NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Brand Name: PIXUVRI

Generic Name: Pixantrone

Therapeutic class: Aza-anthracenedione

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

Disease area to which the patient access scheme applies: as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (NHL) with tumour histology confirmed by pathological review in third- and fourth-line treatment.

3.2 Please outline the rationale for developing the patient access scheme.

To enable access to Pixantrone in England and Wales for whom currently there is no licensed product available for the treatment of multiply relapsed or refractory aggressive Non Hodgkin B-cell Lymphomas.

CTI Life Sciences has submitted previously a PAS at Final Appraisal Determination stage which consisted of a financially-based scheme in which CTI Life Sciences would provide a [redacted] discount on the UK list price for a vial of pixantrone. As a response the Second Appraisal Consultation Document (ACD 2), CTI Life Sciences is now submitting an additional [redacted]

discount on the UK list price for a vial of pixantrone (a total of [redacted] discount). This PAS submission describes the revised [redacted] discount scheme.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The text highlighted below in turquoise is confidential text.

The patient access scheme will be a financially-based scheme in which CTI Life Sciences would provide a [redacted] discount on the UK list price for a vial of pixantrone. The list price and discounted price are shown in Table 1 below.

Table 1. List price and discounted price with patient access scheme for pixantrone

List price(ex VAT)	Discounted price
£553.50	[redacted]

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

This scheme would apply to patients with histologically confirmed aggressive B-cell NHL who have previously received treatment with rituximab and will be receiving pixantrone as a third or fourth line treatment.

The conditional license via the EMA process was granted based on the benefit in third and fourth line and not fifth line and beyond, for which the EMA noted there was no benefit demonstrated.[i,ii] According to the Summary of

Product Characteristics “the benefit of pixantrone has not been established when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.” Furthermore, in the ERG’s response to CTI Life Sciences’ comments on the ACD 1, it was stated that “clinical expert opinions is that people with aggressive B-cell NHL rarely receive fifth-line treatment.” The ACD 2 thus concluded that “it was also appropriate to evaluate a subgroup of these patients receiving third- or fourth-line treatment”.

To be in line with UK clinical practice, the patient access scheme is limited to those with histologically confirmed aggressive B-cell NHL. Biopsy samples are likely to undergo review by at least one clinician in NHL prior to treatment commencement.

In addition in England and Wales rituximab is an integral part of standard first-line treatment in the NHS and is also often used as a second-line treatment.

Thus the corresponding subgroup in the PIX301 trial is the subgroup of patient who:

- had disease confirmed by central independent pathological evaluation (rather than onsite pathological evaluation) **and**
- had received 2 or 3 lines of treatment **and**
- had previously received rituximab (as in UK clinical practice).

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Not applicable. The scheme is not dependent upon any criteria.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Based on the incidence data from the EU cancer observatory 2008, we estimate that approximately 5,555 patients in the UK will suffer from aggressive NHL of which 1,830 patients are likely to have multiply relapsed aggressive NHL.[iii] Table 2 below shows the proportion of these patients that will be eligible for 3rd or 4th line treatment (i.e. meet the scheme criteria)[iv]. It is assumed that all of these patients will have received prior rituximab based on the following statement in the draft FAD – "The Committee was aware that the smallest minority of patients would not receive rituximab in clinical practice in England and Wales because rituximab is not commonly contraindicated and it is almost always used."

Table 2. Population Expected to Meet Scheme Criteria

Year	3+ Line	3rd/4th Line – prior rituximab
2013	1830	1650
2014	1848	1665
2015	1867	1682
2016	1885	1698
2017	1904	1715

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

CTI Life Sciences will provide a [redacted] discount on the UK list price for a vial of pixantrone. The discount will be for the price of each pack, thus no rebate calculations are required.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

Not applicable. The scheme is a straight forward discount on the price of the vial and no additional information or administration burden is required.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable. The scheme is a straight forward discount on the price of the vial and no funding flows are required.

3.10 Please provide details of the duration of the scheme.

If there are no changes in the circumstances, the scheme will be in place for an indefinite duration. However, CTI Life Sciences may withdraw the patient access scheme nationally if there is a change in market authorisation post the conditional approval study, which is due in 2015/16.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No equity or equality issues are associated with the scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Not applicable. The scheme is a straight forward discount on the price of the vial and does not require any additional forms or guides for patients, pharmacists, or physicians.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable. An outcome-based scheme is not being submitted.

Cost effectiveness

3.14 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

This population has previously been included as subgroup in our response to the Appraisal Consultation Document (ACD 1) [Response to ACD 1 pixantrone, which was submitted on 7/05/2, which revised sections 5.5, 6.7, and 6.9 from the "specification for manufacturer/sponsor submission of evidence" document] and was used as the basis of the prior PAS submission also. .

A summary of the clinical evidence of pixantrone (versus standard of care) in this subgroup – patients with histologically confirmed aggressive B-cell NHL who have previously received treatment with rituximab and will be receiving pixantrone as a third or fourth line treatment – was included in our response to the ACD 1. See the revised version of the mislabelled Table 5, section 3 from our response to the ACD 1 (page 14) in Appendix 1.

The base-case and sensitivity analyses' results from the cost-effectiveness model were provided in our response to the ERG's prior response to our comments on the ACD 1. In addition to that, further changes described in Section 3.16 were implemented in the model based on ERG's recommendations prior to ACD 2. The Appendix and questions 3.20 – 3.23 below provide the results from the cost-effectiveness model (with and without the patient access scheme).

No further analyses or subgroups are relevant in the current context as only one particular subgroup is covered under the proposed patient access scheme.

3.15 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

The model has been updated to reflect the proposed patient access scheme. The models that will be submitted (which have also been updated based on feedback from the ERG) with this patient access scheme integrated are named:

M-11146 Pixantrone CE model_24Oct2013_UpdatedBasedOnERG_With Pix Discount_FINAL_CIC.xlsm.

M-11146 Pixantrone CE model_24Oct2013_UpdatedBasedOnERG_With Pix Discount_FINAL_CIC_Discount Visible.xlsm.

In the first file, the discount and the discounted price have been removed from the “Drug Costs” worksheet (the discounted price has been hardcoded into the model so the results reflect the PAS). In the second file, the discount and the discounted price are visible on the “Drug Costs” worksheet, but have been marked as CiC.

3.16 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The text highlighted below in turquoise is confidential text.

Pixantrone is priced at £553.50 per 20 ml vial containing 29 mg free base pixantrone, which is equivalent to 50 mg pixantrone dimaleate (excluding

VAT; costs from manufacturer's submission). The updated economic model includes one additional input cell (cell O10) on the "Drug Costs" worksheet, which specifies the [redacted] discount on the UK list price for each vial of pixantrone. This discount is applied to the £553.50, resulting in a discounted price of [redacted] (shown in cell Q10 on the same worksheet). Thus, the cost of each vial of pixantrone applied in the model is[redacted]

Furthermore, the model was modified based on feedback provided by the Evidence Review Group (ERG) in their response to CTI Life Sciences' comments on the ACD 1 (feedback provided by ERG on 10/5/2013).

Revisions were made to AE costs ("Unit Costs" worksheet) according to ERG's recommendations (see table 3) and drug costs ("Drug Costs" worksheet) were checked in the eMIT database. In the drug costs worksheet, two modifications were made:

- An additional vial size for methotrexate that has been previously excluded as it is not relevant for this indication due to its vials size and price, has now been included for transparency, although it is not used in the drug cost calculations;
- The price of methotrexate 100 mg/mL in 10 mL vial has been updated.

No additional revisions were required, as the concentration and vial sizes presented by CTI is equivalent to the ones found by the ERG in the eMIT database. The eMIT database presents the milligrams as total milligrams in the vial, while the submission presented the milligrams per milliliter and the number of milliliters in the vial separately (please see details in Appendix). The appendix also contains the deterministic and probabilistic results once the recommended changes by the ERG were implemented – without a PAS. The probabilistic results are only presented for the histologically confirmed aggressive B-cell NHL population who have previously received treatment with rituximab and will be receiving pixantrone as a third or fourth line treatment. The revised AE costs and vial cost for methotrexate 100 mg/mL in 10 mL vial resulted in marginally different ICERs.

Table 3. Summary of adverse event cost changes between the manufacturer's submission and the ERG recommended costs

Adverse event (Grade 2)	Costs used in the manufacturer's analysis (£)	Costs used by ERG (£)
Neuropathy	6	17
Abdominal pain	4	11
Asthenia	49	147
Pain in extremity	4	11
Fatigue	56	84

3.17 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The proposed patient access scheme is not an outcome-based scheme, and thus did not require any additional clinical effectiveness data beyond what has already been provided in our response to the ACD 1. See the revised version of the mislabelled Table 5, section 3 from our response to the ACD 1 (page 14) in Appendix 1 for a summary on the clinical efficacy of pixantrone (versus standard of care) in patients with histologically confirmed aggressive B-cell NHL who have previously received treatment with rituximab and will be receiving pixantrone as a third or fourth line treatment.

3.18 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference sources of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence.'

Since the patient access scheme is a straight forward discount on the UK list price for each vial of pixantrone, no additional costs would be required for the implementation or operation of the proposed patient access scheme.

3.19 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Since the patient access scheme is a straight forward discount on the UK list price for each vial of pixantrone, no additional treatment-related costs would be incurred by implementing the proposed patient access scheme.

