministic base case cost-effectiveness results presented in the MS, the manufacturer presented deterministic estimates of disaggregated costs and benefits for patients treated with pixantrone or TPC. The costs and benefits for each treatment, disaggregated by clinical outcome and health state, are summarised in Table 48 and Table 49, respectively. The results in Table 49 demonstrate that 100% of the incremental QALY gain (i.e., 0.62) for pixantrone versus TPC, is

accrued in the PFS health states. In addition, a comparison of the model outcomes against the clinical results of PIX301 is presented in Table 50. This comparison indicates that the manufacturer's model under-predicts the relative OS benefit and over-predicts the relative PFS benefit of pixantrone versus TPC. The consequence of this disparity in relative (OS and PFS) benefit, between the clinical and economic results, is to extend the relative duration of median time in PFS in favour of pixantrone, providing the opportunity for pixantrone to accrue more QALYs. In addition, the relative duration of OS between pixantrone and TPC is reduced; however, it is PFS rather than OS that is the major driver of QALY gain within the manufacturer's model (Table 49). Therefore, the ERG considers that the manufacturer's model may be biased towards pixantrone.

Table 48. Summary of discounted costs and benefits for each treatment by clinical outcome (adapted from MS; Tables 41 and 42, pg 182)

Health state	Outcome		
	Cost (£)[a]	LY	QALY
Pixantrone			
Progression-free survival	39,535	1.41	1.15
Post-progression survival	46,753	1.01	0.60
Overall survival	86,288	2.42	1.75
TPC			
Progression-free survival	12,364	0.48	0.39
Post-progression survival	56,285	1.23	0.74
Overall survival	68,650	1.71	1.13

[a] Costs are based on originally submitted price of pixantrone.
Abbreviations used in table: LY, life years; QALY, quality-adjusted life year.

Table 49. Summary of discounted costs and benefits for each treatment by health state (adapted from MS; Tables 43 and 44, pg 183)

Health state	Treatment		Increment	Absolute increment	% Absolute increment
	Pixantrone	TPC			
QALYs					
PFS[b]	1.15	0.39	0.76	0.76	123%
PD	0.60	0.74	-0.14	0.14	23%
Total	1.75	1.13	0.62	0.62	100%
Costs[a]					
PFS[b]	39,535	12,364	27,171	27,171	154%
PD	46,753	56,285	-9,532	9,532	54%
Total	86,288	68,650	17,638	17,638	100%

[a] Costs are based on originally submitted price of pixantrone.
[b] Including "the PFS, on 3rd (or 4th) line treatment "and "PFS, discontinued 3rd (or 4th) line treatment" health states.
Abbreviations used in table: PD, progressive disease; PFS, progression free survival; QALY, quality adjusted life years.

Table 50. Summary of model results compared with clinical data (adapted from MS; Table 40; pg 180)

Outcome	Pixantrone			TPC		
	Clinical trial result (median)	Model result (median)	Absolute difference (model versus clinical data)	Clinical trial result (median)	Model result (median)	Absolute difference (model versus clinical data)
Progression-free survival	6.4 months	7.8 months	+1.4 months (22%)	3.5 months	3.2 months	–0.3 months (–9%)
Overall survival	13.8 months	13.1 months	–0.7 months (–5%)	7.6 months	9.2 months	1.6 months (21%)
Abbreviation used in table: TPC, treatment of physician's choice.						

5.2.11 Subgroup analysis

In addition to the base case cost-effectiveness analysis, the manufacturer carried out analyses in the ITT population and DLBCL (~74% of the ITT population) subgroup population of PIX301. Furthermore, as part of the clarification process, the ERG requested an additional subgroup analysis based on patients with histologically confirmed aggressive B-cell NHL. The manufacturer provided an updated model incorporating the requested analysis, along with the details of parametric estimation of OS and PFS supplied for the manufacturer's original analyses (base case, ITT and DLBCL). The ERG notes that appropriate patient level data have been used to inform all submitted analyses and that identical methods have been used to select the parametric distributions used to inform OS and PFS (log-normal as used in the base case). Table 51 summarises the deterministic and probabilistic results (using the correct price for pixantrone, as submitted at clarification) of these subgroup analyses.

Table 51. Results of manufacturer's subgroup analyses (adapted from MS [Tables 50 and 51, pg 196] and manufacturer's clarification response [Tables B1–5, pg 19])

Analysis	Treatment	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
ITT population (not retrospectively histologically confirmed)								
Deterministic	TPC	57,132	1.47	0.99	–			
	Pixantrone	76,987	2.03	1.45	19,854	0.56	0.46	43,200
Probabilistic Mean (95% CI)	TPC	57,975 (33,582 to 87,808)	1.50 (0.94 to 2.20)	1.01 (0.63 to 1.48)	–			
	Pixantrone	77,578 (43,820 to 119,563)	2.05 (1.27 to 2.98)	1.47 (0.92 to 2.14)	19,603 (-24,881 to 68,689)	0.55 (-0.48 to 1.66)	0.46 (-0.18 to 1.16)	42,899 (Dominant to 304,552)

DLBCL population (not retrospectively histologically confirmed)								
Deterministic	TPC	52,953	1.26	0.83	–			
	Pixantrone	62,836	1.70	1.25	9,883	0.44	0.42	23,800
Probabilistic Mean (95% CI)	Unavailable, probabilistic analysis was not functional within the manufacturer's model for this patient population							
Aggressive B-cell population (histologically confirmed)								
Deterministic	TPC	46,109	1.13	0.77	–			
	Pixantrone	60,964	1.64	1.22	14,855	0.50	0.45	32,830
Probabilistic Mean (95% CI)	TPC	47,076 (26,435 to 73,759)	1.17 (0.69 to 1.79)	0.79 (0.48 to 1.22)	–			
	Pixantrone	62,433 (38,811 to 100,172)	1.67 (0.98 to 2.53)	1.24 (0.73 to 1.85)	15,358 (–22,068 to 57,441)	0.50 (–0.42 to 1.48)	0.45 (–0.14 to 1.09)	34,342 (Dominant to 248,756)
Abbreviations used in table: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALYs, quality-adjusted life years.								

The ERG notes that the manufacturer's model is sensitive to changes in patient characteristics, with analysis in the DLBCL population producing the most favourable mean result. However, as discussed in Section 5.2.2, the ERG considers the subgroup of patients with disease that is histologically confirmed as aggressive to be the population that is most appropriate to the decision problem that is the focus of this STA. In this population the manufacturer's analysis suggests that the ICER of pixantrone versus TPC is £32,830 per QALY. However, probabilistic analysis indicates that the ICER has a 95% chance of falling between the dominance of pixantrone over TPC and £248,756 per QALY (pixantrone versus TPC). The spread of probabilistic ICER estimates in the cost-effectiveness plane observed in the manufacturer's probabilistic analysis is summarised in Table 52. The ERG notes that, in about 8% of the iterations, pixantrone is either less costly and less effective than or dominated by TPC.

Table 52. Proportion of probabilistic iterations in each quadrant of the cost-effectiveness plane (estimated from the manufacturer's model based on a histologically confirmed aggressive B-cell patient population)

Concept	Definition of concept with reference to pixantrone	Proportions of iterations
Dominant	Better outcomes and costs than the comparator	16.10%
Needs evaluation	Costs and outcomes higher than comparator	76.72%
	Less effective and less expensive than comparator	6.92%
Dominated	Less effective and more expensive than the comparator	0.26%

In addition to the cost-effectiveness results in the histologically confirmed aggressive B-cell population, the ERG requested a tabular comparison (similar to that presented in Table 50) of model and clinical trial results in this patient population (Table 53).

Table 53. Summary of model results compared with clinical data (adapted from manufacturer's clarification response; Tables B1–4, pg 19)

Outcome	Pixantrone			TPC		
	Clinical trial result (median)	Model result (median)	Absolute difference (model versus clinical data)	Clinical trial result (median)	Model result (median)	Absolute difference (model versus clinical data)
Progression-free survival	5.9 months	6.8 months	+0.9 months (15%)	3.0 months	2.7 months	–0.3 months (–10%)
Overall survival	8.2 months	9.2 months	+1.0 month (12%)	6.2 months	6.1 months	–0.1 months (2%)
Abbreviation used in table: TPC, treatment of physician's choice.						

Based on the comparison of model and clinical results displayed in Table 53, the ERG notes that the model is biased towards pixantrone for both PFS and OS (i.e., overestimates the relative benefit of pixantrone versus TPC). Moreover, the overestimation of the relative PFS benefit (the clinical outcome for which 100% of the modelled incremental QALYs are accrued) of pixantrone versus TPC is greater than that seen in the originally submitted model.

5.2.12 Sensitivity analyses

In support of the pixantrone STA, the manufacturer carried out several sensitivity analyses to assess the impact of parameter and structural uncertainty on the cost-effectiveness results. One-way sensitivity analyses (OWSA) and scenario analyses were carried out on the deterministic cost-effectiveness results. In addition, probabilistic sensitivity analysis (PSA) was incorporated into the manufacturer's model. The following sections summarise the methods and results of each analysis. As discussed in Section 5.2.2, the ERG considers the subgroup of patients with histologically confirmed aggressive B-cell NHL to be the most representative of the patient population that is the focus of this STA. Therefore, the sensitivity analyses results presented in this Section are based on the updated model, provided by the manufacturer at clarification, in which the relevant subgroup is considered. The results of sensitivity analyses on the manufacturer's base case are presented in Appendix 14. The ERG notes that the results of sensitivity analyses on the manufacturer's base case were similar to the results of sensitivity analyses in the subgroup of patients with histologically confirmed aggressive B-cell NHL.

One-way sensitivity analyses

OWSA was carried out on all model parameters; however, some parameters (e.g., adverse event utility decrements) were aggregated (i.e., the individual components of adverse event disutility were varied individually but the average adverse event disutility was applied in the OWSA), whereas other parameters (e.g., individual components of cost categories) were first aggregated and then subjected to OWSA (i.e., the average cost was subject to variation rather than the individual components of that cost). The parameters varied and the values used are provided in Appendix 15. To summarise, parameter values were alternated between low and high values and the resultant ICER recorded. Where possible 95% confidence intervals (CIs) were used to inform the low and high values used; however, for parameters for which CIs could not be estimated, the mean value was varied by ±20%. The ERG considers that appropriate values have been used in the manufacturer's OWSA. The ERG notes that only 6 of the 102 analyses considered resulted in a deterministic ICER of greater than £35,000 (Table 54). In addition, using the lower bound of the parameters informing PFS with pixantrone (i.e., assuming a greater relative difference in PFS for pixantrone versus TPC) resulted in the dominance of pixantrone over TPC. By contrast, pixantrone was found to be less costly and less effective than TPC when the upper and lower bounds of the parameters informing OS for pixantrone and TPC, respectively, were used (i.e., assuming a greater relative difference in OS for TPC versus pixantrone, Table 54).

Table 54. Selected results of manufacturer's one-way sensitivity analysis on the histologically confirmed aggressive B-cell NHL population

Parameter	Baseline value	Alternate value (lower/upper)	ICER (£/QALY)[a]
Manufacturer's deterministic ICER			**32,830**
Health discount rate	3.5%	0%	28,372
		6%	35,871
Cost discount rate	3.5%	0%	36,244
		6%	31,160
Professional and social services progressive state	£1,993.89	£1,595.11	35,341
		£2,392.67	30,319
Utility PFS heath states	0.81	0.62	46,650
		0.94	27,130
Drug cost per administration pixantrone	1665.18	1332.14	25,918
		1998.21	39,742
Treatment discontinuation risk factor for pixantrone	1.00	0.80	37,078
		1.20	29,407
Progression free survival: pixantrone	Mean	2.5% Lower	Dominated
		97.5% Upper	96,580
Progression free survival: TPC	Mean	2.5% Lower	66,594
		97.5% Upper	20,307

Overall survival: pixantrone	Mean	2.5% Lower	55,827
		97.5% Upper	75,389[b]
Overall survival: TPC	Mean	2.5% Lower	195,940[b]
		97.5% Upper	48,682
[a] Including correct price for pixantrone. [b] Less costly and less effective. Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TPC, treatment of physician's choice.			

Based on the results presented in Table 54, the ERG notes that, with the exception of parameters used to inform PFS and OS estimates, the manufacturer's cost-effectiveness result is relatively insensitive to changes in individual parameters. Furthermore, the direction of impact of the OWSAs carried out on PFS and OS parameters indicate that the deterministic results are more sensitive to changes in assumptions around PFS than OS. In particular, increasing the relative PFS benefit of pixantrone versus TPC results in more favourable cost-effectiveness results than increasing the relative OS benefit of pixantrone versus TPC.

Scenario analyses

To investigate the impact of structural assumptions on the deterministic cost-effectiveness results, the manufacturer carried out the following scenario analyses:

- using alternative forms of parametric extrapolation for PFS and OS (generalised gamma and log-logistic distributions);
- permitting vial sharing for pixantrone and TPC (no wastage);
- using an alternative definition of PFS (to include death, progressive disease and treatment switch);
- using alternative sources of health state utilities.

The alternative values or assumptions used and results of each scenario analysis carried out by the manufacturer are summarised in Table 55.

The ERG notes that the manufacturer's deterministic result appears to be stable with respect to alternative assumptions around utility and cost. In addition, the ERG notes that the manufacturer's cost-effectiveness result appears to be more sensitive to changes in the utility value associated with PFS than that associated with PD. In particular, decreasing the utility associated with PFS by 0.01 while simultaneously increasing the utility associated with PD by 0.16 resulted in an overall ICER increase. Furthermore, the ERG notes that the scenario analysis incorporating an alternative definition of PFS (of time to progression, death or treatment discontinuation primary definition of PFS used in PIX301) was not applied to the population of patients with histologically confirmed aggressive B-cell NHL. However, the ERG considers that this scenario analysis represented an implausible scenario which double-counted the impact of treatment discontinuation.

Table 55. Results of manufacturer's scenario analyses in the histologically confirmed B-cell NHL population

Parameter	Baseline value	Alternate value		ICER (£/QALY)[a]
Manufacturer's deterministic ICER				**32,830**
PFS defined as time to progression, death or treatment discontinuation	Death and progressive disease	Death, progressive disease and treatment switch		Not available
Parametric fitting for OS and PFS	Log-normal	Generalised gamma		15,610
		Log-logistic		31,072
Wastage	No vial sharing	Vial sharing		27,971
Health state utility values				
Alternative sources		**PFS utility**	**PD utility**	**ICER (£/QALY)**
2nd line treatment in patients with chronic myelogeneous leukaemia,	Base case utility value: PFS = 0.81; PD = 0.60	0.85	0.73	32,797
3rd line treatment in patients with chronic lymphocytic leukaemia		0.65	0.47	40,647
1st line maintenance treatment in patients with follicular lymphoma		0.78	0.62	34,832
1st line treatment in patients with metastatic renal cell carcinoma		0.70	0.59	39,579
2nd line treatment in patients with renal cell carcinoma		0.76	0.68	37,236
2nd line treatment in patients with malignant melanoma		0.8	0.76	36,203

[a] Including correct price for pixantrone.

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QALY, quality adjusted life year.

Probabilistic sensitivity analysis

The simultaneous impact of parameter uncertainty on the manufacturer's cost-effectiveness results was explored using PSA. With the exception of time horizon, discount rates applied to costs and benefits, drug costs and the number of drug administrations per cycle; all model parameters were included in the PSA. The manufacturer stated that the parameters excluded from the PSA were not considered to be subject to uncertainty; the ERG considers this to be a reasonable assumption. Each parameter that was included in the PSA was assigned a probability distribution from which estimates were simultaneously sampled for 5,000 iterations. Table 56 summarises the type of distribution used for each group of parameters considered within the sensitivity analyses (for full details of parameters used to inform each distribution see Table 24). The ERG notes that the manufacturer has chosen appropriate distributions to assess parameter uncertainty. In particular, the ERG considers that the use of Cholesky decomposition techniques to account for correlation in PFS and OS parameters strengthens the reliability of the manufacturer's PSA.

