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

ERG's response to CTI Life Sciences' comments on ACD

BMJ Technology Assessment Group

Evidence Review Group comments on CTI Life Sciences' responses to the Appraisal Committee Document for pixantrone monotherapy for treating relapsed or refractory aggressive non-Hodgkin's lymphoma

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The Evidence Review Group's (ERG) comments are numbered in accordance with CTI Life Sciences' responses to the Appraisal Committee Document (ACD) as outlined in the document forwarded to the National Institute for Health and Care Excellence (NICE) dated 30th April 2013.

In summary, the ERG considers the key points to be:

- Based on the licensed indication and UK clinical practice, the ERG considers it important to evaluate patients with retrospective histological confirmation of aggressive B-cell non-Hodgkin's lymphoma (NHL) and who had previously received treatment with rituximab. The ERG considers it appropriate to evaluate patients receiving pixantrone as a third or fourth line treatment as a subgroup.

- The deterministic cost-effectiveness results associated with this patient population (incremental cost-effectiveness ratio [ICER]: £46,389; Inc. costs: £9,394; Inc. quality adjusted life years [QALYs]: 0.20) are likely to be accompanied by substantial uncertainty.

Section 1: Population under consideration

1. Licensed indication

The manufacturer asserts that the report issued by the European Medicines Agency (EMA) outlining the conditional marketing authorisation clearly limits the use of pixantrone to third and fourth line treatment.

The conditional marketing authorisation available on the EMA website states:[1]

"Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas. 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."

Within the response to ACD, the manufacturer has provided additional clarification around the marketing authorisation based on review of the Summary of Product Characteristics, European Public Assessment Reports (EPAR) and Committee for Medicinal Products for Human Use (CHMP) correspondences by "regulatory counsel". The manufacturer states that the "review confirmed that the licensed patient population excludes use in fifth line or beyond". The ERG considers it important to note that the wording of the conditional marketing authorisation available on the EMA website[1] remains as cited above. Therefore, the ERG maintains that the wording of the conditional approval does not specifically preclude use of pixantrone as a fifth or subsequent line treatment of aggressive B-cell NHL. However, the ERG recognises that it is implicit that, because of the paucity of evidence on the clinical effectiveness of pixantrone in this line of therapy, pixantrone is unlikely to be used in

this setting. In addition, as the manufacturer identifies, clinical expert opinion is that people with aggressive B-cell NHL rarely receive fifth-line treatment.

Taken together, the ERG acknowledges that it is appropriate to evaluate patients receiving pixantrone as a third or fourth line treatment as a distinct subgroup. The ERG presented these data for the population with retrospective histological confirmation of aggressive B-cell NHL in the report submitted to NICE on 13th February 2013. The ERG reiterates that it does not consider number of prior lines of treatment to be the key issue relevant to the UK population likely to be eligible for treatment with pixantrone.

1a: Histological confirmation of disease

In PIX301, patients were initially evaluated histologically for aggressive NHL 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. 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 manufacturer highlights that retrospective review of histology was included in the PIX301 protocol as a sensitivity analysis.

PIX301 included patients with aggressive *de novo* or transformed NHL, which includes subtypes of NHL not derived from B-cells. Based on the conditional marketing authorisation and statements in the manufacturer's original submission, the ERG determined that results for those with aggressive B-cell NHL would be more relevant than the full trial population of PIX301. Additionally, based on clinical expert feedback on typical UK practice in confirmation of a diagnosis of aggressive B-cell NHL, the ERG determined that the subgroup of patients with retrospective histological confirmation of disease would be more generalisable to patients in the UK. The ERG's clinical experts fed back that, initially, a patient has a biopsy at their local hospital, where the local pathologist (who might not be a lymphoma specialist) diagnoses and subtypes the lymphoma. Subsequently, the sample is sent to a tertiary referral unit where it is centrally reviewed by a specialist haematopathologist. An NHS Professional submitting an online comment on the ACD reported that biopsy samples are typically reviewed by a pathologist with expertise in lymphoma, which supports the opinion of the ERG's clinical experts. The ERG acknowledges that it is unlikely that a biopsy sample would be reviewed by 2 or 3 clinicians, as occurred in central review in PIX301. However, based on the experts' comments, the ERG asserts that biopsy samples are likely to undergo review by at least one clinician specialising in NHL before treatment commences.