Summary results

Base-case analysis

3.20 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below.

This following list includes the key parameter values for the base case:

- Time horizon – lifetime
- Discount rate for cost and health outcomes – 3.5%
- Parametric fitting for OS and PFS – lognormal
- Utility for stable, no progression state – 0.76
- Utility for progressive/relapse disease – 0.68

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Clinical and cost outcomes from the cost-effectiveness model without the patient access scheme (PAS) are shown in Tables 4 and 5. Results with the PAS are shown in Tables 6 and 7. When considering quality-adjusted life-years (QALYs) based on utilities, pixantrone resulted in a discounted mean of 0.87 QALYs, while the comparator arm yielded 0.66 QALYs (Tables 4, 6). The QALY gain in the pixantrone arm is mainly attributable to QALY gains during the progression-free survival stage, similarly to life years (LYs).

Mean total costs incurred over the life-time time horizon (discounted at 3.5% per annum) among patients receiving pixantrone was £48,054 without the PAS (Table 5) and [redacted] with the PAS (Table 7). Drug costs are predicted to be lowered by [redacted] with the presence of a PAS.

Table 4. Discounted and undiscounted model outputs by clinical outcome - without PAS

Outcome	**LY**		**QALY**		**Cost (£)**	
Discounted						
	PIX	**SOC**	**PIX**	**SOC**	**PIX**	**SOC**
Progression-free survival	0.88	0.33	0.67	0.24	31,772	8,868
Post-progression survival	0.29	0.61	0.20	0.42	16,282	29,738
Overall survival	1.17	0.94	0.87	0.66	48,054	38,606
Undiscounted						
Progression-free survival	0.92	0.33	0.23	0.25	32,381	8,933
Post-progression survival	0.34	0.68	0.70	0.46	18,152	32,402
Overall survival	1.26	1.01	0.93	0.71	50,533	41,335
LY, life years; QALY, quality-adjusted life year; PIX, pixantrone; SOC, standard of care						

Table 5. Summary of predicted resource use by category of cost (discounted) – without PAS

Item	Cost (£) pixantrone	Cost (£) standard of care
Drug costs	15,429	284
Administration costs	1,992	1,560
AE costs	822	437
Post-treatment drug & administration costs	2,083	1,863
Post-progression drug & administration costs	3,285	3,350
Pre-progression non-drug costs	11,445	4,724
Post-Progression non-drug costs	12,223	25,599
One-off progression costs	773	788
Total	48,054	38,606

Table 6. Discounted and undiscounted model outputs by clinical outcome - with PAS [redacted]

Outcome	LY		QALY		Cost (£)	
Discounted						
	PIX	**SOC**	**PIX**	**SOC**	**PIX**	**SOC**
Progression-free survival	0.88	0.33	0.67	0.24	[redacted]	8,868
Post-progression survival	0.29	0.61	0.20	0.42	[redacted]	29,738
Overall survival	1.17	0.94	0.87	0.66	[redacted]	38,606
Undiscounted						
Progression-free survival	0.92	0.33	0.23	0.25	[redacted]	8,933
Post-progression survival	0.34	0.68	0.70	0.46	[redacted]	32,402
Overall survival	1.26	1.01	0.93	0.71	[redacted]	41,335

LY, life years; QALY, quality-adjusted life year; PIX, pixantrone; SOC, standard of care

Table 7. Summary of predicted resource use by category of cost (discounted) – with PAS [redacted]

Item	Cost (£) pixantrone	Cost (£) standard of care
Drug costs	[redacted]	284
Administration costs	1,992	1,560
AE costs	822	437
Post-treatment drug & administration costs	2,083	1,863
Post-progression drug & administration costs	3,285	3,351
Pre-progression non-drug costs	11,445	4,724
Post-Progression non-drug costs	12,223	25,599
One-off progression costs	773	788
Total	[redacted]	38,606

3.21 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented below.

Tables 8 and 9 present the base case incremental results (discounted) without and with the PAS respectively. Incremental costs are lowered from £9,448 to [redacted] when the PAS is incorporated; this result in the incremental cost-effectiveness ratio (ICER) of the cost per QALY gained decreasing from £46,654 to £18,462. As a result the deterministic ICER, which was based on the most plausible inputs, and thus represents the most plausible ICER, was below both the £20,000/QALY and the £30,000/QALY thresholds which is rare for treatments in advanced oncology indications.

Table 8. Base-case incremental results – without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Standard of Care	£38,606	0.94	0.66	-	-	-	-
Pixantrone	£48,054	1.17	0.87	£9,448	0.23	0.20	£46,654

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 9. Base-case incremental results – with PAS [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Standard of Care	£38,606	0.94	0.66	-	-	-	-
Pixantrone	[redacted]	1.17	0.87	[redacted]	0.23	0.20	£18,462

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

3.22 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of

evidence for the technology appraisal. Consider using tornado diagrams.

Tables 10 and 11 below present the deterministic sensitivity analysis results as described in the main manufacturer submission of evidence for the technology appraisal with the PAS.

This ddeterministic sensitivity analysis looks at changes in the different parameters in isolation, leaving all other parameters unchanged, leading to unrealistic scenarios. For example the changes in the PFS parameters for pixantrone are unlikely to occur in isolation, without the corresponding changes in the PFS for standard care and OS in both treatment arms. In addition the uncertainty in the values of the parameters does not only reflect the uncertainty of the data (e.g the clinical trial results in the case of the OS and PFS parameters), but also the significant uncertainty inherent in the methodology (e.g. parametric modeling used for the extrapolation).

The deterministic sensitivity analysis presented for the OS and PFS parameters in Table 10 shows that using extreme values, which parameters influence the results the most. The values used for the lower and upper limits are the limits for the 95% confidence intervals for the parameters of the distributions used for extrapolating the survival curves. These values are extreme values that would occur in 2.5% of the cases for both upper and lower limits. The ICERs estimated with these limits represent ICERs estimated with the extremes of the parameters.

Due to all of these issues and the unrealistic scenarios, the deterministic sensitivity analyses do not characterize the magnitude of the uncertainty, but the areas of uncertainty.

The 0–6% discount rate used for cost and health affected the ICER -7.6% to +4.5% and -7.4% to +5.0% respectively. Methodological assumptions on modelling OS and PFS have a major impact on the ICER. Changing the approach from log-normal distribution to generalised gamma distribution for both OS and PFS leads to a dominant ICER outcome. Using a log-logistic

function fit for both OS and PFS leads to an ICER of £15,950/QALY versus standard of care (Table 10).

In the sensitivity analyses involving utility inputs, when the utility for stable/no progression decreased to 0.70 and to 0.59 for the progressed disease state, the ICER increased to £18,871/QALY. When utility for stable/no progression increased to 0.81 and to 0.60 for the progressed disease state, the ICER decreased to £14,607/QALY versus standard of care. The lower ICER is observed because patients in the pixantrone arm spend more time in the no progression state, while patients in the standard of care arm spend more time in the progressed disease state. The utility value associated with the former state is increased, while it is decreased with the latter state (relative to the base case) (Table 11).

Table 10. Parameters varied in deterministic sensitivity analysis and results (with PAS [redacted])

Parameter	Baseline value	Alternate value	ICER (£/QALY) – discounted*	INB (£) - discounted
All parameters at baseline values			£18,462	£ 2,336
Time horizon	life time	£2,143	£19,201	£2,143
Health discount rate	3.5%	0.0%	£17,091	£2,824
		6.0%	£19,394	£2,045
Cost discount rate	3.5%	0.0%	£17,059	£2,621
		6.0%	£19,294	£2,168
Parametric fitting for OS and PFS	log-normal	Generalised Gamma	Dominant	£9,787
		Log-logistic	£15,950	£3,355
Progression free survival: Pixantrone	Mean	97.5% Upper	Dominant	£ 11,575
		2.5% Lower	£ 116,119	-£ 13,733
Progression free survival: comparator	Mean	97.5% Upper	£ 82,152	-£ 9,083
		2.5% Lower	Dominant	£ 6,597
Overall survival: Pixantrone	Mean	97.5% Upper	£ 54,074	-£ 29,205
		2.5% Lower	Less costly and less effective (£ 43,464)	£ 4,180
Overall survival: comparator	Mean	97.5% Upper	Less costly and less effective (£ 72,200)	£ 33,338
		2.5% Lower	£ 46,579	-£ 10,344

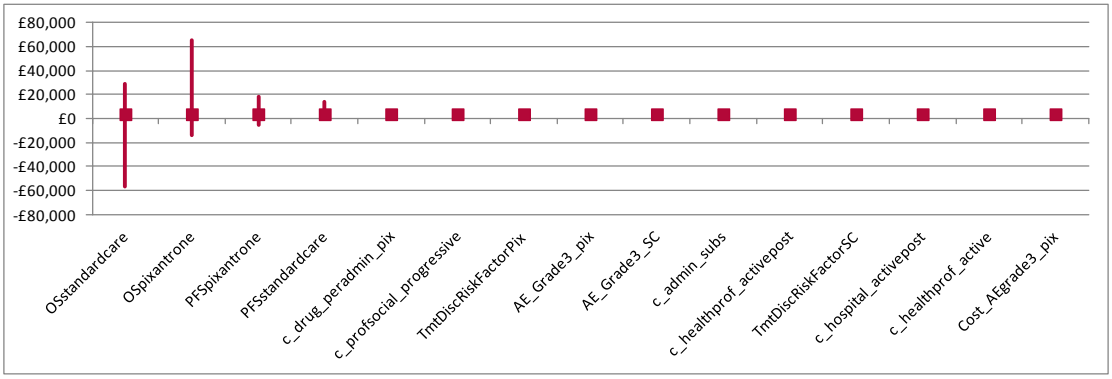
*Please note that due to the ICERs with the lower and upper extreme values for the OS and PFS are in many cases in different quadrants of the cost-effectiveness plane, they have different interpretations and implications. Thus the use of the incremental net benefit (INB) is more informative.