Table 56. Inputs and probability distributions used in probabilistic sensitivity analysis

Parameter type	Parameter description	Distribution(s) used	Manufacturer's rationale
PFS and OS	PFS and OS: Intercept and scale parameters of lognormal parametric approximation	Normal Cholesky decomposition matrix incorporated	Cholesky decomposition was used to account for correlation between distributional parameters
Adverse events	Length of adverse event	Gamma	Reference to Briggs *et al*.[74], 2006
	Number of adverse events		
Patient characteristics	BSA	Normal	None provided
	Proportion of male patients	Beta	Reference to Briggs *et al*.[74], 2006
Utilities		Beta	Reference to Briggs *et al*.[74], 2006
Proportions	Distribution of patients across different therapies (post progression, post treatment and TPC)	Dirichlet	To ensure the sum of proportions equals 100%
Costs	Administration costs	Gamma	Reference to Briggs *et al*.[74], 2006
	Adverse event costs		
	Palliative care costs		
	Professional and social services costs		
	Healthcare professional costs		
	Treatment follow-up costs		
	Progression costs		

Abbreviations used in table; BSA, body surface area; OS, overall survival; PFS, progression-free survival; TPC, treatment of physician's choice.

Figures 7 and 8 present the probabilistic estimates and cost-effectiveness acceptability curve (CEAC) for pixantrone (based on correct price for pixantrone, as submitted at clarification) versus TPC, in the subgroup of patients with histologically confirmed aggressive B-cell NHL. In Figure 7, the red line indicates a willingness-to-pay threshold (WTP) of £50,000 while the green line below indicates a WTP of £30,000. Table 57 summarises the probability of each treatment being cost-effective at WTP of £20,000, £30,000 and £50,000.

Figure 7. Scatter plot results of probabilistic sensitivity analysis of pixantrone compared with TPC arm in histologically confirmed aggressive B-cell NHL population (adapted from manufacturer's model)

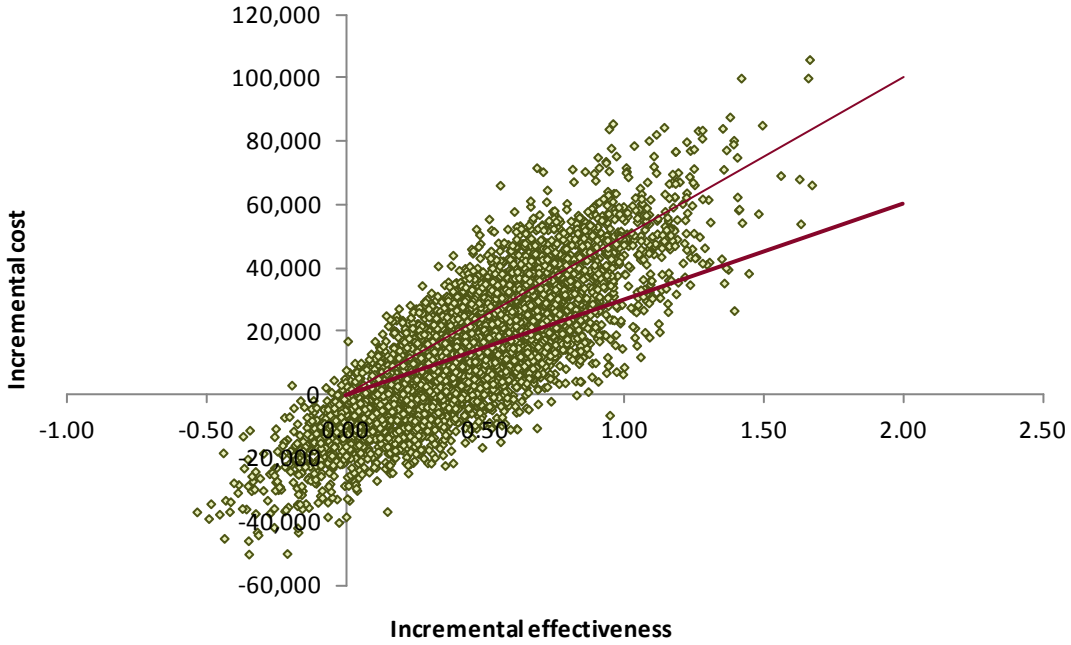


Figure 8. Cost-effectiveness acceptability curve in histologically confirmed aggressive B-cell NHL population (adapted from manufacturer's model)

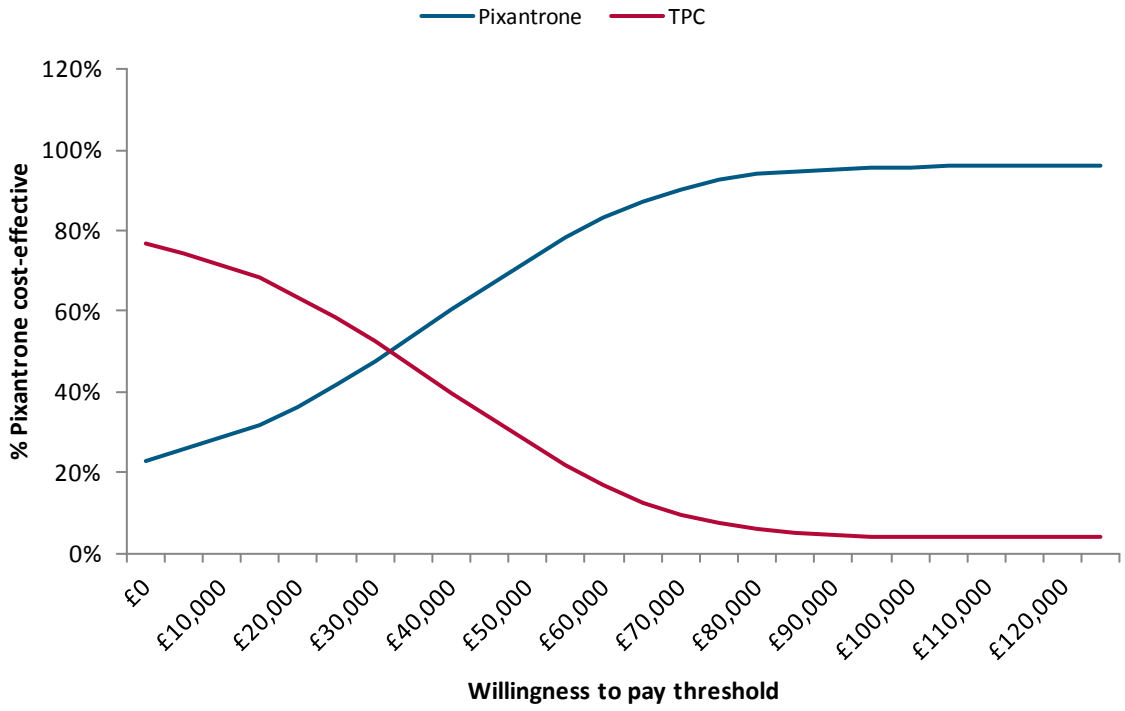


Table 57. Probability of cost-effectiveness with respect to willingness-to-pay thresholds in the histologically confirmed aggressive B-cell patient population

Treatment	WTP (£/QALY)[a]		
	20,000	30,000	50,000
Pixantrone	36.4%	47.7%	72.3%
TPC	63.6%	52.3%	27.7%

[a] Based on correct price for pixantrone.
Abbreviations used in table: QALY, quality adjusted life year; WTP, willingness-to-pay; TPC, treatment of physician's choice.

Overall, the ERG considers that the results of the manufacturer's sensitivity analyses reiterate the sensitivity of the manufacturer's model to assumptions around the relative PFS benefit of pixantrone versus TPC. In addition, the ERG notes the high level of uncertainty regarding the probabilistic ICER for both the manufacturer's base case analysis (see Appendix 14) and analysis carried out in the histologically confirmed aggressive B-cell patient population.

5.2.13 Model validation and face validity check

The manufacturer states that the following measures were taken to validate and verify the economic model:

- internal verification "by two modelling experts not previously involved in model development" (MS; pg 191) – including extreme value testing;
- comparison of median PFS and OS obtained from statistical predictions used in the economic model with median values observed in PIX301;
- major model assumptions and PFS and OS estimates were validated against expert clinical opinion, based on the opinion of five UK clinical experts;
- external verification through an independent health economics consultancy, "using the Drummond checklist and Glasgow checklist, as well as a proprietary internal checklist" (MS; pg 192).

The ERG notes that the internal and external validity of the model has been assessed in accordance with ISPOR Good Research Practices Task Force 7 on model transparency and validation.[75] In addition, the ERG notes that good practice modelling guidance[43] and guidance from NICE's Decision Support Unit have been closely followed.[44] Furthermore, the ERG has not identified any computational errors within the model engine. However, the ERG considers it important to note that the model is likely to be biased towards pixantrone, as a result of overestimates of the relative PFS benefit of pixantrone versus TPC; particularly as 100% of the incremental QALY gain is as result of differences in PFS between treatment arms.

5.3 Conclusions of the cost-effectiveness section

In support of this STA, the manufacturer has submitted an economic evaluation considering the following patient populations:

- ITT population of PIX301;
- subgroup of PIX301 patients with aggressive B-cell NHL (not retrospectively histologically confirmed);
- subgroup of PIX301 patients with aggressive B-cell NHL (histologically confirmed);
- subgroup of PIX301 patients with DLBCL (not retrospectively histologically confirmed).

Based on the licensed indication for pixantrone, the ERG considers the economic evaluation in a patient population with histologically confirmed aggressive B-cell disease to be the most informative to the decision problem at hand. However, the ERG notes that *post-hoc* subgroup data was used to inform this evaluation. Moreover, the ERG notes that as a result of low patient numbers recruited to PIX301, subgroup data were not powered to detect a difference in efficacy between treatment with pixantrone versus TPC. Consequently, the ERG notes that the level of uncertainty surrounding the manufacturer's estimate of cost-effectiveness in this patient population is high.

In addition, the ERG notes that the results of the manufacturer's economic model are biased towards pixantrone as a result of an overestimation of the relative PFS benefit of pixantrone versus TPC. Furthermore, the ERG has identified further areas of inaccuracy or uncertainty in the assumptions and parameter estimates used in the manufacturer's model. The impact of these is discussed in detail in Section 6.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Following detailed examination of the MS and economic model, the ERG identified the following areas of inaccuracy or uncertainty in the assumptions and parameter estimates used:

- the impact of treating a patient population previously treated with rituximab (in-line with expected UK patient population);
- the potential double-counting of treatment discontinuation as a result of disease progression;
- the assumption that OS benefit from further treatment with monotherapy is equivalent to that of further treatment with combination therapies;
- the use of utility values for patients with PFS and PD assumed to be equal to the utility experienced by elderly patients receiving first line treatment for aggressive NHL;
- the exclusion of adverse event disutilities for patients on further lines of therapy;
- discrepancies in AE disutilities between the manufacturer's and ERG's interpretation of the literature;
- the use of weighted average adverse event rates to inform costs and disutilities associated with adverse events for patients on original therapy;
- the exclusion of age adjustment of utility data;
- 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.

Where possible, the ERG has carried out sensitivity analyses to investigate the impact of alternative assumptions or parameters on the manufacturer's cost-effectiveness results. Of these sensitivity analyses, the following have been combined to provide revised cost-effectiveness estimates:

- the use of utility data from chronic lymphocytic leukaemia patients receiving 3rd line therapy to inform the utility of PFS and PD (see Section 5.2.8);
- alternative estimates of disutility for anaemia, renal failure, weight loss and Grade 3 vomiting (see Section 5.2.8);
- the use of costs from BNF 64 (see Section 5.2.9).

In addition, scenario analyses of the ERG's revised cost-effectiveness estimates have been carried out as follows:

- including costs associated with the treatment of leukopaenia and thrombocytopaenia (see Section 5.2.9);
- excluding potentially missing data from the calculation of average AE cost (5.2.9).

Table 58 displays the results of the ERG's sensitivity and scenario analyses on the manufacturer's deterministic economic evaluation in the histologically confirmed aggressive B-cell patient population. The impact of the ERG's sensitivity and scenario analyses on the manufacturer's base case is presented in Appendix 16.

Table 58. Individual and cumulative impact of ERG sensitivity and scenario analyses on the manufacturer's economic evaluation in a population of patients with histologically confirmed aggressive B-cell NHL

Analysis	Treatment	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. 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	
Treatment effectiveness in a patient population previously treated with rituximab	Not assessed, likely to result in a substantial ICER increase due to reduced benefit in this patient population						
Removal of double counting of treatment discontinuation as a result of disease progression	Not possible without access to IPD, likely to result in a small decrease in the ICER as a higher proportion of patients in TPC group discontinued as a result of disease progression and "PFS, discontinued 3rd (or 4th) line treatment was associated with a higher overall utility as a result of the exclusion of adverse event related disutilities for patients on subsequent lines of treatment						
The use of OS data from combination rather than monotherapies	No data available to inform this, however likely to result in a small increase in the ICER as a result of a prolonged sojourn in the "PD" health state						
The application of adverse event related disutilities for patients on further lines of therapy	No data available to inform this, likely to result in a small decrease in the ICER as patients in the TPC group experience higher levels of discontinuation and spend longer in the PD health state.						
Use of accurate timing of each adverse event experienced across the course of original treatment	Not assessed, direction of effect unclear but likely to be minimal						
Age adjustment of utility data	Not assessed, direction of effect unclear but likely to be minimal						
ERG's base case	**TPC**	**46,140**	**0.377**	**–**	**–**	**–**	**60,154**
	Pixantrone	**60,997**	**0.624**	**14,857**	**0.247**	**60,154**	

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; Inc., 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.

The ERG notes that of the sensitivity analyses carried out, the use of utility data from a third-line patient population had the largest impact; increasing the ICER to £60,129. In addition, the ERG recognises the importance of the probabilistic ICER on the decision problem that is the focus of this STA. Therefore, where appropriate, the alternative parameters used to inform the ERG's base case were assigned probability distributions in line with those used in the manufacturer's probabilistic sensitivity analyses. In particular, the standard error associated with utility and disutility values used was estimated ([mean value-0.8*mean value]/1.96) and used along with the mean value to inform a beta distribution. Drug costs were excluded from the manufacturer's probabilistic sensitivity analysis. The probabilistic result for the ERG's base case is displayed in Table 59, with the proportion of ICERs distributed across the four quadrants of the cost-effectiveness plane summarised in Table 60.

Table 59. Probabilistic result for the ERG's base case in a population of patients with histologically confirmed aggressive B-cell NHL

Treatment	Mean (95% CI)				
	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALYs)
TPC	47,401 (25,973 to 74,869)	0.389 (0.238 to 0.585)	–		
Pixantrone	62,431 (38,797 to 99,669)	0.632 (0.383 to 0.939)	15,029 (–22,408 to 58,611)	0.242 (–0.041 to 0.565)	62,000 (dominated to 373,454)

Abbreviations used in table: CI, confidence interval; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; QALYs, quality adjusted life years; TPC, treatment of physician's choice.