In PIX301, consensus for aggressive histology was reached in 77% and 71% of patients in the pixantrone and comparator groups, respectively. The ERG agrees with the manufacturer that difficulties associated with retrospective categorisation of patients have been identified but, for the reasons outlined above, maintains that patients with retrospective histological confirmation of aggressive B-cell NHL and who received prior rituximab treatment is the most relevant population to the decision problem that is the focus of this Single Technology Appraisal (STA).

1b: Prior use of rituximab

The ERG was unable to identify the statements below in the EPAR, as reported by the manufacturer:

"There is limited data in patients previously treated with rituximab (38 patients in the Pixuvri arm and 39 patients in the comparator arm)";

"The results in the rituximab pre-treated patients still showed superior treatment benefit with Pixuvri over the comparator for overall response rate (31.6% with Pixuvri versus 17.9% with the comparator) and median progression-free survival (3.3 months with Pixuvri versus 2.5 months with the comparator)".

The ERG notes that the EPAR states:[(2)]

"Response rates to pixantrone were superior to comparator irrespective of prior rituximab use, however the benefit of pixuvri in patients that had received prior treatment with rituximab was not as favourable as in the patients without prior rituximab. Therefore additional efficacy data is needed in the context of a conditional MA to further confirm the benefit of pixuvri in the subgroup of pre-treated patients with rituximab".

The ERG has no additional comments on the use of prior rituximab treatment.

2. Trial design of PIX301

Power

The ERG thanks the manufacturer for highlighting that, at the conclusion of a trial, it is the p-value that determines whether a difference in treatment effect is or is not a chance finding. However, the ERG considers it important to note that power is important in the initial planning of a trial to reduce the risk of Type II errors and, as the manufacturer highlights, is based on evidence-based clinical assumptions to determine the required sample size. The p-value presented by the manufacturer for the effectiveness of pixantrone over treatment of physician's choice (TPC) for the outcome of complete response (CR)/unconfirmed CR ($p = 0.021$) is based on the intention to treat (ITT) population for the full trial. As a result of slow accrual, PIX301 recruited 70 patients to each group, compared with the planned 160 patients in each group. The original power calculation indicated that 160 patients in each

group would be needed 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, and assuming CR/CRu response rates of 15% and 5% in the pixantrone and TPC groups, respectively. In the full publication of PIX301, it is stated that "according to original sample size assumptions, a sample size of 70 in each group would have about 40% power".[3]

The ERG notes that studies that are potentially underpowered are more likely to be imprecise and have considerable variation around the effect size, that is, wide confidence intervals.

As discussed in an earlier section, the ERG considers the subgroup of patients with retrospective histological confirmation of aggressive B-cell NHL and having received prior rituximab to be the population of greatest generalisability to patients in the UK likely to receive treatment with pixantrone. In this subgroup of patients, the p value for the difference in clinical effect between pixantrone and TPC for the outcome of CR/CRu was 0.431, which denotes a non-statistically significant difference between groups. Considering the subgroup of patients within this group who received pixantrone as a third or fourth line treatment, the p value remains statistically non-significant but decreases to 0.184. The ERG reiterates that subgroup analyses based on line of treatment, retrospective histological confirmation of aggressive B-cell NHL, and prior treatment with rituximab are all *post hoc* analyses based on small numbers of patients in each group and should be interpreted with caution. As noted in the ERG report, the ERG considers that there is considerable uncertainty around the robustness of the results of these subgroup analyses.

Patient reported outcomes

The ERG has no additional comment.

Comparators

The ERG has no additional comment.

CRu as an endpoint

The CHMP did not consider the choice of CR/CRu for the primary outcome acceptable for a single Phase III trial, commenting that progression-free survival (PFS) or overall survival (OS) would have been more appropriate.[1] The CHMP went on to state 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.

In its report, the ERG discussed the difficulties associated with categorisation of CRu in particular and subsequent amendments of International Working Group (IWG) criteria for CRu, which rendered CRu obsolete. The criteria were updated after PIX301 had started. The ERG also recognised that the manufacturer had taken steps to ensure consistency of categorisation of CR/CRu during PIX301.