Table 11. Utilities varied in deterministic sensitivity analysis and results (with PAS [redacted]

Description of data sources	Pre-progression Utility	Post-progression utility	ICER (£/QALY) – discounted
Base case			
2nd line treatment in patients with renal cell carcinoma	0.76	0.68	£18,462
Alternative utility scenarios			
2nd line treatment in patients with chronic myelogenous leukiemia,	0.85	0.73	£15,816
3rd line treatment in patients with chronic lymphocytic leukemia	0.65	0.47	£17,895
1st line maintenance treatment in patients with Follicular lymphoma	0.78	0.62	£16,054
1st line treatment in patients with metastatic renal cell carcinoma	0.70	0.59	£18,871
Self-reported quality of life during chemotherapy in elderly patients with aggressive non-Hodgkin lymphoma	0.81	0.60	£14,607
2nd line treatment in patients with malignant melanoma	0.80	0.76	£18,787

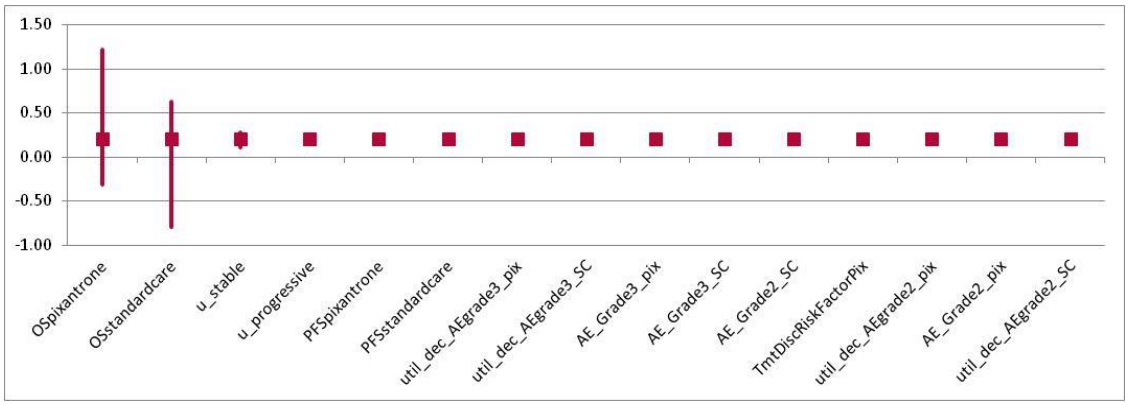
Figures 1-4 represent tornado diagrams that highlight the fifteen parameters that have the greatest impact on incremental costs, incremental QALYs, incremental cost/QALY gained and incremental net benefit (computed using a willingness to pay threshold of £30,000 per QALY gained).

Figure 1. Tornado diagram – incremental costs (with PAS [redacted]



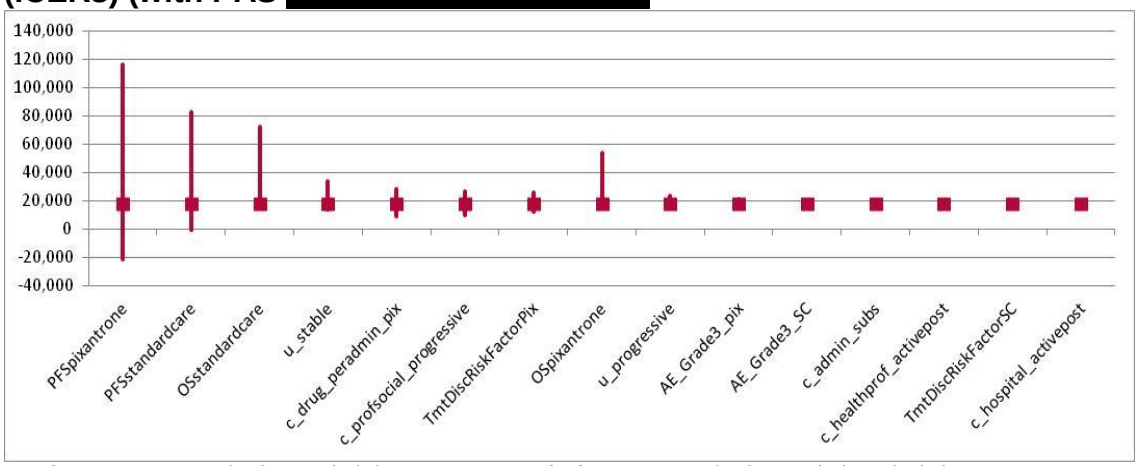
OSstandarecare = overall survival standard of care**; OSpixantrone** = overall survival pixantrone; **PFSpixantrone** = progression free survival pixantrone; **PFSstandardcare** = progression free survival standard of care**; c_drug_peradmin_pix =** drug cost per administration pixantrone; **c_profsocial_progressive =** professional and social services progressive state; **TmtDiscRiskfactorPix =** treatment discontinuation risk factor pixantrone; **AE_Grade3_pix =** grade 3 and 4 rate for adverse events pixantrone; **AE_Grade3_SC =** grade 3 and 4 rate for adverse events standard of care; **c_admin_subs =** administration costs subsequent cycles; **c_healthprof_activepost =** health care professional costs (28 days) active therapy post treatment; **TmtDiscRiskFactorSC =** treatment discontinuation risk factor for standard of care; **c_hospital_activepost =** hospital costs (annual) active therapy post treatment; **c_healthprof_active =** health care professional costs (28 days) active therapy; **cost_AEgrade3_pix =** cost grade 3 and 4 adverse events for pixantrone

Figure 2. Tornado diagram – incremental QALYs (with PAS [redacted]



OSpixantrone = overall survival pixantrone; **OSstandarecare** = overall survival standard of care; **u_stable =** utility stable disease; **u_progressive =** utility progressive disease; **PFSpixantrone** = progression free survival pixantrone ; **PFSstandardcare** = progression free survival standard of care; **util_dec_AEgrade3_pix =** utility decrement grade 3 and 4 adverse events pixantrone; **util_dec_AEgrade3_SC =** utility decrement grade 3 and 4 adverse events standard of care; **AE_Grade3_pix =** grade 3 and 4 rate for adverse events pixantrone; **AE_Grade3_SC =** grade 3 and 4 rate for adverse events standard of care ; **AE_Grade2_SC=** grade 2 rate for adverse events standard of care; **TmtDiscRiskfactorPix =** treatment discontinuation risk factor pixantrone; **Util_dec_AEgrade2_pix =** utility decrement grade 2 for adverse events pixantrone; **AE_Grade2_pix =** grade rate for adverse events pixantrone; **util_dec_AEgrade2_SC** = utility decrement grade 2 for adverse events standard of care

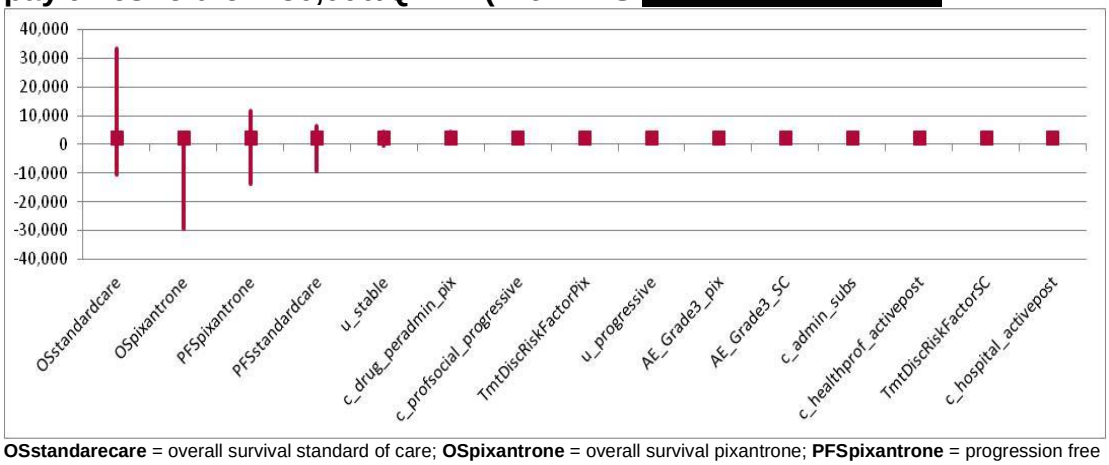
Figure 3. Tornado diagram – incremental cost-effectiveness ratios (ICERs) (with PAS [redacted]