Table 60. Proportion of probabilistic iterations in each quadrant of the cost-effectiveness plane for ERG base case (histologically confirmed population)

Concept	Proportions of iterations	Definition of concept
Dominant	19.3%	Both outcomes and costs of pixantrone are favourable (pixantrone is cheaper and more effective compared to TPC)
Needs Evaluation	76.0%	Costs and outcomes of pixantrone are higher than those of the TPC
Inferior	4.6%	Pixantrone is less effective and cheaper compared to TPC
Dominated	0.2%	Pixantrone is more expensive and less effective compared to TPC
Abbreviation used in table: TPC, treatment of physician's choice.		

The deterministic and probabilistic ICERs obtained following application of the ERG's sensitivity analyses suggest an ICER for pixantrone versus TPC of £60,000. In addition, probabilistic analysis suggests that the ICER has a 95% chance of falling between the dominance of pixantrone over TPC and £373,454 per additional QALY. The ERG notes 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 notes that these analyses do not account for the potentially inferior treatment effect likely to be seen in patients previously treated with rituximab (see Section 4.3.2).

7 END OF LIFE

As part of the manufacturer's submission (MS), the manufacturer puts forward a case for pixantrone as an "End of Life" treatment for patients with multiply relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL). The "End of Life" guidance published by the National Institute for Health and Clinical Excellence (NICE) sets out three key criteria:[76] (i) treatment is indicated for patients with a short life expectancy, normally less than 24 months; (ii) 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 National Health Service (NHS) treatment; and (iii) the treatment is licensed, or otherwise indicated, for small patient populations.

7.1 Life expectancy of less than 24 months

The manufacturer highlights that the overall survival (OS) of treated patients in the PIX301 trial was less than 12 months, with a median OS of 10.2 months in the pixantrone group and of 7.6 months in the treatment of physician's choice (TPC) group. However, in the full trial (intention-to-treat [ITT]) population, mean OS is projected to be 28.6 (standard deviation [SD] 7.1) months and 20.0 (SD 4.7) months in the pixantrone and TPC group, respectively. Estimated mean OS is considerably longer for the ITT population than for patients with histologically confirmed aggressive B-cell NHL (11.3 [SD 8.80] months with pixantrone vs 8.9 [SD 7.91] months with TPC). Taken together, the ERG agrees with the manufacturer that the life expectancy of patients with aggressive NHL and who have received at least two prior chemotherapeutic regimens is likely to be less than 24 months.

7.2 Extension to life by an additional 3 months

In the manufacturer's submission (MS), the manufacturer presents results for median OS in the full population (ITT) of the PIX301 trial and in the subgroup of patients whose disease was retrospectively histologically confirmed to be aggressive NHL (HITT). As part of the clarification process, the ERG requested data for the subgroup of patients with histologically confirmed aggressive B-cell NHL, which the ERG considers to be the most relevant population to the decision problem. The median life extension in the subgroup of patients with histologically confirmed aggressive B-cell NHL was reported to be 1.8 months (median OS: 8.1 months with pixantrone vs 6.3 months with TPC; HR 0.72; 95% CI 0.45 to 1.13), but the difference between groups did not reach statistical significance. The manufacturer helpfully provided mean OS based on data at the end of the study, together with an estimate of mean OS based on extrapolation of data using the log-normal distribution. At the end of the study, mean OS in patients with histologically confirmed aggressive B-cell NHL was calculated to be 11.3 (SD 8.80) months in the pixantrone group and 8.9 (SD 7.91) months in the TPC group, giving a mean OS prolongation of 2.4 months. Extrapolation of data generated a mean OS gain of 7.2 (SD 7.4) months with pixantrone (mean OS [SD]: 22.6 [6.2] months with pixantrone vs 15.2 [4.1] months with TPC), but the difference between groups is not statistically

significant. Median OS gain observed with pixantrone in the histologically confirmed aggressive B-cell NHL subgroup is similar to that reported for the ITT population (2.6 months; HR 0.79; 95% CI: 0.53 to 1.18) but longer than that reported for the HITT subgroup (1.3 months; HR 0.74; 95% CI: 0.48 to 1.14). Estimated mean OS for the ITT population provided by the manufacturer during clarification suggests an OS gain of 8.6 months associated with pixantrone (mean OS [SD]: 28.6 [7.1] months with pixantrone vs 20.0 [4.7] months with TPC) However, as noted earlier, the ITT population includes patients who were subsequently identified as having disease types other than aggressive NHL. When data on extrapolated mean OS from the ITT population and the subgroup of patients with histologically confirmed aggressive B-cell NHL are considered, the OS gain with pixantrone is longer than 3 months, but the difference between treatment groups does not reach statistical significance in either analysis.

7.3 Licensed for a small population

The ERG notes that there are limited data available on the number of patients receiving treatment for multiply relapsed or refractory aggressive NHL. In the Executive Summary of the MS (pg 9), the manufacturer estimates that 1,650 patients per year will be eligible for treatment with pixantrone. In Section 2 of the MS, based on incidence data from the European Union cancer observatory, the manufacturer estimates that approximately 5,555 patients in the UK have aggressive NHL. Of these patients, the manufacturer estimates that 1,830 patients are likely to have received multiple prior regimens of chemotherapy, and that 30–40% of this subgroup could be eligible for treatment with pixantrone. Based on the data reported by the manufacturer, the ERG calculated that between ~550 and ~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.

7.4 Summary

When data on extrapolated mean OS from the ITT population and the subgroup of patients with histologically confirmed aggressive B-cell NHL are considered, the three criteria for ‘End of Life’ treatment seem to be met, but the OS gain with pixantrone over TPC is not statistically significant. However, when median OS for the subgroups of patients with histologically confirmed aggressive NHL are considered (HITT and aggressive B-cell), together with the mean OS at the end of the study for patients with histologically confirmed aggressive B-cell NHL, the OS gain seems likely to be less than 3 months.

8 OVERALL CONCLUSIONS

8.1 Summary of clinical effectiveness results

The manufacturer presents the case for the use of pixantrone compared with treatment of physician's choice (TPC) for the treatment of multiply relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL) based on data derived from the PIX301 randomised trial.[18] Patients had received prior treatment with at least two chemotherapeutic regimens and their NHL was anthracycline sensitive.

PIX301 provides the only direct evidence presented within the manufacturer's submission (MS). The Evidence Review Group (ERG) considers it important to note that there is a paucity of evidence on the comparative clinical effectiveness of treatments for multiply relapsed or refractory aggressive NHL. Moreover, there is no consensus on the standard of care in the UK for this patient population. The ERG considers the choice of comparator of TPC to be pragmatic. Guidance from the Committee for Medicinal Products for Human USE (CHMP) states that use of TPC is acceptable where there is no regimen with an evidence-based favourable benefit-risk relationship for a specific population.

In PIX301, the primary outcome evaluated was proportion of patients achieving complete response (CR) or unconfirmed CR (CRu) at the end of treatment (evaluated by an Independent Assessment Panel [IAP]), which is generally not considered to be as robust an outcome as overall survival (OS), or even progression-free survival (PFS), in trials evaluating treatments for cancer. Moreover, it has been recognised that CRu is open to misinterpretation. Considering the patient population, patients were enrolled after initial histological evaluation for aggressive disease at the pathology laboratory of the individual participating sites. Subsequently, histology was retrospectively reviewed at a central laboratory, where consensus from two of three pathologists was required to confirm a diagnosis of aggressive NHL. After review, 36 randomised patients were judged not to have aggressive NHL. The ERG considers the manufacturer's approach to be pragmatic and appreciates the difficulties encountered in carrying out central histological review prior to study entry. However, as the pathology and prognosis of indolent and aggressive NHL differ, the ERG does not consider the results of the full trial population of PIX301 to be the most relevant to the decision problem. A small number of patients with T-cell-derived NHLs were also included in the PIX301 trial (10%). As part of the clarification process, the ERG requested data in the subgroup of patients with histologically confirmed aggressive B-cell NHL.

As a result of slow accrual, enrolment to the PIX301 trial was stopped before the target sample size had been achieved. Of the required 320 patients, only 140 patients were recruited. Of these, 104 were histologically confirmed by the central review panel as having aggressive NHL. As a result, the PIX301 trial is likely to be underpowered to detect a difference between pixantrone and TPC in the

primary outcome of CR/CRu at the end of treatment in the subgroups of patients with histologically confirmed disease.

The PIX301 protocol was amended to ensure that patients recruited from participating countries in which rituximab was available had previously received rituximab as a component of their care. In the UK, addition of rituximab to a combination chemotherapy regimen for the treatment of first-line aggressive NHL is standard clinical practice. Thus, the ERG considers the subgroup of patients having received prior rituximab and with retrospective histological confirmation of aggressive B-cell NHL to be the most relevant to the decision problem. However, the low number of patients in this subgroup generates uncertainty around the results. The CHMP indicated that additional data are required to establish the benefit of pixantrone in patients previously treated with rituximab. Results of an ongoing clinical trial are expected in June 2015 and should go some way to clarifying this issue.

Randomisation in PIX301 was stratified by geographic location. The three strata were: North America; Western Europe; and Rest of World. The largest proportion of patients was recruited from the Rest of World locations. Patients from Western Europe (7 patients from the UK) had more aggressive NHL and were more heavily pretreated than patients from the Rest of World subgroup. The results for the Western Europe subgroup favour TPC for PFS and OS. The ERG's clinical expert indicated that the Western Europe subgroup could potentially have more severe disease than a patient who would typically be eligible for treatment with pixantrone in the UK. That is, compared with the Western Europe subgroup, patients in clinical practice in the UK might have received fewer lines of treatment before being considered eligible for treatment with pixantrone, with pixantrone being given as a third-line treatment rather than fourth or fifth line treatment. In the subgroup of patients who had received prior rituximab treatment and had histological confirmation of aggressive B-cell NHL, there was no statistically significant difference between pixantrone and TPC in any clinical outcome. However, the ERG emphasises that all analyses based on subgroups are *post hoc* analyses and as such are likely to be underpowered to detect a difference between groups and should be interpreted with caution.

8.2 Summary of cost-effectiveness results

The manufacturer presented an economic evaluation of pixantrone versus TPC in the following patient populations:

- aggressive B-cell NHL (not retrospectively histologically confirmed) – manufacturer's base case;
- ITT (not retrospectively histologically confirmed);
- diffuse large B-cell lymphoma (DLBCL, not retrospectively histologically confirmed);
- histologically confirmed aggressive B-cell NHL (submitted at clarification).

Deterministic assessment of the cost-effectiveness of pixantrone in these patient populations resulted in incremental cost-effectiveness ratios (ICERs) (per quality adjusted life year [QALY]) of £28,503, £32,830, £43,200 and £23,800 in the aggressive B-cell NHL (not retrospectively histologically confirmed), histologically confirmed aggressive B-cell NHL, ITT and DLBCL patient populations, respectively. However, assessment of the probabilistic sensitivity of each ICER revealed a high level of uncertainty (with 95% CIs ranging from the dominance of pixantrone over TPC to approximately £300,000 per additional QALY). The ERG notes that the high level of uncertainty observed in the manufacturer's cost-effectiveness results is unsurprising given the statistical power of the clinical data used to inform each analyses (i.e., most analyses were based on *post hoc* subgroup analyses of an ITT population that was likely to be underpowered to detect a 15% difference in the primary outcome of CR/CRu).

In addition, the ERG identified a number of areas of inaccuracy and uncertainty related to the parameters and assumptions used in the manufacturer's model. Where possible, the ERG carried out sensitivity analyses to investigate the impact of these on the manufacturer's cost-effectiveness results. Sensitivity analysis around the utility data used to inform the health states of PFS and progressive disease (PD) had the largest impact on the cost-effectiveness results (increasing from £32,830 to £60,129 in the histologically confirmed aggressive B-cell NHL population). The remaining sensitivity analyses carried out by the ERG (on disutility and unit cost values used in the model) collectively increased the ICER by £25 (from £60,129 to £60,154).

There were some areas of potential inaccuracy and uncertainty that the ERG was unable to investigate, for example, structural assumptions around treatment discontinuation and the implementation of adverse-event-related disutility. However, the majority of these were expected to have a minimal impact on the cost-effectiveness results. Moreover, the ERG notes that the key area of uncertainty that the ERG was not able to address was the cost-effectiveness of pixantrone versus TPC in a population of patients previously treated with rituximab, and, in particular, a histologically confirmed aggressive B-cell NHL population. Based on inspection of the clinical trial results, the ERG considers that the ICER in this patient population may be substantially higher than £60,000; however, the ERG notes that the evidence base in this patient population is weak and that any findings may be a result of random chance.

8.3 Implications for research

At this time, there is no standard of care for the treatment of multiply relapsed or refractory aggressive NHL in the UK. Moreover, there is limited evidence available on the clinical effectiveness of interventions currently used in clinical practice, with evidence on effectiveness predominantly coming from trials in cancers other than multiply relapsed or aggressive NHL. In the PIX301 trial, in the subgroup of patients with histologically confirmed aggressive B-cell NHL, pixantrone was associated

with improved response (CR/CRu) and prolonged PFS and OS. However, in patients who had received prior rituximab, although the direction of effect favoured pixantrone in all outcomes, benefit in this subgroup of patients seemed to be reduced. Further research into the potential benefit of pixantrone in a patient population more characteristic of UK patients would be warranted. The ERG considers that studies investigating the comparative clinical effectiveness of pixantrone and other chemotherapeutic regimens used in UK clinical practice would broaden the available evidence base on effective treatments in a population for which there is a clinical unmet need, in addition to being informative for service provision within the NHS.

Furthermore, the ERG notes that there is a paucity of data pertaining to the health-related quality of life of NHL patients experiencing third or subsequent lines of treatment. Further research into the utility of these patients and the impact of treatment on patients' quality of life would help to inform future cost-utility evaluations in this patient population.

9 REFERENCES

(1) Cancer Research UK. Non-Hodgkin's lymphoma: statistics. Cancer Research UK. 2013. [last accessed 2013 February]; Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/nhl/

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

(3) Cancer Research UK. Non-Hodgkin's lymphoma. Cancer Research UK. 2013. [last accessed 2013 February]; Available from: http://www.cancerresearchuk.org/cancer-help/type/non-hodgkins-lymphoma/

(4) Hill M, Kyle F. NHL (diffuse large B-cell lymphoma). Clinical Evidence. 2010. [last accessed 2013 February]; Available from: http://clinicalevidence.bmj.com/x/systematic-review/2401/background.html

(5) Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, *et al*. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; **84**(5):1361-92.

(6) Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, *et al*. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November, 1997. *Ann Oncol* 1999; **10**(12):1419-32.

(7) Swerdlow SH, Campo E, Harris NL. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th Edition. IARC Press, Lyon, France. 2008.

(8) Tilly H, Dreyling M. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21 Suppl 5**:v172-v174.

(9) Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. *Hematology Am Soc Hematol Educ Program* 2011; **2011**:498-505.

(10) Vinjamaram S. Non-Hodgkin lymphoma. eMedicine. 2013. [last accessed 2013 February]; Available from: http://emedicine.medscape.com/article/203399-overview#aw2aab6b2b5aa

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

(12) Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, *et al*. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 2007; **109**(5):1857-61.

(13) National Institute for Health and Clinical Excellence. Guidance on Cancer Services. Improving Outcomes in Haematological Cancers. The manual. NICE. 2003. [last accessed 2013 February]; Available from: http://www.nice.org.uk/nicemedia/live/10891/28786/28786.pdf

(14) National Institute for Health and Clinical Excellence. Rituximab for aggressive non-Hodgkin's lymphoma. NICE. 2003. [last accessed 2013 February]; Available from: http://www.nice.org.uk/nicemedia/live/11506/32679/32679.pdf

(15) National Institute for Health and Clinical Excellence. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma. NICE. 2008. [last accessed 2013 February]; Available from: http://www.nice.org.uk/nicemedia/live/11923/39618/39618.pdf

(16) Knight C, Hind D, Brewer N, Abbott V. Rituximab (MabThera) for aggressive non-Hodgkin's lymphoma: systematic review. NICE. 2013. [last accessed 2013 February]; Available from: http://www.nice.org.uk/nicemedia/live/11505/32676/32676.pdf

(17) Committee for Medicinal Products for Human Use. Pixuvri (pixantrone). Summary of opinion (initial authorisation). CHMP. 2012. [last accessed 2013 February]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002055/WC500122928.pdf

(18) Pettengell R, Coiffier B, Narayanan G, de Mendoza FH, Digumarti R, Gomez H, *et al*. Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. *Lancet Oncol* 2012; **13**(7):696-706.