PFSpixantrone = progression free survival pixantrone ; **PFSstandardcare** = progression free survival standard of care; **OSstandarecare** = overall survival standard of care; **u_stable =** utility stable disease; **c_drug_peradmin_pix =** drug cost per administration for pixantrone; **c_profsocial_progressive =** professional and social services progressive state; **TmtDiscRiskfactorPix =** treatment discontinuation risk factor pixantrone; **OSpixantrone** = overall survival pixantrone; **u_progressive =** utility progressive disease; **AE_Grade3_pix =** grade 3 and 4 rate for adverse events pixantrone; **AE_Grade3_SC =** grade 3 and 4 rate for adverse events standard of care; **c_admin_subs=** administration cost subsequent cycles; **c_healthprof_activespost=** health care professional costs (28 days) active therapy post treatment; **TmtDiscRiskfactorSC=** treatment discontinuation risk factor for standard of care; **c_hospital_activepost =** hospital costs (annual) active therapy post treatment

***Please note that due to the ICERs with the lower and upper extreme values for the OS and PFS are in many cases in different quadrants of the cost-effectiveness plane, they have different interpretations and implications. Thus the use of the incremental net benefit (INB) is more informative.**

Figure 4. Tornado diagram – incremental net benefit with willingness to pay threshold of £30,000/QALY (with PAS [redacted]



OSstandarecare = overall survival standard of care; **OSpixantrone** = overall survival pixantrone; **PFSpixantrone** = progression free survival pixantrone; **PFSstandardcare** = progression free survival standard of care; **u_stable =** utility stable disease; **c_drug_peradmin_pix =** drug cost per administration for pixantrone; **c_profsocial_progressive =** professional and social services progressive state; **TmtDiscRiskfactorPix =** treatment discontinuation risk factor pixantrone; **u_progressive =** utility progressive disease; **AE_Grade3_pix =** grade 3 and 4 rate for adverse events pixantrone; **AE_Grade3_SC =** grade 3 and 4 rate for adverse events standard of care; **c_admin_subs=** administration cost subsequent cycles; **c_healthprof_activespost=** health care professional costs (28 days) active therapy post treatment; **TmtDiscRiskfactorSC=** treatment discontinuation risk factor for standard of care; **c_hospital_activepost =** hospital costs (annual) active therapy post treatment

3.23 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Figure 5 presents the scatter plot from the probabilistic sensitivity analysis for 5,000 simulations. The x-axis represents incremental outcomes in terms of QALYs, while the y-axis represents incremental costs. Each point on the chart represents a single probabilistic iteration of the model. Table 12 presents the proportion of iterations in each quadrant of the scatter plot.

The plot indicates that in 55% of the model iterations, pixantrone yields more QALYs than the comparator arm at higher cost (Table 12). Figure 6 presents the cost-effectiveness acceptability curves for each model comparator. The x-axis represents a health care payer's willingness to pay for an additional QALY, while the y-axis represents the probability of being cost-effective. At a willingness to pay value of £25,000/QALY, pixantrone is more likely to be cost-effective than standard of care.

Figure 5. PSA Scatter plot (5,000 simulations) with PAS [redacted]

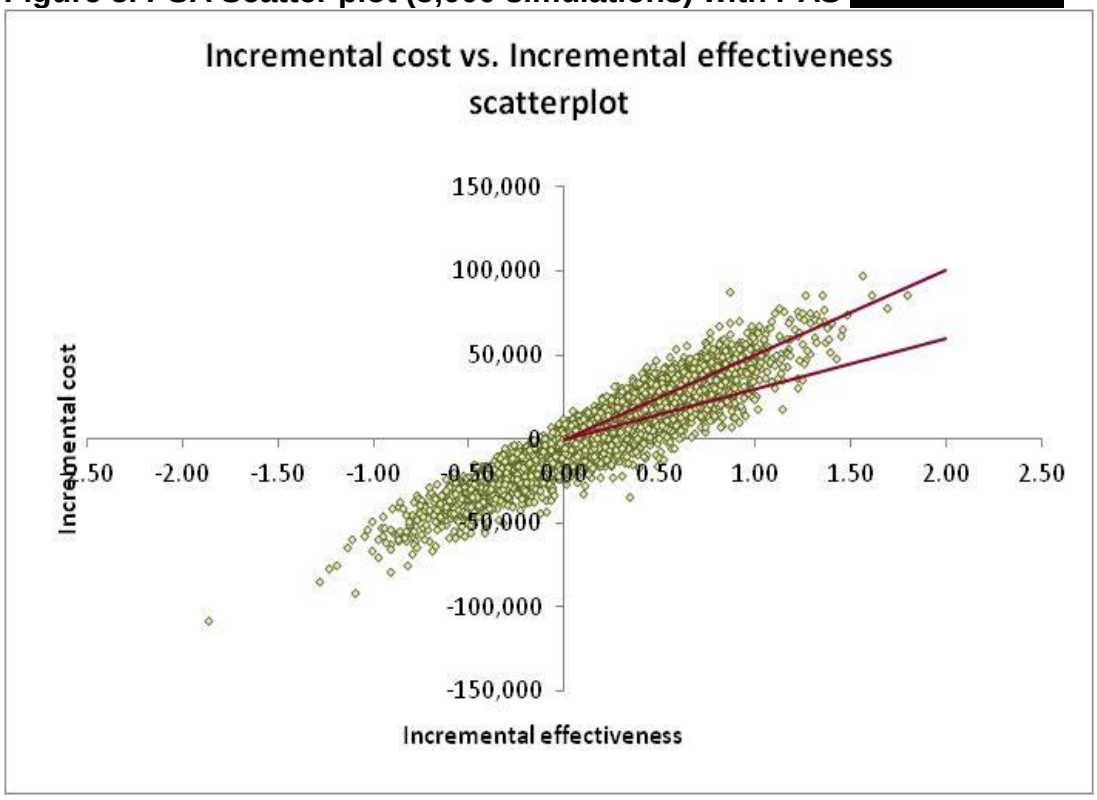
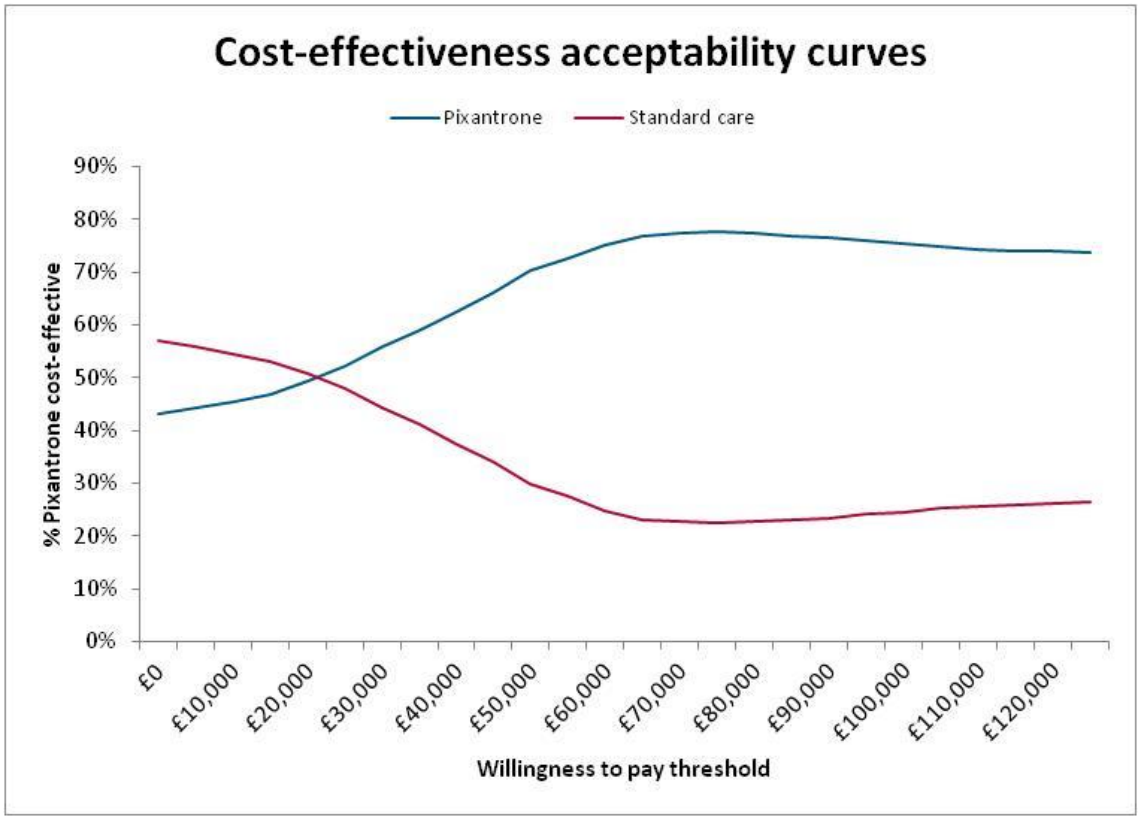


Table 12. Proportion of Iterations in each Quadrant of Scatter Plot with PAS [redacted]

Quadrant	Proportion of Simulations
Quadrant I – Pixantrone has higher costs and higher effectiveness	55%
Quadrant III – Pixantrone has lower costs and lower effectiveness	31%
Quadrant IV – Pixantrone is dominant (i.e. has lower costs and higher effectiveness)	13%
Quadrant II – Pixantrone is dominated (i.e. has higher costs and lower effectiveness)	1%

Figure 6. Cost-effectiveness acceptability curves with PAS [redacted]



The mean costs and health benefits from the probabilistic analysis is presented in Table 13. This calculation however has numerous limitations assuming the following:

- OS and PFS are assumed to be independent of each other and between comparators,

- Incremental QALYs and costs are both assumed to follow normal distribution,
- Incremental QALYs and costs are assumed to be independent, thus correlation between them were not taken into account.

The first assumption of the independence of OS and PFS can lead to scenarios, where the PFS curve is above the OS curve throughout the time horizon or where the curves cross, i.e. for a time period more patients are progression-free than alive. Appendix 3 show two examples of these scenarios generated in the analyses. The model in these cases artificially reduces the PFS, to avoid these scenarios, and thereby reducing the advantage of pixantrone. This occurs in 30% of the PSA simulations. Thus the PSA overestimates the effect of the uncertainty around the survival curves on the ICER and underestimates the advantage of pixantrone.

In addition a recent review of randomized clinical trials of aggressive and indolent NHL found that in aNHL differences in 3-year PFS were highly correlated with differences in 5-year OS (r =0.90; 0.73-0.96) (Lee et al. 2011)[v]

To show the effect of this assumption for PFS and OS, the probabilistic analysis was ran using the same random numbers in the Cholesky decomposition for OS and PFS for pixantrone and a different set of random numbers for OS and PFS for standard care, thus not allowing for OS and PFS to move separately, while still not correlating the survival curves between comparators. This results in pixantrone being more likely to be cost-effective than standard of care from a willingness to pay value of approximately £15,000/QALY and a probabilistic ICER of £9,938/QALY. (Please see Appendix 3 for further details.)

Although this analysis highly underestimates the uncertainty, since OS and PFS do not completely move together for each comparator, it shows that the more realistic simulations are between the two scenarios, i.e. between the one where OS and PFS parameters change completely independently, and the one where OS and PFS parameters change together. Similar analysis can be

conducted to assess the effect of the assumption of independent survival curves between the two comparators.

Secondly this analysis assumes joint normality in incremental QALYs and costs that does not seem to stand in the current analysis. For example when plotting the all ICERs observed in the North-East quadrant from the probabilistic results, it is apparent that the joint uncertainty of incremental QALYs and incremental costs does not follow a normal distribution. Thus looking at the median results rather than the mean results, the probabilistic ICER would be £14,692/QALY (Table 14). (Please see histograms and median results in Appendix 3.)

Lastly, the scatter-plot demonstrates a high positive correlation between incremental costs and incremental QALYs. As such disregarding this would provide an overestimate of the uncertainty.

Thus in the current analysis the probabilistic results are conservative estimates based on the above assumptions and likely to overestimate the uncertainty of the cost-effectiveness results.

Table 13. Probabilistic mean results – with PAS [redacted]

Technologies	Total costs (£) Mean (SD)	Total LYG Mean (SD)	Total QALYs Mean (SD)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Standard of Care	£41,558 (£16,893)	1.02 (0.40)	0.72 (0.28)	-	-	-	-
Pixantrone	[redacted]	1.22 (0.40)	0.90 (0.30)	[redacted]	0.20	0.18	£ 22,024

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; SD: standard deviation.

Table 14. Probabilistic median results – with PAS [redacted]

Technologies	Total costs (£) Median	Total LYG Median	Total QALYs Median	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Standard of Care	£38,795	0.96	0.67	-	-	-	-
Pixantrone	[redacted]	1.17	0.86	[redacted]	0.21	0.18	£14,692

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

3.24 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Please see the response to 3.22.

3.25 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable. The scheme is a straight forward discount on the price of the vial and does not depend on any clinical variables.

Impact of patient access scheme on ICERs

3.26 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 15 presents the impact of the patient access scheme on the ICERs for the base case and the scenario analyses with and without the PAS.

Table 15. Impact of PAS [redacted] on ICERs

	Alternate value	ICER (discounted) for intervention (£/QALY) versus:	
		Standard of Care	
		Without PAS	With PAS
Base-case - patients with histologically confirmed aggressive B-cell NHL who have previously received treatment with rituximab and will be receiving pixantrone as a third or fourth line treatment.		£46,654	£18,462
Time Horizon	10 years	£47,966	£19,201
Health discount rate	0%	£43,188	£17,091
	6%	£49,008	£19,394
Cost discount rate	0%	£45,421	£17,059
	6%	£47,367	£19,294
Parametric fitting for OS and PFS	Generalised Gamma	£16,702	Dominant
	Log-logistic	£39,597	£15,950
Progression free survival: Pixantrone	97.5% upper	£4,555	Dominant
	2.5% lower	£147,856	£ 116,119
Progression free survival: comparator	97.5% upper	£114,932	£ 82,152
	2.5% lower	£25,867	Dominant
Overall survival: Pixantrone	97.5% upper	£58,765	£ 54,074
	2.5% lower	Less costly and less effective (£25,912)	Less costly and less effective (£ 43,464)
Overall survival: comparator	97.5% upper	Less costly and less effective (£64,974)	Less costly and less effective (£ 72,200)
	2.5% lower	£55,730	£ 46,579

Sensitivity analyses around utility inputs			
2nd line treatment in patients with chronic myelogenous leukemia,	PreP: 0.85 PostP:0.73	£39,967	£15,816
3rd line treatment in patients with chronic lymphocytic leukemia	PreP:0.65 PostP:0.47	£45,220	£17,895
1st line maintenance treatment in patients with Follicular lymphoma	PreP:0.78 PostP:0.62	£40,569	£16,054
1st line treatment in patients with metastatic renal cell carcinoma	PreP:0.70 PostP:0.59	£47,686	£18,871
Self-reported quality of life during chemotherapy in elderly patients with aggressive non-Hodgkin lymphoma	PreP:0.81 PostP:0.60	£36,912	£14,607
2nd line treatment in patients with malignant melanoma	PreP:0.80 PostP:0.76	£47,475	£18,787

PAS: patient access scheme; PreP: pre-progression utility; PostP: post-progression utility.

Appendix 1

Summary of efficacy for HITT population third or fourth lines of therapy, with prior rituximab (based on central review)

	Pixantrone (n=20)	Comparator (n=18)	HR (95% CI)
CR/Cru, n (%)	6 (30)	1 (6)	-
ORR†, n	9	2	-
Median PFS, months‡	5.4	2.8	0.52 (0.26, 1.04)
Median OS, months‡	7.5	5.4	0.76 (0.38,1.55)

HR=hazard ratio

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

‡Kaplan-Meier analysis

Appendix 2

Drug procurement costs' changes between the manufacturer's original (version - M-11146 Pixantrone CE model_01May2013 model.xlsm) and revised economic models (either model included in this submission)

Drug	Concentration	Tablet or vial size	Price (£)		Comments from ERG	Comment from CTI and revisions made in updated model included in this submission
			Original submission	Response to ACD 1		
Cyclophosphamide	500 mg	500 mg	£ 5.66	£ 6.92	-	-
	1,000 mg	1,000 mg	£ 10.66	£ 12.94	-	-
Cytarabine	20 mg/mL	5 mL	£ 3.90	£ 3.15	-	-
	100 mg/mL	5 mL	£ 19.50	£ 8.65	-	-
	100 mg/mL	10 mL	£ 39.00	£ 6.58	-	-
	100 mg/mL	20 mL	£ 77.50	£ 10.01[a]	ERG identified this cost to correspond to a 200 mg/mL concentration and 20 mL vial.	No change made. The price of £10.01 corresponds to 2000mg per 20mL vial solution. This is equivalent to a 100mg/mL concentration in a 20mL vial.
Cisplatin	1 mg/mL	10 mL	£ 5.85	£ 2.04	-	-
	50 mg	50 mg	£ 17.00	£ 7.89	-	-
	1 mg/mL	100 mL	£ 50.22	£ 12.17	-	-
Dexamethasone	2 mg	2 mg	£ 0.14	£ 0.02	-	-
	2 mg/mL	150 mL	£ 42.30	£ 22.46	-	-
Doxorubicin	10 mg	10 mg	£ 18.72	£ 1.80	-	-
	50 mg	50 mg	£ 96.86	£ 6.68	-	-
	2 mg/mL	100 mL	£ 275.00	£ 46.77	-	-

Drug	Concentration	Tablet or vial size	Price (£)		Comments from ERG	Comment from CTI and revisions made in updated model included in this submission
			Original submission	Response to ACD 1		
Epirubicin	2 mg/mL	5 mL	£ 19.04	£ 3.12	-	-
	50 mg	50 mg	£ 91.54	£ 12.99	-	-
	2 mg/mL	50 mL	£ 95.54	£ 21.86	-	-
	2 mg/mL	100 mL	£ 386.16	£ 39.16	-	-
Etoposide IV (100 mg)[b]	20 mg/mL	5 mL	£ 12.15	£ 2.09	Etoposide IV (100 mg) 10 mL vials no longer produced.	No changes made Etoposide IV (100mg) 10mL vials were not considered in the model
	20 mg/mL	25 mL	£ 60.75	£ 7.98		
Gemcitabine[c]	200 mg	200 mg	£ 32.00	£ 3.22	Gemcitabine 1,500 mg no longer available.	No changes made Gemcitabine 1,500mg was not considered in the model
	1,000 mg	1,000 mg	£ 162.00	£ 12.64		
	2,000 mg	2,000 mg	£ 324.00	£ 24.70		
Methotrexate	2.5 mg/mL	2 mL	£ 1.68	£ 5.14[d]	ERG identified this cost as corresponding to 5 mg/2mL concentration.	No changes made The eMIT has a price of £25.69 (pack size of 5) corresponding to a 5mg per 2mL vial solution. This is equivalent to a 2.5mg/mL concentration in a 2mL vial. The price was divided by 5 in order to obtain the price of 1 pack.
	25 mg/mL	2 mL	£ 3.00	£ 1.34[e]	ERG identified this cost as corresponding to 50mg/2ml concentration.	No changes made. The eMIT has a price of £1.34 corresponding to a 50mg per 2mL vial solution. This is equivalent to a 25mg/mL concentration in a 2mL vial.