(19) European Medicines Agency. Pixuvri: summary of product characteristics. EMA. 2013. [last accessed 2013 February]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002055/WC500127968.pdf

(20) International Agency for Research on Cancer. World Health Organization. European Cancer Observatory. Cancer factsheets: non-Hodgkin lymphoma. WHO. 2008. [last accessed 2013 February]; Available from: http://eco.iarc.fr/EUCAN/Cancer.aspx?Cancer=38

(21) National Institute for Health and Clinical Excellence. Pixantrone dimaleate monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma. Final scope. NICE. 2012. [last accessed 2013 February]; Available from: http://www.nice.org.uk/nicemedia/live/13311/57684/57684.pdf

(22) Food and Drug Administration. Briefing Document. Oncologic Drugs Advisory Committee Meeting. NDA 22481 Pixuvri (pixantrone). FDA. 2010. [last accessed 2013 February]; Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM204335.pdf

(23) Pocock N. FDA requests further study of pixantrone in NHL prior to approval. National Electronic Library for Medicines. 2010. [last accessed 2013 February]; Available from: http://www.nelm.nhs.uk/en/NeLM-Area/News/2010---April/12/FDA-requests-further-study-of-pixantrone-in-NHL-prior-to-approval-/

(24) Horenstein MS, Vander Heide RS, L'Ecuyer TJ. Molecular basis of anthracycline-induced cardiotoxicity and its prevention. *Mol Genet Metab* 2000; **71**(1-2):436-44.

(25) Committee for Medicinal Products for Human Use. Guideline on the evaluation of anticancer medicinal products in man. EMA. 2005. [last accessed 2013 February]; Available from: http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf

(26) Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, *et al*. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999; **17**(4):1244.

(27) Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, *et al*. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25**(5):579-86.

(28) Cell Therapeutics Inc. Pixantrone (BBR 2778) versus other chemotherapeutic agents for third-line single agent treatment of patients with relapsed aggressive non-Hodgkin's lymphoma: a randomized, controlled, Phase III comparative trial. Clinical Study Report. 2004.

(29) Food and Drug Administration. Guidance for industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. FDA. 2007. [last accessed 2013 February]; Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf

(30) Lee L, Wang L, Crump M. Identification of potential surrogate end points in randomized clinical trials of aggressive and indolent non-Hodgkin's lymphoma: correlation of complete response, time-to-event and overall survival end points. *Ann Oncol* 2011; **22**(6):1392-403.

(31) Pettengell R, Coiffier B, Narayanan G, Mendoza F, Digumarti R, Gomez H, et al. Phase III trial of pixantrone dimaleate compared with other agents as third-line, single-agent treatment of relapsed aggressive non-Hodgkin's Lymphoma (EXTEND): results from the treatment and follow-up periods [abstract]. Annual Meeting of the American Society of Hematology (ASH). 5–8 December 2009, New Orleans, Louisiana, USA.

(32) Pettengell R, Zinzani PL, Narayanan G, Mendoza F, Digumarti R, Gomez H, *et al*. Phase III trial of pixantrone dimaleate compared with other agents as third-line, single-agent treatment of relapsed aggressive non-Hodgkin's lymphoma (EXTEND): end of study results [abstract]. Annual Meeting of the American Society of Hematology (ASH). 4–7 December 2010, Orlando, Florida, USA.

(33) Van der Jagt R, Pettengell R, Mendoza F, Narayanan G, Cernohous P, Wang L, *et al*. Overview of pixantrone dimaleate activity in non-Hodgkin's Lymphoma. Pan Pacific Lymphoma. 22–26 June 2009, Hawaii, USA.

(34) Van der Jagt R, Pettengell R, Rizzieri D, Schiller G, Cernohous P, Wang L, *et al*. Pixantrone: an overview of Phase II and Phase III studies in non-Hodgkin's lymphoma. Lymphoma & Myeloma. 22–24 October 2009, New York, USA.

(35) National Horizon Scanning Centre. Pixantrone dimaleate for relapsed or refractory aggressive non-Hodgkin's lymphoma. National Horizon Scanning Centre. 2009. [last accessed 2013 February]; Available from: http://www.hsc.nihr.ac.uk/topics/pixantrone-dimaleate-bbr2778-for-non-hodgkins-lymp/

(36) Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in healthcare. 2011. [last accessed 2013 February]; Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

(37) National Institute for Health and Clinical Excellence. Single Technology Appraisal (STA): Specification for manufacturer/sponsor submission of evidence. NICE. 2012. [last accessed 2013 February]; Available from: http://www.nice.org.uk/media/D6D/E2/SpecificationForManufacturerSponsorSubmissionEvidence.doc

(38) Delbeke D, Stroobants S, de KE, Gisselbrecht C, Meignan M, Conti PS. Expert opinions on positron emission tomography and computed tomography imaging in lymphoma. *Oncologist* 2009; **14 Suppl 2**:30-40.

(39) Gisselbrecht C, Glass B, Mounier N, Singh GD, Linch DC, Trneny M, *et al*. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010; **28**(27):4184-90.

(40) Cell Therapeutics Inc., Comparison of pixantrone + rituximab with gemcitabine + rituximab in patients with aggressive B-cell non-Hodgkin lymphoma or follicular grade 3 lymphoma who have relapsed after therapy and are not eligible for stem cell transplant (PIX-R). Clinicaltrials.gov. 2012. [last accessed 2013 February]; Available from: http://www.clinicaltrials.gov/ct2/show/NCT01321541?term=pix306&rank=1

(41) Herbrecht R, MacDonald D, Weissonger F, Wilhem M, Holladay C, Dang NH, *et al*. CPOP-R versus CHOP-R as first-line therapy for diffuse large B-cell lymphoma (DLBCL): a Phase 2, randomized, open-label, multicenter study. American Society of Haematology Annual Meeting. 10–13 December 2011, San Diego, California, USA.

(42) National Institute for Health and Clinical Excellence. Guide to the single technology appraisal (STA) process. NICE. 2006. [last accessed 2013 February]; Available from: http://www.nice.org.uk/nicemedia/pdf/STA_Process_Guide.pdf

(43) Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004; **8**(36):iii-xi, 1.

(44) Latimer N. NICE DSU Technical Support Document 14: undertaking survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data. NICE DSU. 2011. [last accessed 2013 February]; Available from: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis_finalv2.pdf

(45) Groot MT, Lugtenburg PJ, Hornberger J, Huijgens PC, Uyl-de Groot CA. Cost-effectiveness of rituximab (MabThera) in diffuse large B-cell lymphoma in The Netherlands. *Eur J Haematol* 2005; **74**(3):194-202.

(46) National Institute for Health and Clinical Excellence. Trabectedin for the treatment of relapsed ovarian cancer. National Institute for Health and Clinical Excellence. 2011. [last accessed 2013 February]; Available from: http://www.nice.org.uk/nicemedia/live/13466/54212/54212.pdf

(47) National Institute for Health and Clinical Excellence. Ovarian cancer: topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced recurrent disease only (Review of TA 91). National Institute for Health and Clinical Excellence. 2013. [last accessed 2013 February]; Available from: http://guidance.nice.org.uk/TA/WaveR/139

(48) National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. National Institute for Health and Clinical Excellence. 2008. [last accessed 2013 February]; Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

(49) British National Formulary. BNF 62. 2010.

(50) Department of Health. NHS Trusts and PCTs combined reference cost schedules 2010–11.

(51) Doorduijn J, Buijt I, Holt B, Steijaert M, Uyl-de GC, Sonneveld P. Self-reported quality of life in elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy. *Eur J Haematol* 2005; **75**(2):116-23.

(52) National Institute for Health and Clinical Excellence. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance TA 241. NICE. 2012. [last accessed 2013 February]; Available from: http://guidance.nice.org.uk/TA241

(53) Ferguson J TK, Gilmour L, Priaulx. Health state preference study mapping the change over the course of the disease process in chronic lymphocytic leukaemia (CLL). *Value in Health* 2010; **11**(6):A485.

(54) Wild D, Walker M, Pettengell R, Lewis G. Utility elicitation in patients with follicular lymphoma. *Value in Health* 2006; **9**(6):A294

(55) Pettengell R, Donatti C, Hoskin P, Poynton C, Kettle, PJ, Hancock B, *et al*. The impact of follicular lymphoma on health-related quality of life. *Ann Oncol* 2008; **19**:570-6.

(56) National Institute for Health and Clinical Excellence. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma TA226. NICE. 2011. [last accessed 2013 February]; Available from: http://guidance.nice.org.uk/TA226

(57) National Institute for Health and Clinical Excellence. Pazopanib for the first-line treatment of advanced renal cell carcinoma (TA 215). NICE. 2013. [last accessed 2013 February]; Available from: http://guidance.nice.org.uk/TA215

(58) National Institute for Health and Clinical Excellence. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (TA 178). NICE. 2009. [last accessed 2013 February]; Available from: http://www.nice.org.uk/ta178

(59) Dickson R, Boland A, Bagust A, Blundell M, Massey G, Dundar Y, *et al*. Ipilimumab for previously treated unresectable malignant melanoma: a Single Technology Appraisal. LRiG, The University of Liverpool, 2011. [last accessed 2013 February]; Available from: http://www.nice.org.uk/nicemedia/live/12092/56688/56688.pdf

(60) Kind P, Hardman G, Macran S. UK population norms for EQ-5D. 1999.

(61) Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer* 2006; **95**(6):683-90.

(62) Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer 2008 Dec;62(3):374-80.

(63) Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. *Curr Med Res Opin* 2010; **26**(5):1091-6.

(64) Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes* 2008; **6**:84.

(65) Tolley K, Goad C, Yi Y, Maroudas PA, Thompson G. Utility elicitation study in the UK general public for late stage chronic lymphocytic leukemia. *Value in Health* 2010; **13(**7):A273-A274.

(66) Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, *et al*. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes* 2010; **8**:50.

(67) Poole CD, Nielsen SK, Currie CJ, Marteau P, Masure J.A. Quality of life (health-related utility) in adults with ulcerative colitis in remission vs.. mild/moderate and severe relapse: findings from the Podium study. *Gastroenterology* 2009; **136**(5):A203.

(68) Sinno H, Thibaudeau S, Tahiri Y, Mok E, Christodoulou G, Lessard L, *et al*. Utility assessment of body contouring after massive weight loss. *Aesthetic Plast Surg* 2011; **35**(5):724-30.

(69) Curtis L. Unit Costs of Health and Social Care 2011. 2011.

(70) National Audit Office. End of Life Care, Report by the Comptroller and Auditor General. HC 1043 Session 2007–2008. 2008.

(71) British National Formulary. BNF 64. 2012.

(72) Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, *et al*. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005; **105**:1417-23.

(73) ASWCS. ASWCS Haematology Chemotherapy Protocols. 2013. [last accessed 2013 February]; Available from: http://www.avon.nhs.uk/aswcs-chemo/HCP/index.htm

(74) Briggs AH, Claxton K, Sculpher M. Decision modelling for health economic evaluation. Oxford University Press, Oxford, United Kingdom. 2006.

(75) Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. *Med Decis Making* 2012; **32**:733-43.

(76) National Institute for Health and Clinical Excellence. Appraising life-extending, end of life treatments. NICE. 2009. [last accessed 2013 February]; Available from: http://www.nice.org.uk/media/E4A/79/SupplementaryAdviceTACEoL.pdf

(77) Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. *Hematology Am Soc Hematol Educ Program* 2009; 523-31.

10 APPENDICES

Appendix 1. World Health Organization classification of lymphomas (2008)[77]

Mature B-cell neoplasms
Chronic lymphocytic leukaemia/small lymphocytic lymphoma
B-cell prolymphocytic leukaemia
Splenic marginal zone lymphoma
Hairy cell leukaemia
Splenic lymphoma/leukaemia, unclassifiable Splenic diffuse red pulp small B-cell lymphoma Hairy cell leukaemia-variant
Lymphoplasmacytic lymphoma Waldenström macroglobulinemia
Heavy chain diseases Alpha heavy chain disease Gamma heavy chain disease Mu heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma (MZL)
Follicular lymphoma
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified T-cell/histiocyte rich large B-cell lymphoma DLBCL associated with chronic inflammation Epstein-Barr virus (EBV)+ DLBCL of the elderly
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK^+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric
Castleman disease
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukaemia
T-cell large granular lymphocytic leukaemia
Chronic lymphoproliferative disorder of NK-cells
Aggressive NK cell leukaemia
Systemic EBV+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
Hydroa vacciniforme-like lymphoma
Adult T-cell leukaemia/ lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorder Lymphomatoid papulosis Primary cutaneous anaplastic large-cell lymphoma
Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic
T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous small/medium $CD4^+$ T-cell lymphoma
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK^+
Anaplastic large cell lymphoma, ALK^-
Hodgkin's lymphoma
Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma Nodular sclerosis classical Hodgkin's lymphoma Lymphocyte-rich classical Hodgkin's lymphoma Mixed cellularity classical Hodgkin's lymphoma Lymphocyte-depleted classical Hodgkin's lymphoma

Appendix 2. Ann Arbor scale of non-Hodgkin's lymphoma[(11)]

Stage	Criteria
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS), or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement
Each stage is further subdivided into two categories based on presence (B) or absence (A) of general symptoms of NHL, which were defined as night sweats, unexplained weight loss of more than 10% of the body weight in the 6 months prior to admission, and unexplained fever.	

Appendix 3. Quality assessment of PIX301[18]

Question	How is the question addressed in the study? (description in MS[a])	Manufacturer's assessment (yes/no/not clear/NA)	ERG's comment
Was randomisation carried out appropriately?	Patients were randomly assigned (1:1) by an IVRS. The randomisation schedule was created by the IVRS vendor	Yes	Agrees
Was the concealment of treatment allocation adequate?	The success of masking was confirmed by external audit of the independent assessment panel	Yes	PIX301 is of open-label design. ERG agrees in that allocation of treatment was adequate as the randomisation schedule was created by the IVRS vendor
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	Agrees
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	Agrees that risk of bias minimised
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	–	No	Agrees

Is there any evidence to suggest that the authors measured more outcomes than they reported?	–	No	Agrees
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	Agrees (for the full trial population)
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination [a] Reproduced from Table 18 (pg 74) of the MS. Abbreviations used in table: ERG, Evidence Review Group; ITT, intention-to-treat; IVRS, interactive voice response system; MS, manufacturer's submission; N/A, not applicable; PFS, progression-free survival.			

Appendix 4. Number of cycles of chemotherapeutic treatment given in histologically confirmed aggressive B-cell NHL subgroup

Outcome	Pixantrone (N = 50)	TPC (N = 47)	p value[a]
Duration of study therapy in PIX301, months			
Number of patients who received study drug	50	45	
Median (range)	3.1 (0.0 to 7.4)	1.9 (0.0 to 4.9)	
Mean (SD)	3.0 (2.07)	2.0 (1.49)	0.004
Number of cycles of therapy given during PIX301			
0	0 (0.0%)	2 (4.3%)	0.149
1	11 (22.0%)	9 (19.1%)	0.232
2	8 (16.0%)	11 (23.4%)	0.805
3	4 (8.0%)	10 (21.3%)	0.446
4	9 (18.0%)	5 (10.6%)	0.084
5	2 (4.0%)	0 (0.0%)	0.391
6	16 (32.0%)	10 (21.3%)	0.495
Median number of cycles (range)	4.0 (1 to 6)	3.0 (0 to 6)	0.259
Mean number of cycles (SD)	3.6 (1.99)	3.0 (1.87)	0.117

[a] 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.