Drug	Concentration	Tablet or vial size	Price (£)		Comments from ERG	Comment from CTI and revisions made in updated model included in this submission
			Original submission	Response to ACD 1		
	25 mg/mL	20 mL	£ 30.00	£ 4.77[f]	ERG identified this cost as corresponding to 500mg/20ml concentration.	No changes made. The eMIT has a price of £4.77 corresponding to a 500mg per 20mL vial solution. This is equivalent to a 25mg/mL concentration in a 20mL vial.
	25 mg/mL	40 mL	-	-	-	This 25mg/mL concentration in a 40mL vial was previously excluded from the model, as it is not used in the per mg drug costs calculations since its cost per mg is higher than the other concentrations and vial sizes and it is not used in the wastage calculations due to its vial size would require an extreme BSA. However we have incorporated it for transparency. The eMIT has a price of £17.15 corresponding to a 1000mg per 40mL vial solution. This is equivalent to a 25 mg/mL concentration in a 40 mL vial. This has been added to the model.
	100 mg/mL	10 mL	£ 78.33	£ 17.15[g]	ERG identified this cost as corresponding to 100mg/40ml	Changed to £30.89 The eMIT has a price of £30.89

Drug	Concentration	Tablet or vial size	Price (£)		Comments from ERG	Comment from CTI and revisions made in updated model included in this submission
			Original submission	Response to ACD 1		
					concentration.	corresponding to a 1000mg per 10mL vial solution. This is equivalent to a 100mg/mL concentration in a 10mL vial. An incorrect price was used originally.
	100 mg/mL	50 mL	£ 380.07	£ 84.90[h]	The ERG was unable to identify this cost.	No changes made. The eMIT has a price of £84.90 corresponding to a 5000mg per 50mL vial solution. This is equivalent to a 100mg/mL concentration in a 50 mL vial.
Mitoxantrone[i]	2 mg/mL	10 mL	£ 100.00	£ 26.06	Mitoxantrone 15 mL no longer available.	No changes made Mitoxantrone 15 mL was not considered in the model
	2 mg/mL	13 mL	£ 152.33	£ 26.96		
Oxaliplatin[j]	50 mg	50 mg	£ 150.00	£ 12.23	Oxaliplatin 5 mg/mL in 40 mL vials is no longer available.	No changes made Oxaliplatin 5 mg/mL in 40 mL vials was not considered in the model
	100 mg	100 mg	£ 299.50	£ 21.46		
Prednisolone	1 mg	1 mg	£ 0.04	£ 0.01	-	-
	2.50 mg	2.50 mg	£ 0.31	£ 0.11	-	-
	5 mg	5 mg	£ 0.04	£ 0.01	-	-
Vincristine	1 mg/mL	1 mL	£ 13.47	£ 4.22	-	-
	1 mg/mL	2 mL	£ 26.66	£ 5.87	-	-
	1 mg/mL	5 mL	£ 44.16	£ 17.93	-	-

Drug	Concentration	Tablet or vial size	Price (£)		Comments from ERG	Comment from CTI and revisions made in updated model included in this submission
			Original submission	Response to ACD 1		
Vinorelbine	10 mg/mL	1 mL	£ 29.00	£ 5.83	-	-
	10 mg/mL	5 mL	£ 139.00	£ 21.83	-	-

[a] ERG identified this cost to correspond to a 200 mg/mL concentration and 20 mL vial.
[b] Etoposide IV (100 mg) 10 mL vials no longer produced.
[c] Gemcitabine 1,500 mg no longer available.
[d] ERG identified this cost as corresponding to 5 mg/2mL concentration.
[e] ERG identified this cost as corresponding to 50mg/2ml concentration.
[f] ERG identified this cost as corresponding to 500mg/20ml concentration.
[g] ERG identified this cost as corresponding to 100mg/40ml concentration.
[h] The ERG was unable to identify this cost.
[I] Mitoxantrone 15 mL no longer available.
[j] Oxaliplatin 5 mg/mL in 40 mL vials is no longer available.
Abbreviation used in table: ACD 1, First Appraisal Committee Document.

Summary of deterministic results from the manufacturer's revised economic model – following update of drug and AE costs

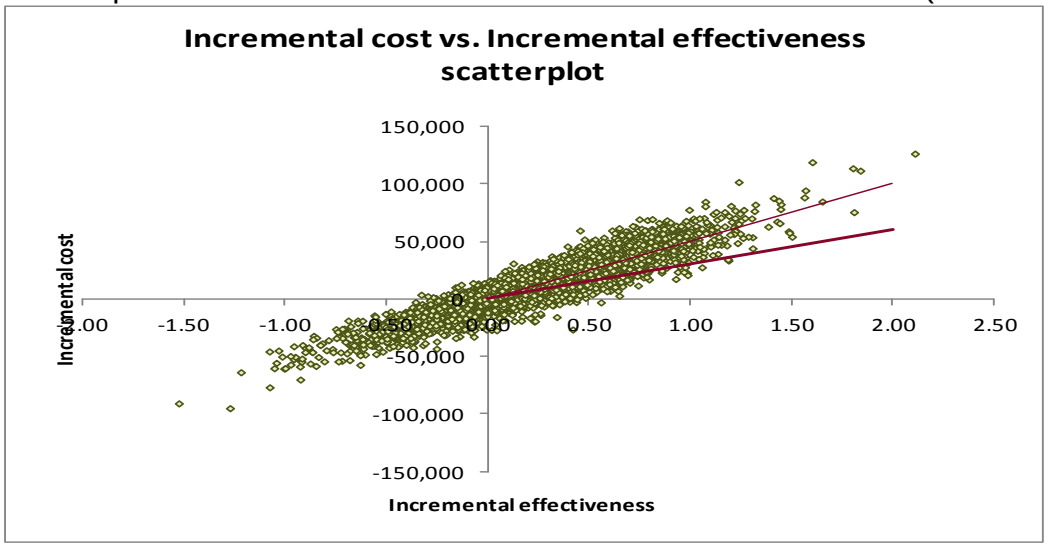
Analysis	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (LYG)	ICER (£) (QALYs)
HITT 3rd and 4th line									
Manufacturer's	TPC	£43,573	1.10	0.78					
	Pixantrone	£62,564	1.77	1.31	£18,991	0.67	0.53	£28,189	£35,924
HITT all lines with prior rituximab									
Manufacturer's	TPC	£38,831	1.00	0.71					
	Pixantrone	£41,306	1.01	0.75	£2,475	0.01	0.04	£167,587	£57,547
HITT 3rd or 4th line prior rituximab									
Manufacturer's	TPC	£38,606	0.94	0.66					

Analysis	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (LYG)	ICER (£) (QALYs)
	Pixantrone	£48,054	1.17	0.87	£9,448	0.23	0.20	£40,432	£46,654
HITT all lines									
Manufacturer's	TPC	£43,970	1.13	0.80					
	Pixantrone	£59,785	1.64	1.20	£15,815	0.50	0.40	£31,447	£39,649

Probabilistic results for the histologically confirmed aggressive B-cell NHL population who have previously received treatment with rituximab and will be receiving pixantrone as a third or fourth line treatment – following update of drug and AE costs

	Pixantrone		Standard Care	
	Mean	**Standard Deviation**	**Mean**	**Standard Deviation**
Life years (Lys)	1.25	0.41	1.00	0.38
Progression-free life-years (PfLYs)	0.84	0.25	0.34	0.09
Quality-adjusted life-years (QALYs) gained	0.91	0.30	0.71	0.27
Total costs	£51,728.36	£16,071.86	£40,513.26	£16,023.05