Abbreviations used in table: SD, standard deviation; TPC, treatment of physician's choice.

Appendix 5. Baseline characteristics of patients in PIX301 (full trial population and those with histologically confirmed aggressive B-cell non-Hodgkin's lymphoma)

Table A5.1. Baseline demographics (characteristics for full trial population reproduced from MS; Table 14, pg 64)

	ITT			Histologically confirmed B-cell NHL subgroup[a]		
	Pixantrone (N = 70)	**TPC (N = 70)**	**p-value[a]**	**Pixantrone (N = 50)**	**TPC (N = 47)**	**p-value**
Age at randomisation (years)						
Mean (SD)	58.2 (13.5)	56.2 (12.9)	0.382	59.6 (12.4)	55.3 (13.4)	0.104
Median (range)	60.0 (18 to 80)	58.0 (26 to 82)		60.0 (28 to 80)	58.0 (26 to 77)	
Age category at randomisation, n (%)			0.230			0.056
18 to <30	5 (7.1%)	2 (2.9%)	0.441	2 (4.0%)	2 (4.3%)	1.000
30 to <40	2 (2.9%)	9 (12.9%)	0.055	2 (4.0%)	8 (17.0%)	0.047
40 to <50	9 (12.9%)	7 (10.0%)	0.791	8 (16.0%)	2 (4.3%)	0.093
50 to <60	18 (25.7%)	21 (30.0%)	0.706	11 (22.0%)	12 (25.5%)	0.812
60 to <70	20 (28.6%)	21 (30.0%)	1.000	14 (28.0%)	18 (38.3%)	0.388
70 to <80	15 (21.4%)	9 (12.9%)	0.262	12 (24.0%)	5 (10.6%)	0.111
≥80	1 (1.4%)	1 (1.4%)	1.000	1 (2.0%)	0	1.000
Sex, n (%)			0.385			0.310
Male	46 (65.7%)	40 (57.1%)		31 (62.0%)	24 (51.1%)	
Female	24 (34.3%)	30 (42.9%)		19 (38.0%)	23 (48.9%)	
Race, n (%)			0.957			0.471
Caucasian	46 (65.7%)	44 (62.9%)	0.860	35 (70.0%)	27 (57.4%)	0.213
Black	0	0	NE	0	0	
Asian	10 (14.3%)	13 (18.6%)	0.649	6 (12.0%)	11 (23.4%)	0.184
Hispanic	7 (10.0%)	6 (8.6%)	1.000	4 (8.0%)	3 (6.4%)	1.000
Native American	1 (1.4%)	1 (1.4%)	1.000	0	1 (2.1%)	0.485
Other	6 (8.6%)	6 (8.6%)	1.000	5 (10.0%)	5 (10.6%)	1.000
Baseline ECOG performance status, n (%)			0.881			0.931
0	26 (37.1%)	23 (32.9%)	0.723	17 (34.0%)	14 (29.8%)	0.670
1	30 (42.9%)	32 (45.7%)	0.865	21 (42.0%)	21 (44.7%)	0.839
2	14 (20.0%)	14 (20%)	1.000	12 (24.0%)	11 (23.4%)	1.000
3	0	1 (1.4%)	1.000	0	1 (2.1%)	0.485
Geographic region, n (%)			1.000			0.514
North America	4 (5.7%)	4 (5.7%)	1.000	3 (6.0%)	4 (8.5%)	0.709
Western Europe	19 (27.1%)	19 (27.1%)	1.000	16 (32.0%)	10 (21.3%)	0.259
Rest of World	47 (67.1%)	47 (67.1%)	1.000	31 (62.0%)	33 (70.2%)	0.520

Weight (kg)						
Mean (SD)	70.9 (15.8)	68.7 (15.3)	0.394	70.9 (16.8)	66.8 (15.7)	0.213
Median (range)	70.0 (45 to 117)	67.5 (37 to 115)		70.0 (45 to 117)	65.0 (37 to 105)	

[a] Data provided by manufacturer during clarification process. 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.

Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; kg, kilogram; NE, not evaluable; NHL, non-Hodgkin's lymphoma; SD, standard deviation; TPC, treatment of physician's choice.

Table A5.2. Baseline history (characteristics for full trial population reproduced from MS; Table 15, pg 65)

Subtype of NHL	**ITT**		**Histologically confirmed B-cell NHL subgroup[a]**		
	Pixantrone (N = 70)	**TPC (N = 70)**	**Pixantrone (N = 50)**	**TPC (N = 47)**	**p-value**
Diffuse large B-cell lymphoma	53 (75.7%)	51 (72.9%)	42 (84.0%)	40 (85.1%)	0.559
Transformed indolent lymphoma	10 (14.3%)	9 (12.9%)	7 (14.0%)	4 (8.5%)	1.000
Follicular lymphoma grade III	1 (1.4%)	2 (2.9%)	0	2 (4.3%)	0.526
Peripheral T-cell lymphoma NOC	3 (4.3%)	7 (10.0%)	1 (2.0%)	1 (2.1%)	0.232
Anaplastic large cell lymphoma/null cell/primary systemic	3 (4.3%)	1 (1.4%)	0	0	1.000

[a] Data provided by manufacturer during clarification process. Fisher exact test was used to compare proportions between the groups. P values reported as presented by manufacturer in clarification response.

Abbreviations used in table: ITT, intention-to-treat; NHL, non-Hodgkin's lymphoma; NOC, not otherwise classified; TPC, treatment of physicians' choice.

Table A5.3. Baseline disease characteristics (characteristics for full trial population reproduced from MS; Table 16, pg 65)

	ITT			Histologically confirmed B-cell NHL subgroup[a]		
	Pixantrone (N = 70)	**TPC (N = 70)**	**p-value[a]**	**Pixantrone (N = 50)**	**TPC (N = 47)**	**p-value[a]**
Duration of NHL (months)						
Mean (SD)	43.6 (35.6)	46.6 (51.7)	0.693	43.1 (36.2)	40.8 (41.6)	0.779
Median (range)	32.0 (7 to 160)	31.6 (0 to 333)		32.0 (7 to 160)	30.9 (0 to 223)	
Ann Arbor stage of NHL, n (%)			0.426			1.000
I/II	19 (27.1%)	14 (20.0%)		13 (26.0%)	12 (25.5%)	
III/IV	51 (72.9%)	56 (80.0%)		37 (74.0%)	35 (74.5%)	
International Prognostic Index, n (%)			0.569			0.817
0, 1	21 (30.0%)	17 (24.3%)	0.569	12 (24.0%)	13 (27.7%)	
≥2	49 (70%)	52 (74.3%)	0.706	38 (76.0%)	34 (72.3%)	
Missing	0	1 (1.4%)	1.000	-	-	
Number of extranodal sites, n (%)			1.000			1.000
0	35 (50%)	35 (50%)	1.000	25 (50.0%)	24 (51.1%)	1.000
≥1	34 (48.6%)	33 (47.1%)	1.000	24 (48.0%)	22 (46.8%)	1.000
Missing	1 (1.4%)	2 (2.9%)	1.000	1 (2.0%)	1 (2.1%)	1.000
Time from last chemotherapy to randomisation (months)						
Mean (SD)	13.6 (15.7)	13.2 (23.5)	0.886	12.6 (15.0)	10.2 (7.11)	0.307
Median (range)	9.0 (1 to 86)	8.0 (1 to 190)		8.5 (1 to 86)	8.0 (1 to 30)	

[a] Data provided by manufacturer during clarification process. 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. P values reported as presented by manufacturer in clarification response.

Abbreviations used in table: ITT, intention-to-treat; NHL, non-Hodgkin's lymphoma; SD, standard deviation; TPC, treatment of physician's choice.

Table A5.4. Baseline prior treatments for non-Hodgkin's lymphoma (characteristics for full trial population reproduced from MS; Table 17, pg 66)

	ITT			Histologically confirmed B-cell NHL subgroup[a]		
	Pixantrone (N = 70)	**TPC (N = 70)**	**p-value[a]**	**Pixantrone (N = 50)**	**TPC (N = 47)**	**p-value[a]**
Chemotherapy regimens						
Mean (SD)	2.9 (1.3)	3.1 (1.2)	0.535	3.0 (1.4)	2.9 (1.2)	0.754
Median (range)	3.0 (2 to 9)	3.0 (2 to 8)		3.0 (2 to 9)	3.0 (2 to 8)	
Number of chemotherapy regimens			0.396			1.000
2	32 (45.7%)	24 (34.3%)	0.227	22 (44.0%)	20 (42.6%)	1.000
3-5	35 (50%)	42 (60%)	0.308	25 (50.0%)	24 (51.1%)	1.000
≥6	3 (4.3%)	4 (5.7%)	1.000	3 (6.0%)	3 (6.4%)	1.000
Category of prior chemotherapy						
Biologics (anti-CD20 mAB)	38 (54.3%)	39 (55.7%)	1.000	30 (60.0%)	26 (55.3%)	1.000
Anthracyclines/anthracenediones	70 (100.0%)	70 (100.0%)	NE	50 (100.0%)	47 (100.0%)	NA
Other topoisomerase inhibitors[b]	53 (75.7%)	55 (78.6%)	0.841	38 (76.0%)	37 (78.7%)	0.811
Platinum-based agents	36 (51.4%)	35 (50.0%)	1.000	27 (54.0%)	25 (53.2%)	1.000
Antimetabolites	42 (60.0%)	44 (62.9%)	0.862	33 (66.0%)	30 (63.8%)	0.835
Alkylating agents	70 (100.0%)	70 (100.0%)	NE	50 (100.0%)	47 (100.0%)	NA
Spindle poison/mitotic inhibitors (SP/MIs)	70 (100.0%)	69 (98.6%)	1.000	50 (100.0%)	46 (97.9%)	0.485
Corticosteroids	66 (94.3%)	65 (92.9%)	1.000	47 (94.0%)	43 (91.5%)	0.709
Other[c]	21 (30.0%)	30 (42.9%)	0.160	15 (30.0%)	18 (38.3%)	0.401
Disease response category			0.544			0.242
Refractory	40 (57.1%)	40 (57.1%)	1.000	32 (64.0%)	26 (55.3%)	0.414
Relapsed	28 (40.0%)	30 (42.9%)	0.864	16 (32.0%)	21 (44.7%)	0.217
Missing	2 (2.9%)	0	0.496	2 (4.0%)	0	0.495

Patients who had radiotherapy, n (%)						
	34 (48.6%)	30 (42.9%)	0.611	25 (50.0%)	24 (51.1%)	1.000
Received SCT, n (%)						
	11 (15.7%)	10 (14.3%)	1.000	7 (14.0%)	8 (17.0%)	0.782
Anthracycline dose equivalent (mg/m^2)						
Mean (SD)	284.8 (98.1)	321.9 (119.0)	0.046	286.0 (95.9)	324.5 (102.7)	0.060
Median (range)	292.9 (51 to 472)	315.5 (15 to 681)		290.5 (78 to 472)	312.7 (75 to 516)	

[a] Data provided by manufacturer during clarification process. P values reported as presented by manufacturer in clarification response.

[b] Other topoisomerase inhibitors were etoposide and teniposide.

[c] Other includes targeted therapies, non-classified anticancer therapies and supportive therapies.

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.

Abbreviations used in table: ITT, intention-to-treat; NE, not evaluable; NHL, non-Hodgkin's lymphoma; SCT, stem cell transplant; SD, standard deviation; TPC, treatment of physician's choice.

Appendix 6. Baseline characteristics of Western Europe versus Rest of World subgroups[17]

	Western Europe		Rest of World	
	Pixantrone (N = 19)	**TPC (N = 19)**	**Pixantrone (N = 47)**	**TPC (N = 47)**
Age at randomisation (years)				
≤ 60 years	8 (42.1%)	8 (42.1%)	29 (61.7%)	33 (70.2%)
> 60 years	11 (57.9%)	11 (57.9%)	18 (38.3%)	14 (29.8%)
Sex, n (%)				
Male	14 (73.7%)	6 (31.6%)	30 (63.8%)	30 (63.8%)
Female	5 (26.3%)	13 (68.4%)	17 (36.2%)	17 (36.2%)
Duration of NHL (months)				
Median, months	32.4	31.3	29.7	33.0
Time from end of last chemotherapy to randomisation (months)				
Median, months	3.0	6.0	5.0	6.0
Number of chemotherapy regimens				
2	6 (31.6%)	3 (15.8%)	25 (53.2%)	20 (42.6%)
3	5 (26.3%)	9 (47.4%)	18 (38.3%)	22 (46.8%)
4	6 (31.6%)	3 (15.8%)	1 (2.1%)	3 (6.4%)
5	1 (5.3%)	3 (15.8%)	3 (6.4%)	1 (2.1%)
6+	1 (5.3%)	1 (5.3%)	0	1 (2.1%)
Received SCT, n (%)				
Yes	5 (26.3%)	5 (26.3%)	4 (8.5%)	4 (8.5%)
No	14 (73.7%)	14 (73.7%)	43 (91.5%)	43 (91.5%)
Received prior biologic treatment (anti-CD20 mAB), n (%)				
Yes	17 (89.5%)	17 (89.5%)	17 (36.2%)	18 (38.3%)
No	2 (10.5%)	2 (10.5%)	30 (63.8%)	29 (61.7%)

Abbreviations used in table: mAB, monoclonal antibody; NHL, non-Hodgkin's lymphoma; SCT, stem cell transplant; SD, standard deviation; TPC, treatment of physician's choice.