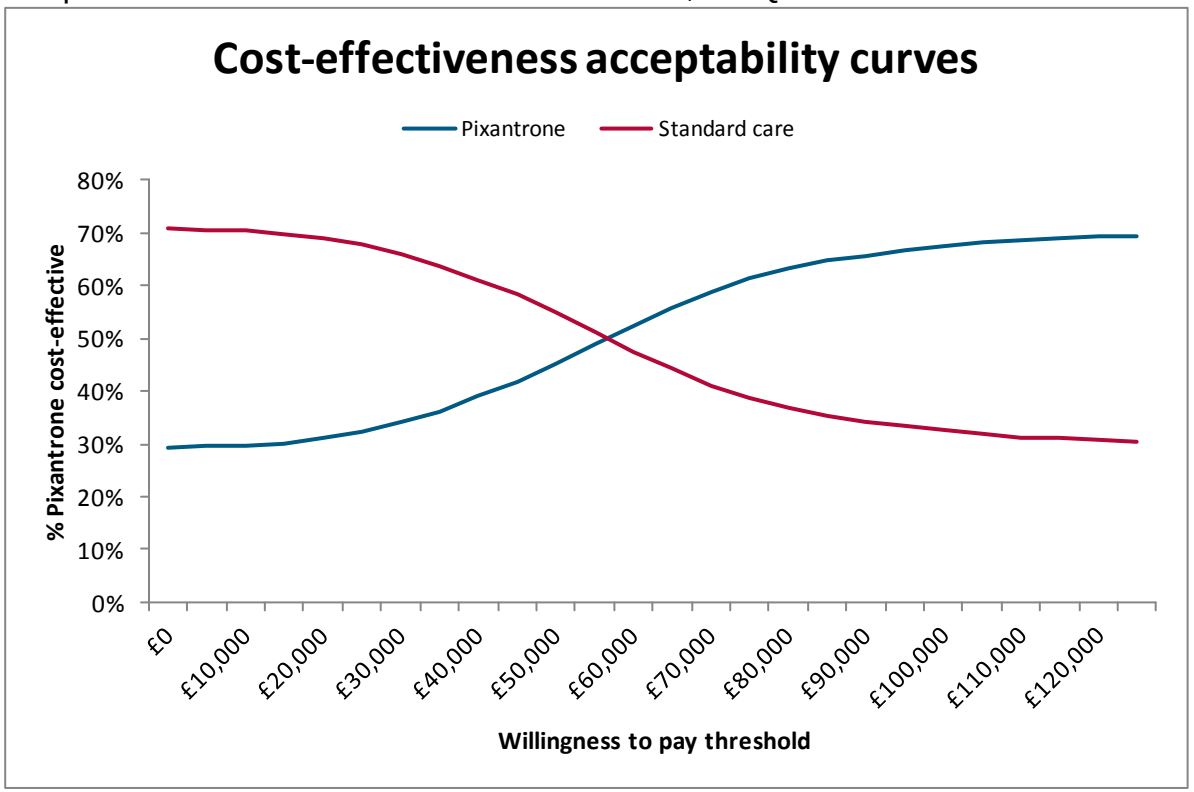
Scatter plot of incremental cost versus incremental effectiveness (results shown for 5000 iterations)



Proportion of iterations that fall in each quadrant of the scatter plot

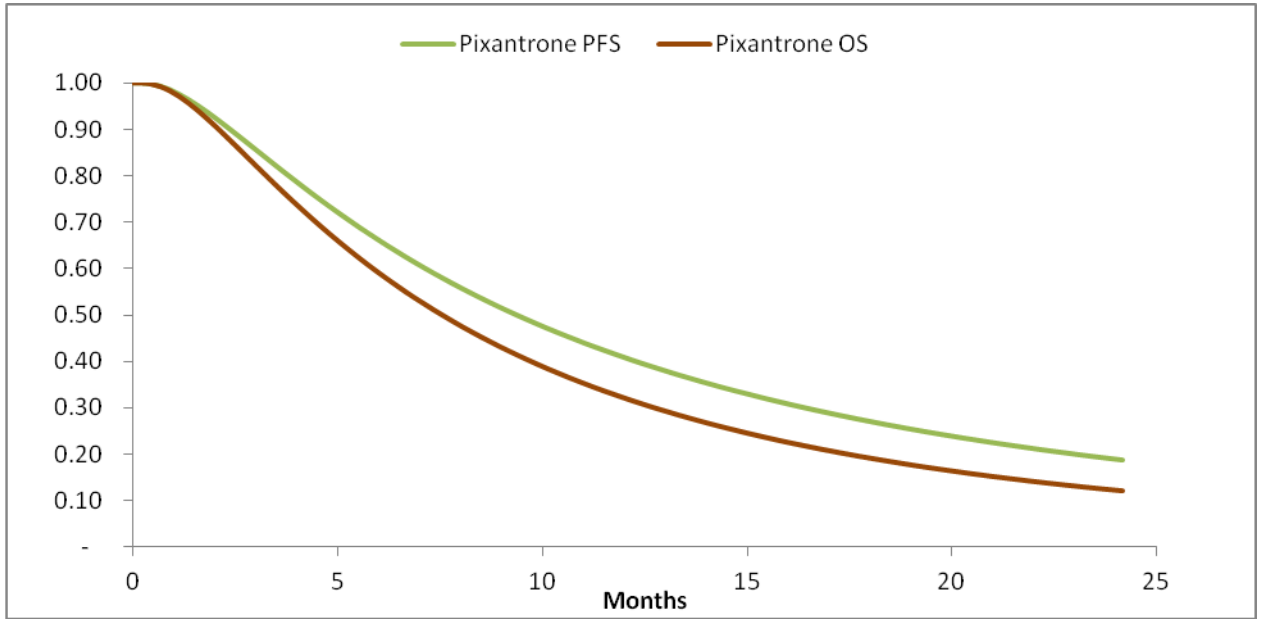
Quadrant	Proportion of Simulations
Quadrant I – Pixantrone has higher costs and higher effectiveness	65.7%
Quadrant III – Pixantrone has lower costs and lower effectiveness	23.2%
Quadrant IV – Pixantrone is dominant, i.e. has lower costs and higher effectiveness	5.9%
Quadrant II - Pixantrone is dominated, i.e. has higher costs and lower effectiveness	5.2%

Cost-effectiveness acceptability curves for pixantrone and standard care. Pixantrone has a higher likelihood of being cost-effective compared to standard care at a threshold of £60,000/QALY.