Appendix 7. Kaplan–Meier estimates of IAP-assessed for overall survival

Figure A7.1. Histologically confirmed aggressive B-cell NHL (provided by manufacturer on request)

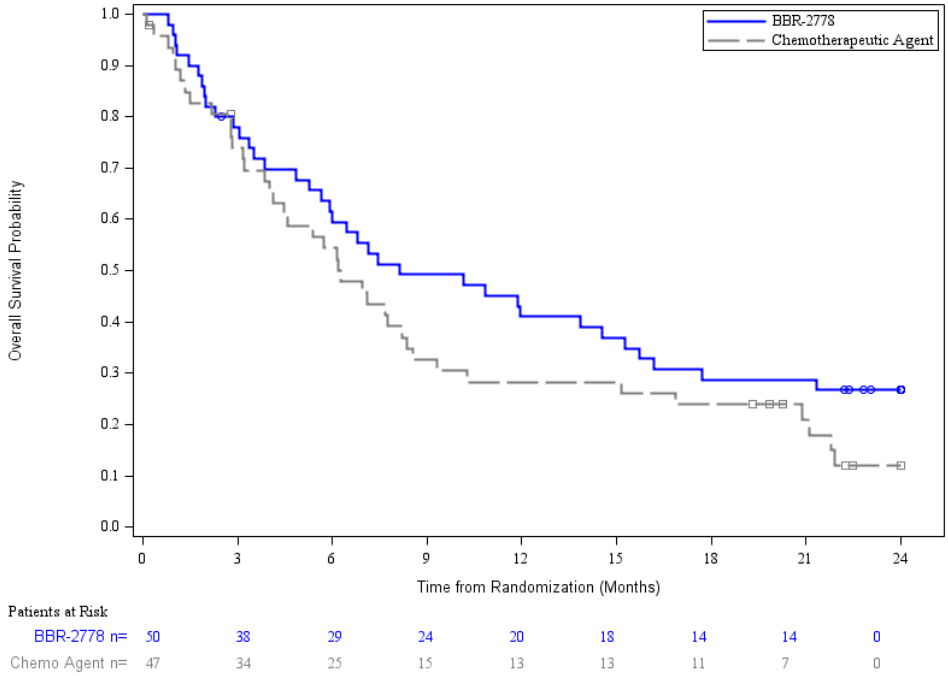
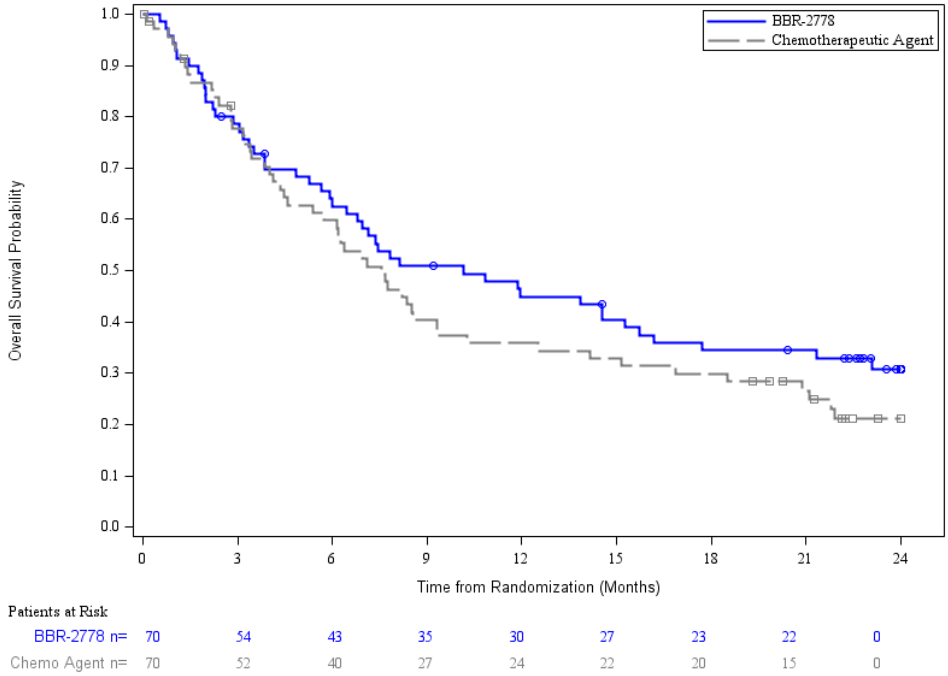


Figure A7.2. ITT population (updated figure provided by manufacturer on request)



Appendix 8. Kaplan–Meier estimates of IAP-assessed for progression-free survival

Figure A8.1. Histologically confirmed aggressive B-cell NHL (provided by manufacturer on request)

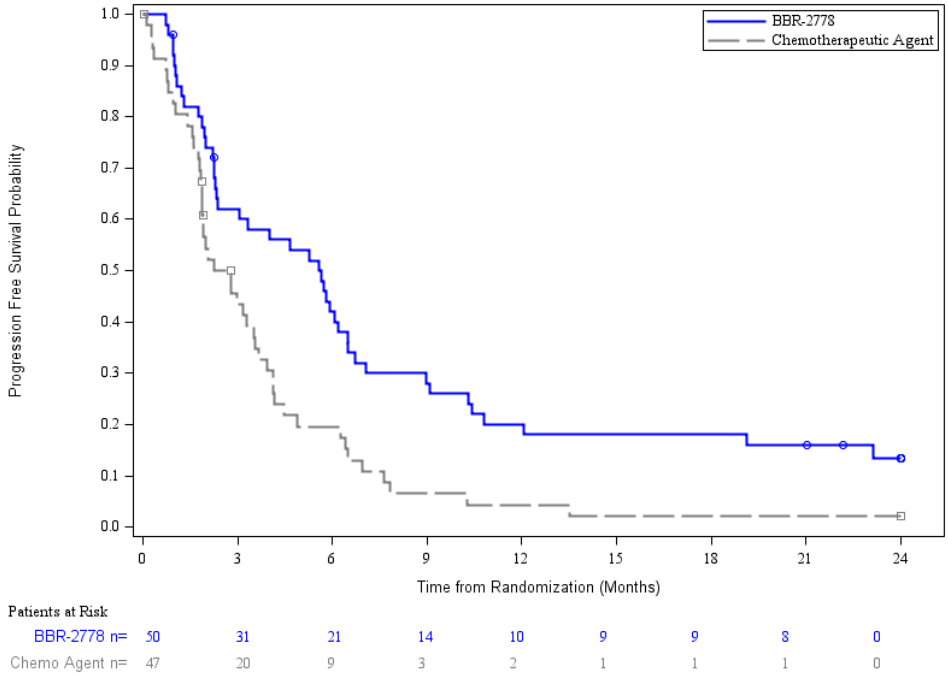
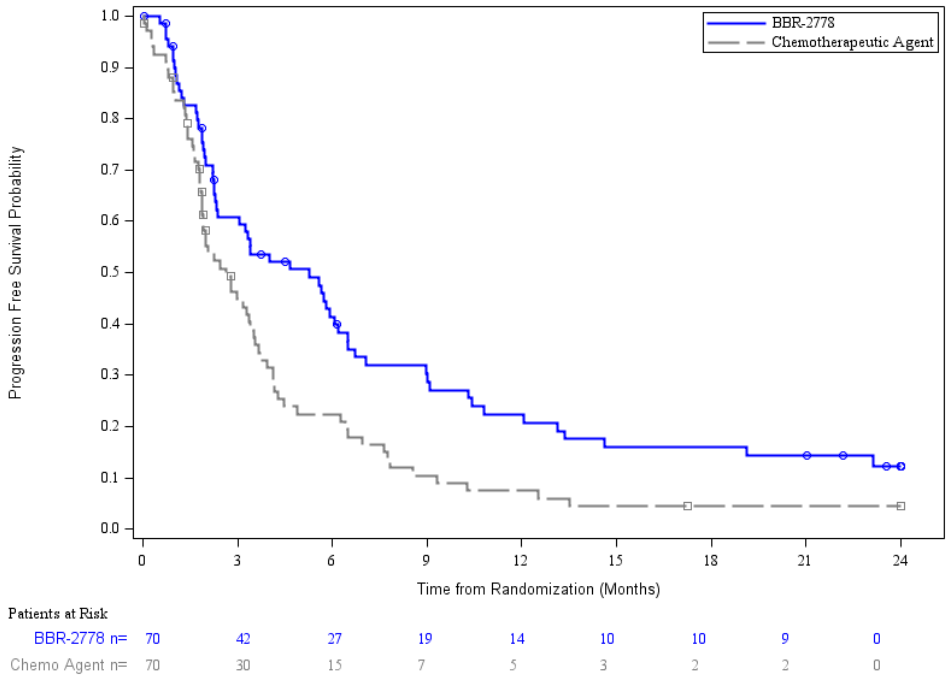


Figure A8.2. ITT population (updated figure provided by manufacturer on request)



Appendix 9. Additional secondary outcomes in subgroup analysis

Table A9.1. Secondary outcomes for subgroups based on prior rituximab treatment

	Prior rituximab treatment			No prior rituximab treatment		
Outcome	**Pixantrone (N = 30)**	**TPC (N = 26)**	**p value or HR (95% CI)**	**Pixantrone (N = 20)**	**TPC (N = 21)**	**p value or HR (95% CI)**
Time to response (CR/CRu/PR)						
Median (range), months	1.8 (1.6 to 6.0)	1.9 (1.8 to 2.3)	0.88 (0.28 to 2.82)	2.4 (1.7 to 8.2)	1.8 (1.6 to 2.8)	0.34 (0.08 to 1.45)
Mean (SD), months	2.3 (1.39)	2.0 (0.18)	–	3.2 (2.07)	2.1 (0.65)	–
Time to response (CR/CRu)						
Median (range), months	1.8 (1.6 to 8.2)	3.7 (2.3 to 19.0)	3.49 (0.67 to 18.3)	2.4 (2.0 to 3.6)	3.6 (3.6 to 3.6)	N/E
Mean (SD), months	2.8 (2.64)	8.3 (9.27)	–	2.7 (0.83)	N/E	–
Duration of response						
Median (range), months	5.5 (3.6 to 22.5)	1.7 (1.0 to 22.2)	0.71 (0.21 to 2.40)	3.9 (2.1 to 21.2)	4.8 (0.0 to 6.0)	0.52 (0.12 to 2.21)
Mean (SD), months	8.5 (6.20)	6.4 (9.04)	–	9.5 (8.56)	3.6 (3.18)	–
Response (CR/CRu/PR) lasting ≥4 months						
Proportion of patients achieving outcome	4	2	0.675	3	2	0.663
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin's lymphoma; SD, standard deviation; TPC, treatment of physician's choice.						

Table A9.2. Secondary outcomes for subgroups based on third or fourth line of treatment

	Third or fourth line of treatment		
Outcome	**Pixantrone (N = 39)**	**TPC (N = 39)**	**p value or HR (95% CI)**
Time to response (CR/CRu/PR)			
Median (range), months	2.0 (1.6 to 6.0)	1.8 (1.6 to 2.8)	0.57 (0.20 to 1.61)
Mean (SD), months	2.5 (1.18)	2.0 (0.48)	–
Time to response (CR/CRu)			
Median (range), months	2.0 (1.6 to 8.2)	3.7 (3.6 to 3.7)	2.36 (0.47 to 11.9)
Mean (SD), months	2.8 (2.13)	3.7 (0.02)	–
Duration of response			
Median (range), months	5.5 (3.0 to 22.5)	4.8 (0.0 to 6.0)	0.40 (0.13 to 1.20)
Mean (SD), months	9.4 (7.29)	3.7 (2.65)	–
Response (CR/CRu/PR) lasting ≥4 months			
Number of patients achieving outcome	7	3	0.310
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; NHL, non-Hodgkin's lymphoma; SD, standard deviation; TPC, treatment of physician's choice.			

Appendix 10. Manufacturer's cost-effectiveness and resource use EMBASE search strategy (reproduced from MS supplementary Numerical appendices document Table 67, pg 24)

	Search term	Hits
S1	'lymphoma'/exp/mj OR lymphoma:ab,ti AND [embase]/lim	127061
S2	'B-cell lymphoma'/exp/mj OR 'B-cell lymphoma':ab,ti AND [embase]/lim	15302
S3	'diffuse lymphoma':ab,ti AND [embase]/lim	180
S4	'high-grade lymphoma':ab,ti AND [embase]/lim	505
S5	'intermediate-grade lymphoma':ab,ti AND [embase]/lim	79
S6	'large cell lymphoma'/exp/mj OR 'large cell lymphoma':ab,ti AND [embase]/lim	6703
S7	'nonhodgkin lymphoma'/exp/mj OR 'nonhodgkin lymphoma':ab,ti AND [embase]/lim	50861
S8	'cd20 antigen'/exp AND [embase]/lim	5359
S9	'b lymphocyte antigen'/exp AND [embase]/lim	1219
S10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	130697
S11	indolent:ab,ti OR 'low-grade':ab,ti AND [embase]/lim	34795
S12	#10 NOT #11	124414
S13	'health care cost'/exp OR cost*:ab,ti AND [embase]/lim	342005
S14	'budget'/exp OR budget*:ab,ti AND [embase]/lim	18295
S15	expenditure*:ab,ti AND [embase]/lim	28070
S16	'health care utilization'/exp OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti AND [embase]/lim	33433
S17	economic*:ab,ti AND [embase]/lim	106658
S18	'pharmacoeconomics'/exp OR pharmacoeconomic*:ab,ti AND [embase]/lim	75567
S19	'health resources':ab,ti AND [embase]/lim	1755
S20	'medical resources':ab,ti AND [embase]/lim	1140
S21	'cost benefit analysis'/exp OR 'cost analysis':ab,ti AND [embase]/lim	38496
S22	'cost effectiveness analysis'/exp OR 'cost effectiveness':ab,ti AND [embase]/lim	82547
S23	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	515984
S24	#10 AND #23	2295
S25	#12 AND #23 NOT (letter:it OR editorial:it OR note:it) AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND [1-1-1995]/sd AND [embase]/lim	**434**

Appendix 11. Visual comparison of Kaplan–Meier data and parametric distributions used in manufacturer's sensitivity analysis

Figure A11.1. Plot of log-logistic parametric distributions and Kaplan–Meier data for OS in B-cell NHL patients whose disease has not been histologically confirmed as aggressive (trial period)

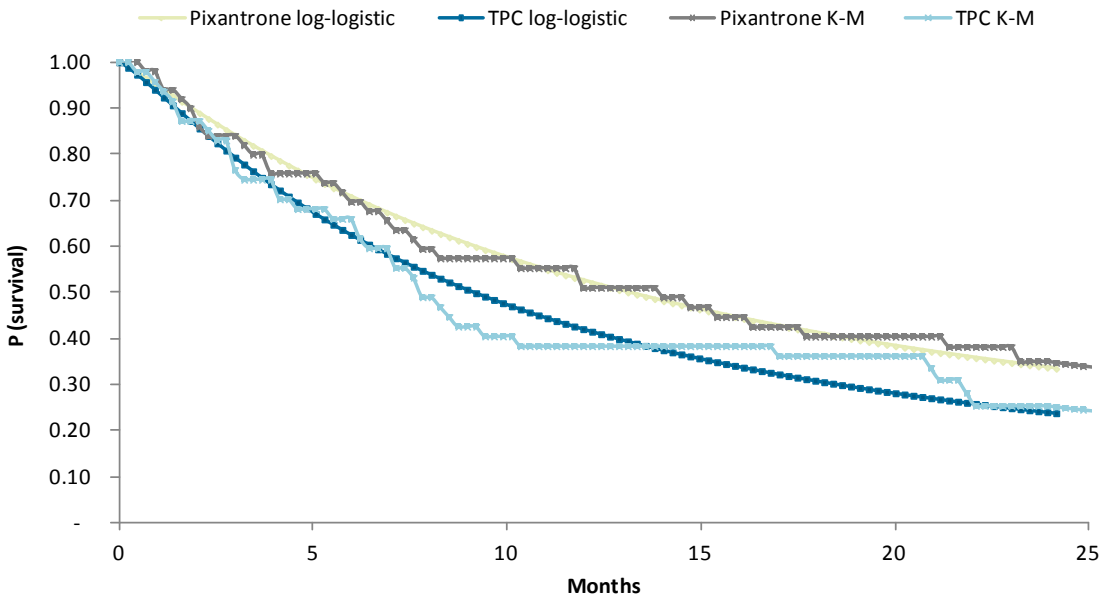


Figure A11.2. Plot of log-logistic parametric distributions and Kaplan–Meier data for PFS in B-cell NHL patients whose disease has not been histologically confirmed as aggressive (trial period)