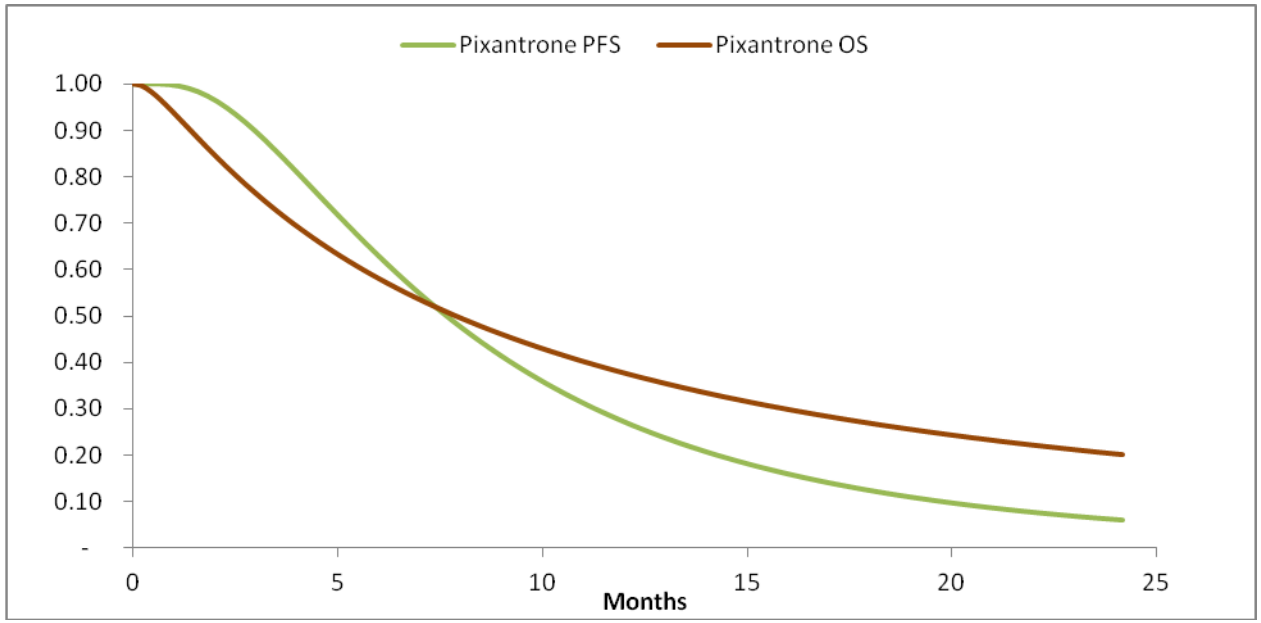


Appendix 3: Exploratory probabilistic analyses

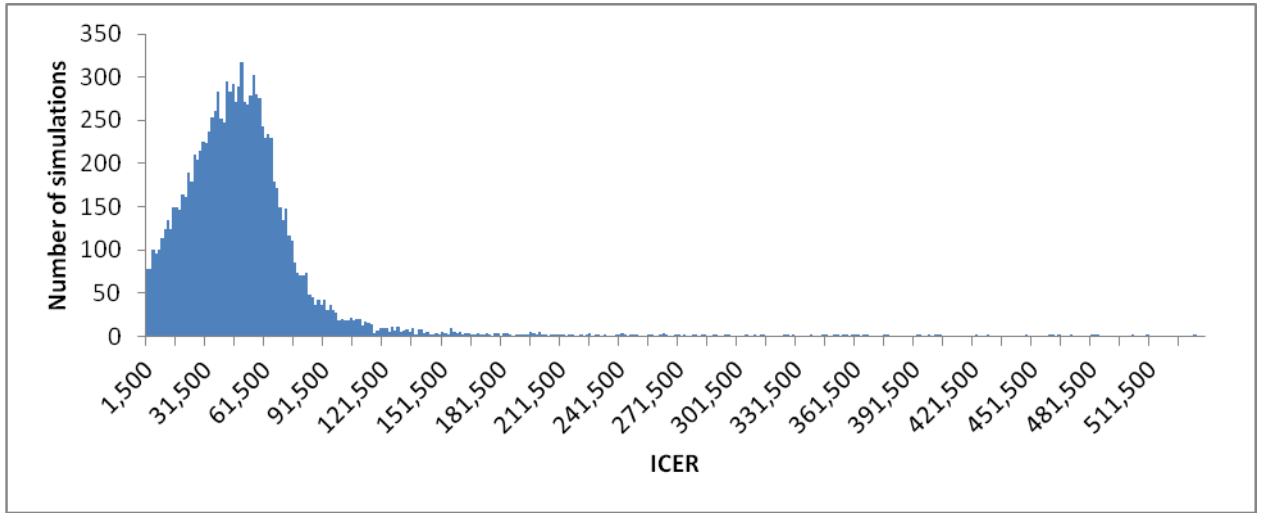
PFS and OS curves for pixantrone in a simulation for the PSA (Random numbers: [PFS intercept and scale: 0.946 and 0.289]; [OS intercept and scale: 0.497 and 0.193])



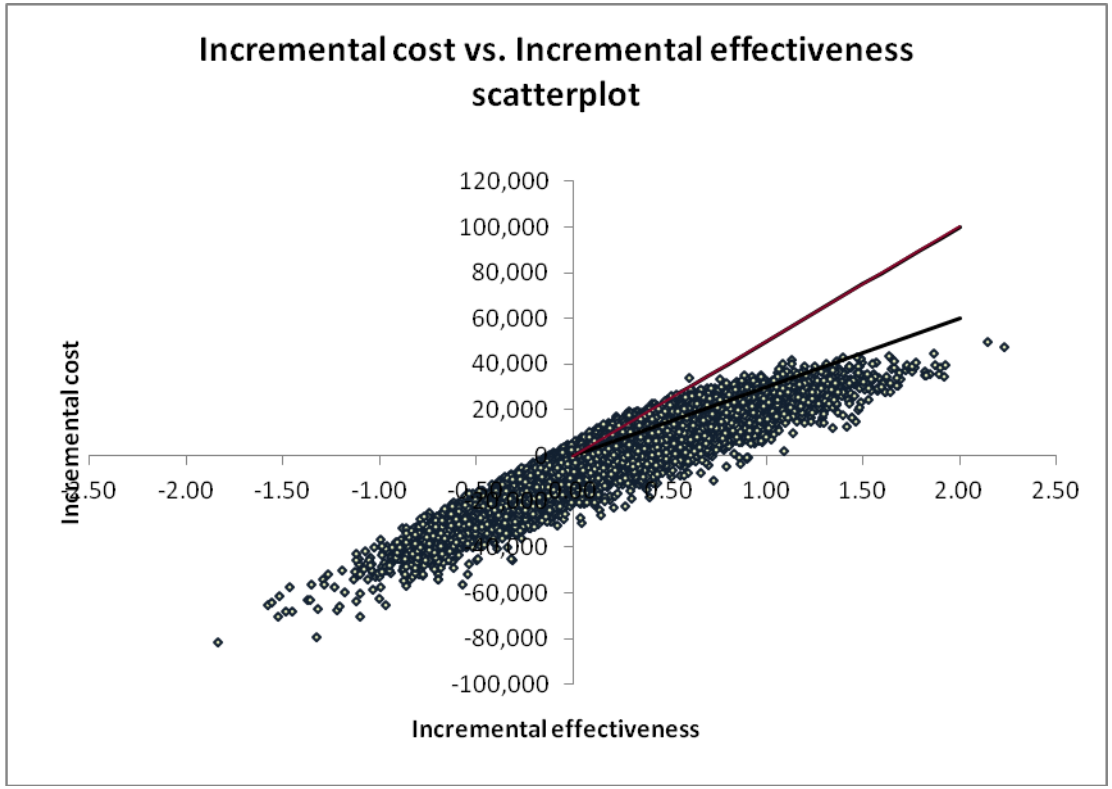
PFS and OS curves for pixantrone in a simulation for the PSA (Random numbers: [PFS intercept and scale: 0.81 and 0.029]; [OS intercept and scale: 0.561 and 0.762])



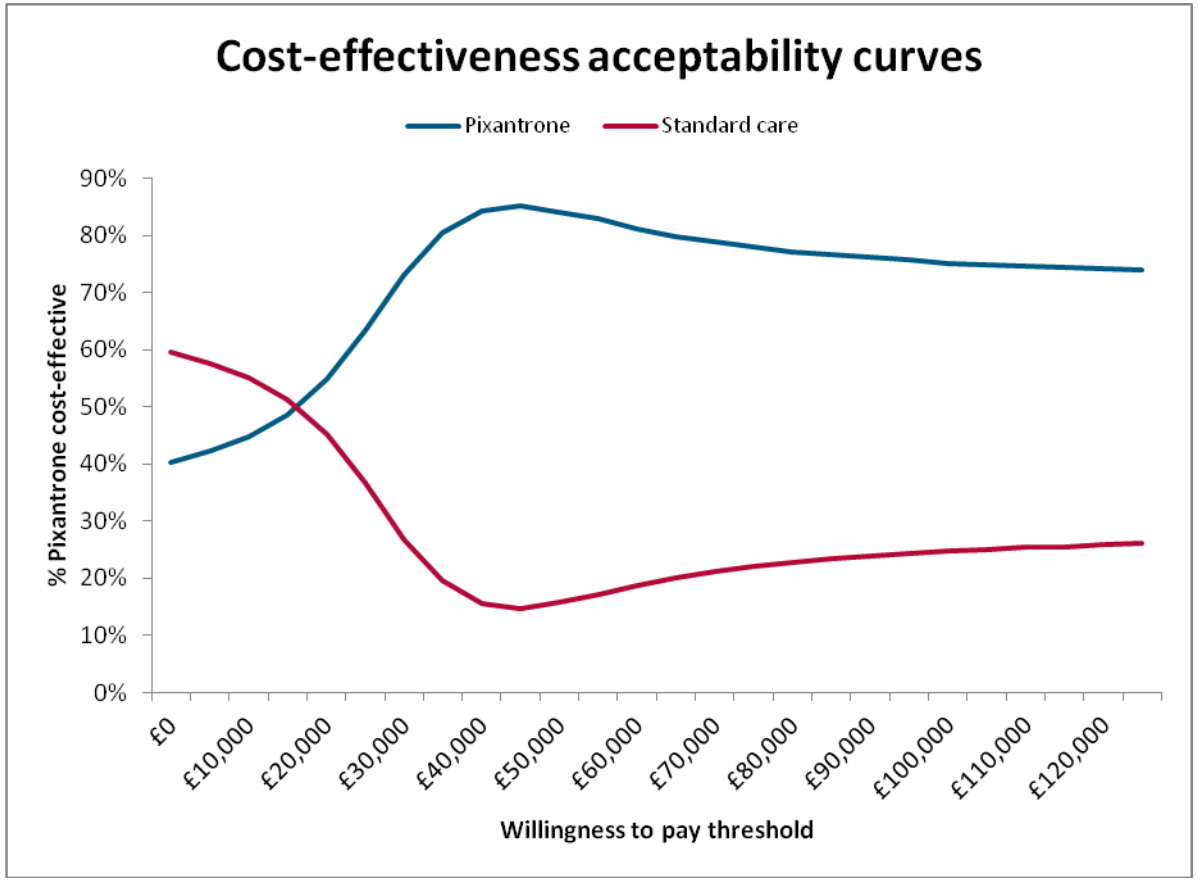
Histogram of ICERs falling in North-East quadrant in base case probabilistic analysis



Scatter-plot – Assuming same random numbers for PFS and OS in the Cholesky decomposition



Cost-effectiveness acceptability curve – Assuming same random numbers for PFS and OS in the Cholesky decomposition



Probabilistic results – with PAS [redacted] Assuming same random numbers for PFS and OS in the Cholesky decomposition

Technologies	Total costs (£) Mean (SD)	Total LYG Mean (SD)	Total QALYs Mean (SD)	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Standard of Care	£40,917 (£13,459)	1.01 (0.38)	0.71 (0.28)	-	-	-	-
Pixantrone	[redacted]	1.24 (0.41)	0.92 (0.32)	[redacted]	0.24	0.21	£ 9,938

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; SD: standard deviation.

References

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[ii] Péan E et al. The European Medicines Agency Review of Pixantrone for the Treatment of Adult Patients with Multiply Relapsed or Refractory Aggressive Non-Hodgkin's B-Cell Lymphomas: Summary of the Scientific Assessment of the Committee for Medicinal Products for Human Use. The Oncologist (2013);18:625-633

[iii] EU Cancer Observatory. Available at: http://eco.iarc.fr/EUCAN/Cancer.aspx?Cancer=38. Last accessed November 2012.

[iv] Kantar Health: Cancer impact model. Internal Report; Feb 2012

[v] 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 Jun;22(6):1392-403.