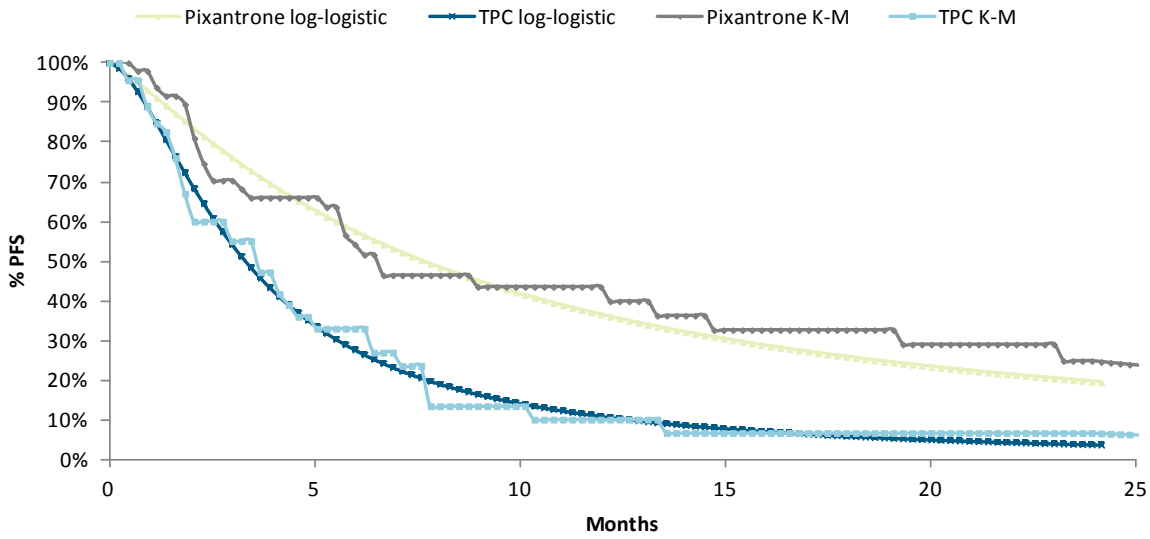


Figure A11.3. Plot of log-logistic parametric distributions and Kaplan–Meier data for OS in B-cell NHL patients whose disease has not been histologically confirmed as aggressive (long-term projection)

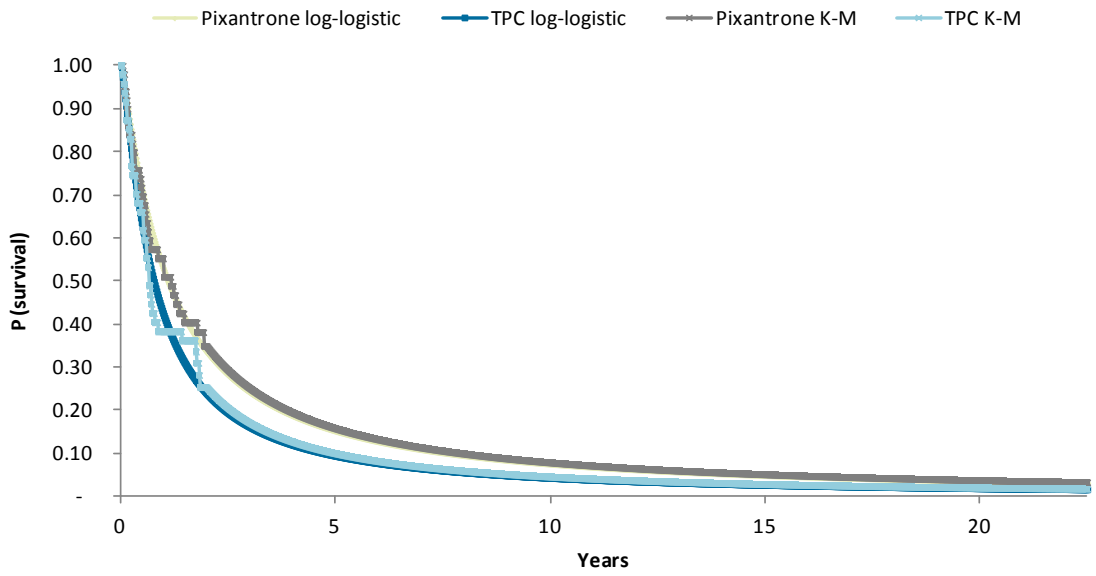


Figure A11.4. Plot of log-logistic parametric distributions and Kaplan–Meier data for PFS in B-cell NHL patients whose disease has not been histologically confirmed as aggressive (long-term projection)

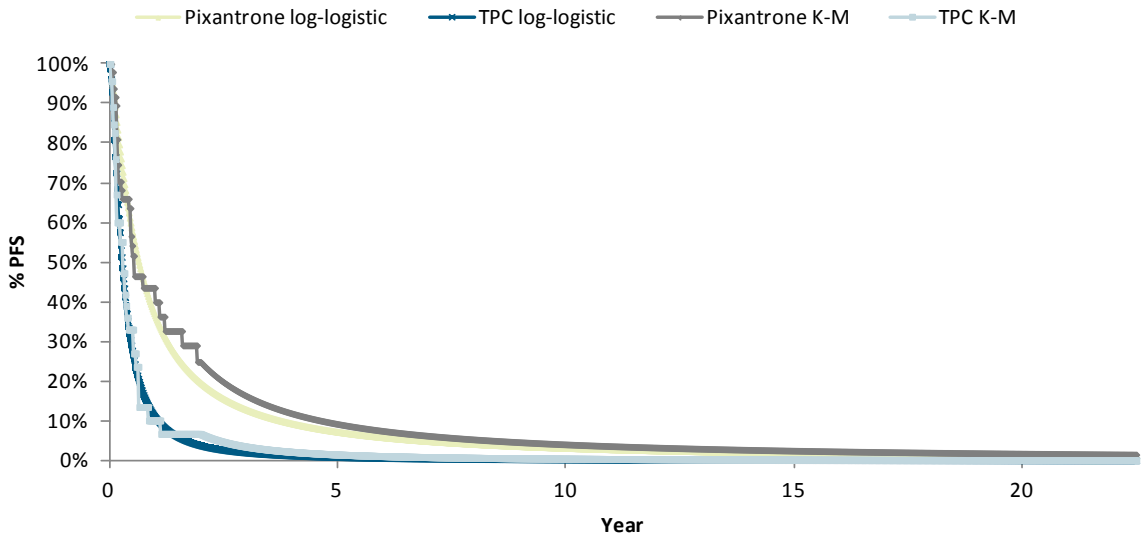


Figure A11.5. Plot of generalised gamma parametric distributions and Kaplan–Meier data for OS in B-cell NHL patients whose disease has not been histologically confirmed as aggressive (trial period)

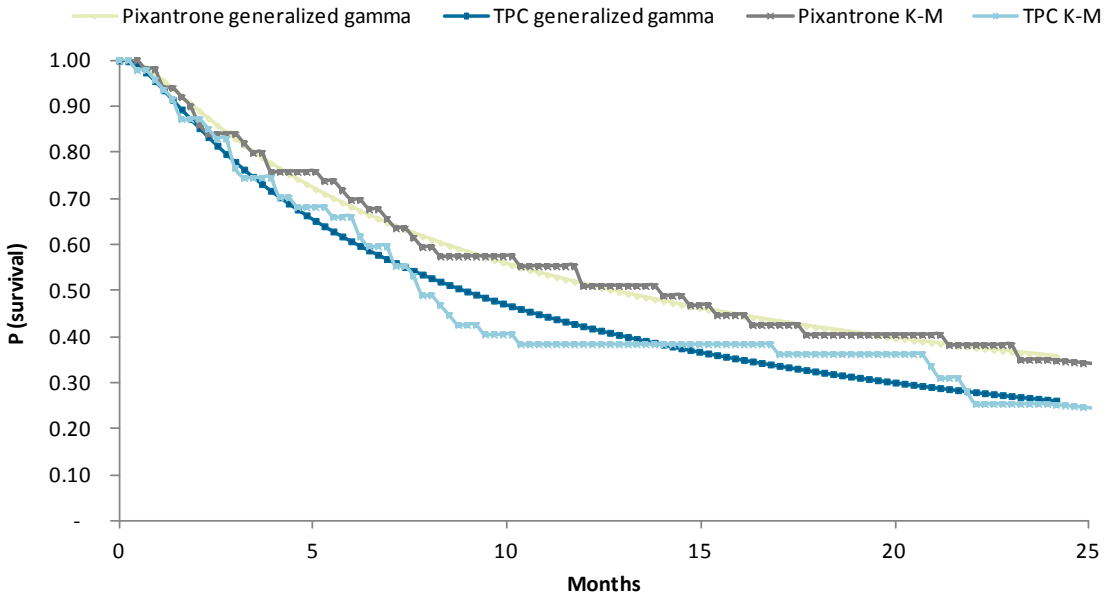


Figure A11.6. Plot of generalized gamma parametric distributions and Kaplan–Meier data for PFS in B-cell NHL patients whose disease has not been histologically confirmed as aggressive (trial period)

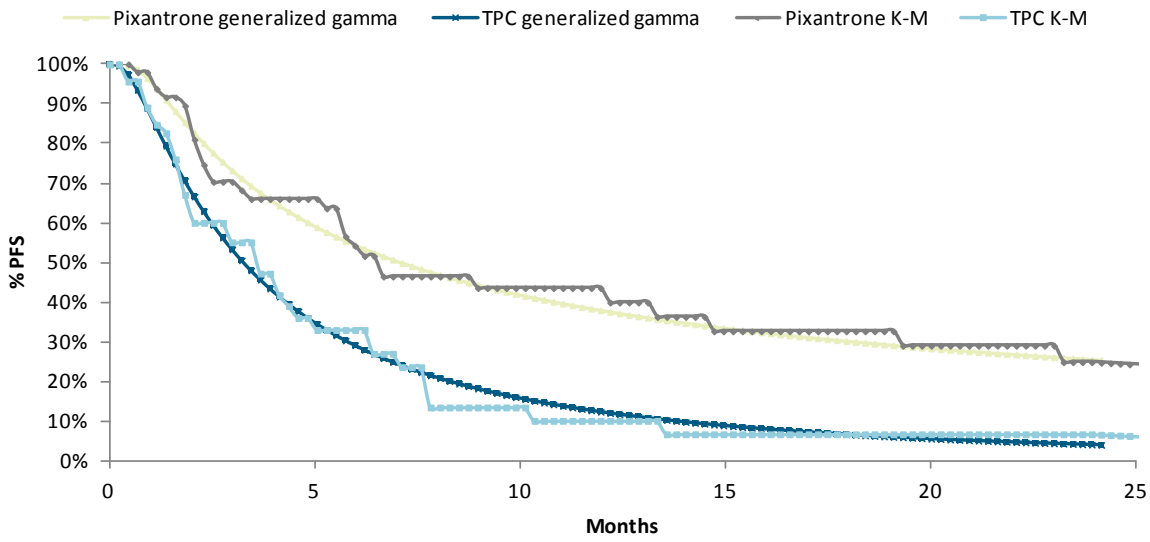


Figure A11.7. Plot of generalized gamma parametric distributions and Kaplan–Meier data for OS in B-cell NHL patients whose disease has not been histologically confirmed as aggressive (long-term projection)

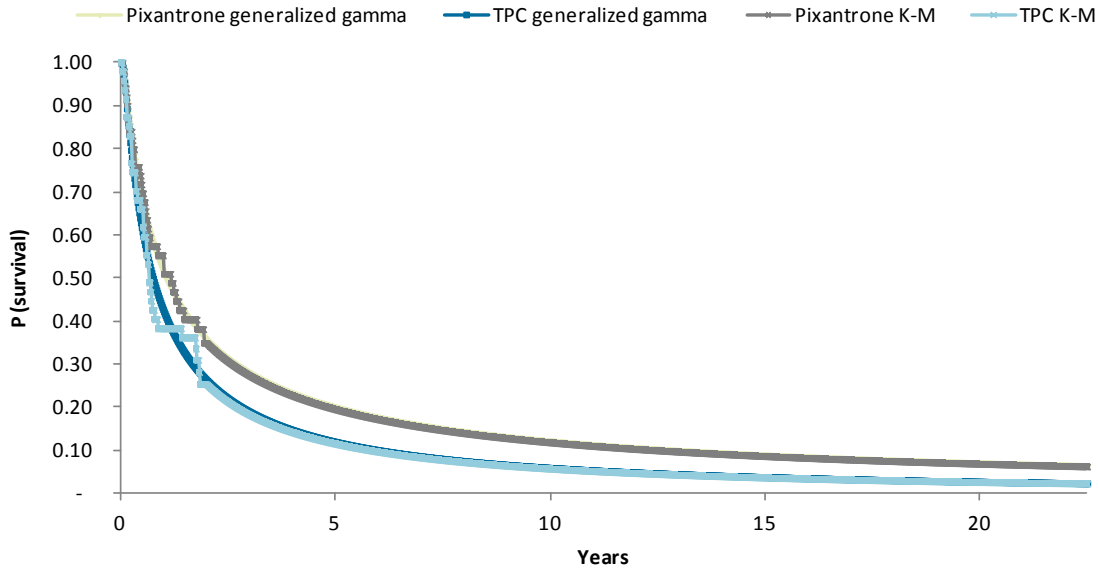
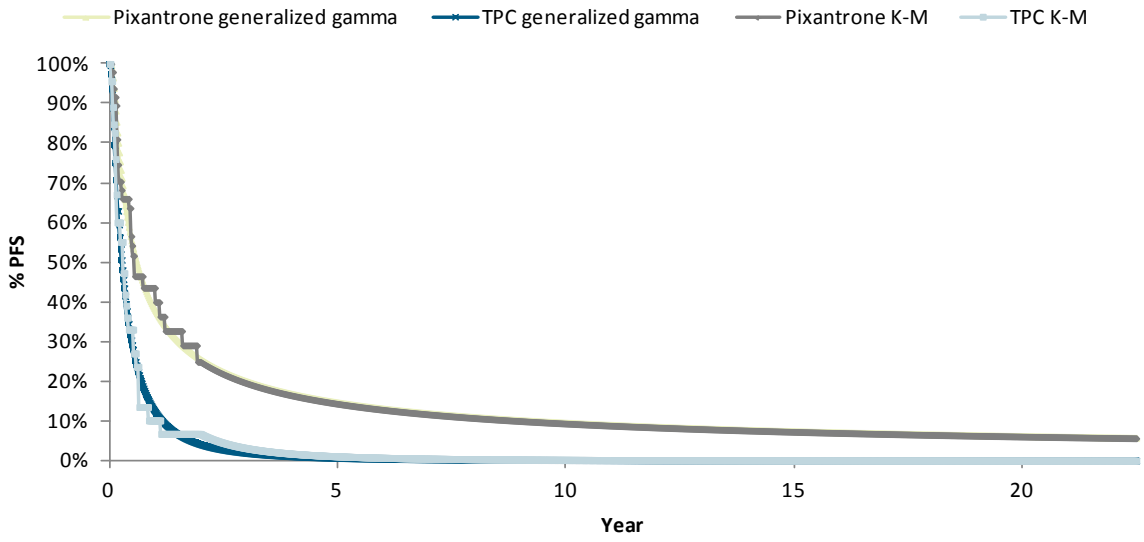


Figure A11.8. Plot of generalized gamma parametric distributions and Kaplan–Meier data for PFS in B-cell NHL patients whose disease has not been histologically confirmed as aggressive (long-term projection)



Appendix 12. Manufacturer's health related quality of life EMBASE search strategy (reproduced from MS supplementary Numerical appendices document Table 73, pg 30)

	Search term	Hits
#1	'lymphoma'/exp/mj OR lymphoma:ab,ti AND [embase]/lim	127494
#2	'B-cell lymphoma'/exp/mj OR 'B-cell lymphoma':ab,ti AND [embase]/lim	15380
#3	'diffuse lymphoma':ab,ti AND [embase]/lim	180
#4	'high-grade lymphoma':ab,ti AND [embase]/lim	508
#5	'intermediate-grade lymphoma':ab,ti AND [embase]/lim	79
#6	'large cell lymphoma'/exp/mj OR 'large cell lymphoma':ab,ti AND [embase]/lim	6742
#7	'nonhodgkin lymphoma'/exp/mj OR 'nonhodgkin lymphoma':ab,ti AND [embase]/lim	51016
#8	'cd20 antigen'/exp AND [embase]/lim	5406
#9	'b lymphocyte antigen'/exp AND [embase]/lim	1221
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	131155
#11	indolent:ab,ti OR 'low-grade':ab,ti AND [embase]/lim	35005
#12	#10 NOT #11	124851
#13	'quality of life'/exp OR 'quality of life':ab,ti OR qol:ab,ti AND [embase]/lim	180105
#14	'quality adjusted life year'/exp OR 'quality adjusted life year':ab,ti AND [embase]/lim	7745
#15	qaly:ab,ti AND [embase]/lim	4129
#16	'disability adjusted life':ab,ti AND [embase]/lim	796
#17	'disability adjusted life year':ab,ti AND [embase]/lim	206
#18	daly:ab,ti AND [embase]/lim	550
#19	'health status'/exp OR 'health status':ab,ti AND [embase]/lim	81783
#20	'health related quality of life':ab,ti AND [embase]/lim	16904
#21	'quality adjusted life':ab,ti AND [embase]/lim	5118
#22	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	248873
#23	#12 AND #22	1217
#24	utilit*:ab,ti AND [embase]/lim	96653
#25	disutil*:ab,ti AND [embase]/lim	207
#26	#22 OR #24 OR #25	338755
#27	#12 AND #26 NOT (letter:it OR editorial:it OR note:it) AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND [1-1-1995]/sd AND [embase]/lim	**614**

Appendix 13. List of participating Key Opinion Leaders (KOLs)/Clinical experts used by the manufacturer (taken from MS Appendices A_B doc Table 12, pg 105)

Name	Title	Contact	Hospital
Dr Ian Chau, MD	Consultant medical oncologist	Ian.Chau@rmh.nhs.uk	Royal Marsden Hospital, Surrey
Dr Tim Illidge	Consultant medical oncologist	tmi@manchester.ac.uk	Christie Hospital in Manchester
Dr David Linch	Consultant medical oncologist	d.linch@ucl.ac.uk	University College London
Dr Kalakonda Nagesh	Consultant medical Haematologist	Nagesh.Kalakonda@liverpool.ac.uk	Royal Liverpool and Broadgreen University
Dr George Follows	Consultant medical Haematologist	george.follows@addenbrookes.nhs.uk	Addenbrooke's Hospital

Appendix 14. Sensitivity analysis on manufacturer's base case

Table A14.1. Selected results of manufacturer's base case one-way sensitivity analysis

Parameter	Baseline value	Alternate value	ICER (£/QALY)[a]
Base case deterministic ICER			**28,503**
Health discount rate	3.5%	0%	23,148
		6%	32,322
Cost discount rate	3.5%	0%	35,086
		6%	25,464
Professional and social services progressive state	£1,993.89	£1,595.11	30,388
		£2,392.67	26,619
Drug cost per administration: pixantrone	£1,665.18	£1,332.14	23,075
		£1,998.21	33,932
Treatment discontinuation risk factor: pixantrone	1.00	0.80	31,748
		1.20	25,886
Progression free survival: pixantrone	Mean	2.5% Lower	Dominant
		97.5% Upper	90,299
Progression free survival: TPC	Mean	2.5% Lower	55,027
		97.5% Upper	17,955
Overall survival: pixantrone	Mean	2.5% Lower	54,115
		97.5% Upper	100,536
Overall survival: TPC	Mean	2.5% Lower	190,300
		97.5% Upper	47,715

[a] Including correct price for pixantrone.

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TPC, treatment of physician's choice.

Table A14.2. Results of manufacturer's scenario analyses (adapted from MS; Tables 47 and 48, pg 187)

Parameter	Baseline value	Alternate value		ICER (£/QALY)[a]
Manufacturer's deterministic base case ICER				**28,503**
PFS defined as time to progression, death or treatment discontinuation	Death and progressive disease	Death, PD and treatment switch		56,278
Parametric fitting for OS and PFS	Log-normal	Generalised gamma		1,207
		Log-logistic		24,264
Wastage	No vial sharing	Vial sharing		24,711
Health state utility values				
Alternative sources		**PFS utility**	**PD utility**	**ICER (£/QALY)**
2nd line treatment in patients with chronic myelogeneous leukaemia,	Base case utility value: PFS = 0.81; PD = 0.60	0.85	0.73	28,135
3rd line treatment in patients with chronic lymphocytic leukaemia		0.65	0.47	35,347
1st line maintenance treatment in patients with follicular lymphoma		0.78	0.62	30,079
1st line treatment in patients with metastatic renal cell carcinoma		0.70	0.59	34,008
2nd line treatment in patients with renal cell carcinoma		0.76	0.68	31,819
2nd line treatment in patients with malignant melanoma		0.8	0.76	30,748

[a] Including correct price for pixantrone.

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QALY, quality adjusted life year,

Figure A14.1. Scatter plot results of probabilistic sensitivity analysis of pixantrone compared with TPC arm (adapted from manufacturer's revised base case model, submitted at clarification)

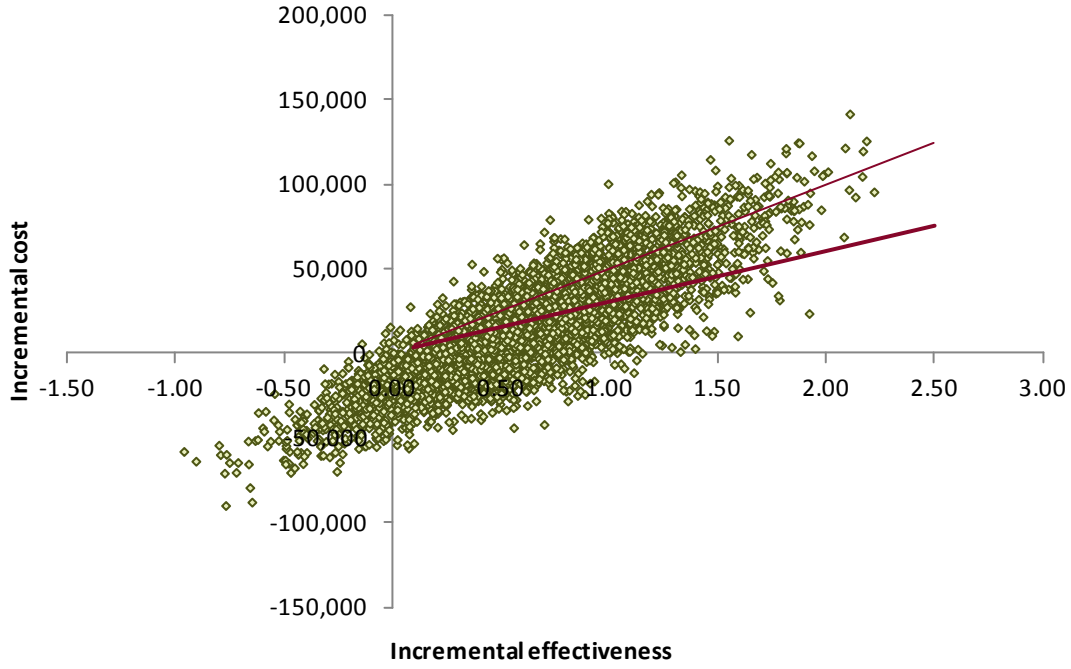


Figure A14.2. Cost-effectiveness acceptability curve (adapted from manufacturer's revised base case model, submitted at clarification)

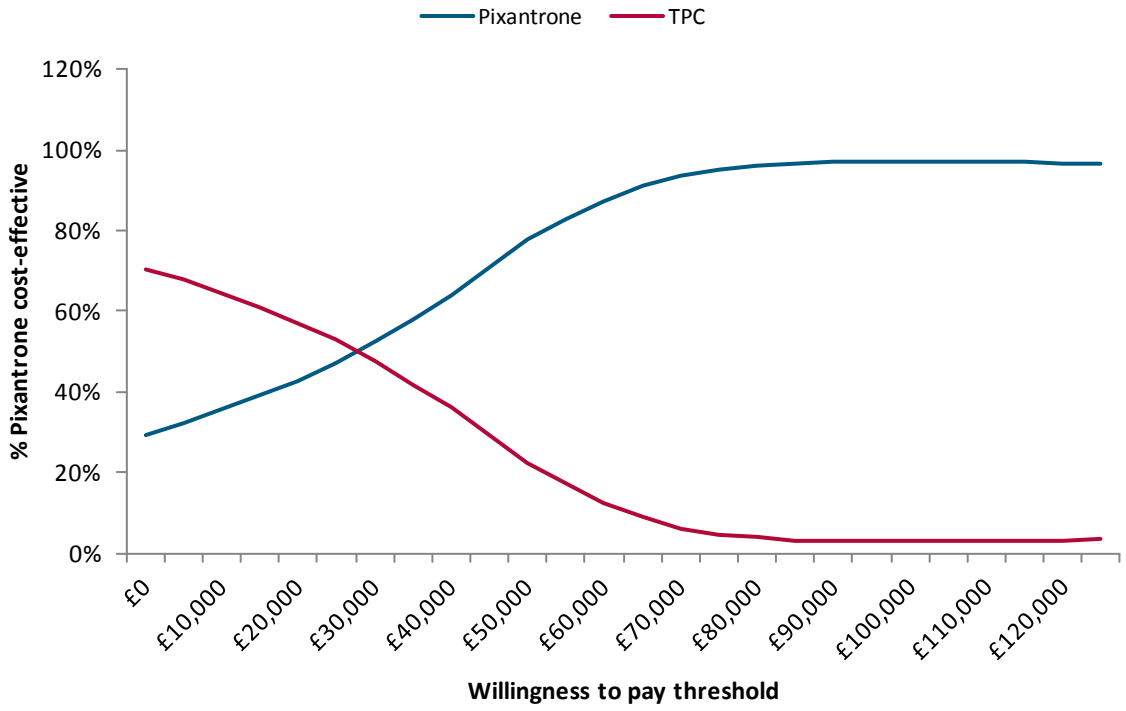


Table A14.3. Probability of cost-effectiveness with respect to willingness-to-pay thresholds

Treatment	WTP (£/QALY)[a]		
	20,000	**30,000**	**50,000**
Pixantrone	42.8%	52.6%	77.5%
TPC	57.2%	47.4%	22.5%

[a] Based on correct price for pixantrone.

Abbreviations used in table: QALY, quality adjusted life year; WTP, willingness-to-pay; TPC, treatment of physician's choice.

Appendix 15. List of parameters varied, the values used in one way sensitivity analysis and the resultant deterministic ICERs (adapted from manufacturer's model)

Parameter	Base	Low Range	High Range
Grade 3/4 rate AE pixantrone	0.12	0.06	0.22
Grade 2 rate AE pixantrone	0.01	0.00	0.03
Grade 3/4 rate AE standard care	0.10	0.03	0.22
Grade 2 rate AE standard care	0.03	0.01	0.05
Utility decrement grade 2 Aes pixantrone	0.01	0.00	0.02
Utility decrement grade 2 Aes SC	0.01	0.00	0.02
Utility decrement grade 3/4 Aes pixantrone	0.01	0.00	0.02
Utility decrement grade 3/4 Aes SC	0.01	0.00	0.02
Cost grade 2 Aes pixantrone	£40	£33	£47
Cost grade 2 Aes SC	£43	£37	£50
Cost grade 3/4 Aes pixantrone	£254	£171	£342
Cost grade 3/4 Aes SC	£386	£280	£472
Professional and social services stable state	£476	£381	£572
Professional and social services progressive state	£1,994	£1,595	£2,393
Health care professional costs (28 days) active therapy	£789	£631	£947
Health care professional costs (28 days) palliative therapy	£991	£793	£1,189
Treatment follow-up costs (28 days) active therapy	£87	£69	£104
Treatment follow-up costs (28 days) palliative therapy	£18	£15	£22
Hospital costs (annual) active therapy	£2,357	£1,886	£2,829
Hospital costs (annual) palliative	£1,982	£1,586	£2,378
Cost at progression active therapy	£1,455	£1,164	£1,746
Cost at progression palliative therapy	£48	£38	£58
Utility stable disease	0.81	0.62	0.94
Utility progressive disease	0.60	0.48	0.72
Administration cost first attendance simple	£231	£185	£277
Administration cost first attendance more complex	£252	£202	£302
Administration cost first attendance complex	£302	£242	£362
Administration cost subsequent cycles	£206	£165	£247
Drug cost per administration pixantrone	£1,665	£1,332	£1,998
Drug cost per administration vinorelbine	£86	£69	£103
Drug cost per administration oxaliplatin	£546	£437	£656
Drug cost per administration ifosfamide	£223	£179	£268
Drug cost per administration etoposide 100 mg	£26	£21	£31
Drug cost per administration etoposide 50mg	£26	£21	£31
Drug cost per administration mitoxantrone	£185	£148	£221
Drug cost per administration gemcitabine	£282	£226	£339

Drug cost per administration rituximab	£1,250	£1,000	£1,500
Gender % Males	0.61	0.53	0.69
BSA of males	1.86	1.82	1.90
BSA of females	1.67	1.61	1.73
Treatment discontinuation risk factor for pixantrone	1.00	0.80	1.20
Treatment discontinuation risk factor for standard care	1.00	0.80	1.20
Professional and social services stable state post treatment	£119	£95	£143
Health care professional costs (28 days) active therapy post treatment	£220	£176	£264
Treatment follow-up costs (28 days) active therapy post treatment	£87	£69	£104
Hospital costs (annual) active therapy post treatment	£2,357	£1,886	£2,829
Cost of oral administration	£163	£130	£196
Progression free survival pixantrone	Mean	2.5% Lower	97.5% Upper
Progression free survival standard care	Mean	2.5% Lower	97.5% Upper
Overall survival pixantrone	Mean	2.5% Lower	97.5% Upper
Overall survival standard care	Mean	2.5% Lower	97.5% Upper

Appendix 16. Individual and cumulative impact of ERG sensitivity and scenario analyses on the manufacturer's base case economic evaluation

Analysis	Treatment	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALYs)	Cumulative ICER
Manufacturer's base case	**TPC**	**68,650**	**1.127**	**–**	**–**	**–**	**28,503**
	Pixantrone	**86,337**	**1.747**	**17,688**	**0.621**	**28,503**	
ERG's sensitivity analyses							
PFS and PD utility from CLL patients on 3rd line therapy	TPC	68,650	0.548	–	–	–	52,629
	Pixantrone	86,337	0.884	17,688	0.336	52,629	
No discounting in year1	TPC	68,994	1.133	–	–	–	52,583
	Pixantrone	86,722	1.755	17,727	0.622	28,486	
ERG alternative utility values for anaemia, renal failure, weight loss and Grade 3 vomiting	TPC	68,650	1.127	–	–	–	52,591
	Pixantrone	86,337	1.747	17,688	0.621	28,506	
Using drug costs from BNF 64	TPC	68,681	1.127			–	52,593
	Pixantrone	86,370	1.747	17,689	0.621	28,505	
ERG's base case	**TPC**	**69,026**	**0.551**	**–**	**–**	**–**	**52,593**
	Pixantrone	**86,754**	**0.888**	**17,728**	**0.337**	**52,593**	
ERG's scenario analyses[a]							
Inclusion of costs for leukopaenia and thrombocytopaenia[b]	TPC	69,095	0.551	–	–	–	53,631
	Pixantrone	87,173	0.888	18,078	0.337	53,631	
Exclusion of potentially missing data	TPC	69,275	0.551	–	–	–	54,189
	Pixantrone	87,191	0.888	17,916	0.337	53,151	

[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; Inc., incremental; LYG, life years gained; NHL, non-Hodgkin's lymphoma; PD, progressive disease; PFS, progression-free survival; QALYs, quality adjusted life years.