Considering the subgroups of patients with retrospective histological confirmation of aggressive B-cell NHL and receiving pixantrone as any line of treatment and as only third or fourth line treatment, there is no statistically significant difference between pixantrone and TPC in rate of CR/CRu at the end of treatment or the end of the study (Table 1). However, as noted by the ERG, no patient in the TPC group achieved a CR. The ERG notes that for CR alone there is no statistically significant difference between pixantrone and TPC in rate of CR at end of treatment in either subgroup (Table 1). However, at the end of the study, in patients receiving pixantrone third or fourth line the difference between groups has reached statistical significance (p = 0.048). The ERG stresses that the number of patients evaluated is small, the event rate is low, and data are based on *post hoc* subgroup analyses. For these reasons, the ERG emphasises that results should be interpreted with caution.

Table 1. CR/CRu for subgroup analyses based on patients receiving prior rituximab treatment in patients with retrospectively histologically confirmed aggressive B-cell NHL (adapted from Tables 14 and 16 of the ERG report)

	All lines of treatment			**Pixantrone as a third or fourth line**		
Outcome	**Pixantrone (N = 30)**	**TPC (N = 26)**	**p value**	**Pixantrone (N = 20)**	**TPC (N = 18)**	**p value**
CR/CRu (end of treatment)						
CR/CRu	5 (16.7%)	2 (7.7%)	0.431	5 (25.0%)	1 (5.6%)	0.184
CR	4 (13.3%)	0 (0%)	0.115	4 (20.0%)	0 (0%)	0.107
CRu	1 (3.3%)	2 (7.7%)	0.592	1 (5.0%)	1 (5.6%)	1.000
CR/CRu (end of study)						
CR/CRu	6 (20.0%)	3 (11.5%)	0.481	6 (30.0%)	1 (5.6%)	0.093
CR	5 (16.7%)	0 (0%)	0.055	5 (25.0%)	0 (0%)	0.048
CRu	1 (3.3%)	3 (11.5%)	0.328	1 (5.0%)	1 (5.6%)	1.000
Abbreviations used in table: CR, complete response, CRu, unconfirmed complete response; ERG, Evidence Review Group; NHL, non-Hodgkin's lymphoma; TPC, treatment of physician's choice.						

The manufacturer proposes that CR/CRu is a predictor of OS and PFS in PIX301. As noted in the ERG report, the use of CR/CRu as a surrogate outcome for PFS or OS has not been validated. In the original submission, 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 acknowledged, this analysis was likely to be underpowered and is not statistically significant. The ERG considers that there is no evidence base to support the use of CR/CRu as a surrogate for PFS or OS in relapsed or refractory aggressive B-cell NHL.

In summary, the ERG suggests that it is key to review data on all clinically relevant outcomes reported, that is, OS, PFS, and CR/CRu. However, as indicated by the CHMP, OS or PFS would have been a more appropriate primary outcome measure in PIX301.

3. Clinical effectiveness of pixantrone

Study end points

The ERG has no additional comment.

Clinical efficacy

The ERG considers it important to note that data provided by the manufacturer in response to ACD comments (Tables 1–5 in the response) are labelled as derived from the retrospectively histologically confirmed ITT (HITT) and ITT populations. In the original submission and full publication of PIX301,[3] the HITT population included those with NHL subtypes other than aggressive B-cell NHL. However, based on the number of patients in each treatment group in the tables presented in the ACD response, the ERG considers that, in the manufacturer's response to ACD comments, ITT has been redefined to denote the subgroup of patients with aggressive B-cell NHL and HITT redefined to denote patients with retrospective histological confirmation of aggressive B-cell NHL. For Tables 2 and 4, which summarise data in the HITT population based on line of therapy "without prior rituximab", the ERG considers that the data presented are for patients irrespective of status of previous rituximab treatments (i.e., includes patients who have previously received rituximab). Results for the subgroups of patients based on line of pixantrone treatment are summarised in Table 2.

The manufacturer also provides data for the subgroup of patients receiving prior rituximab treatment. The ERG notes that the results presented for the subgroup of HITT patients receiving pixantrone as a third or fourth line treatment do not match those supplied by the manufacturer as part of the clarification process. In Table 5 of the manufacturer's response to the ACD, data are presented based on 25 patients in both the pixantrone and TPC group. By contrast, data provided to the ERG during clarification for this subgroup of patients are derived from 20 patients in the pixantrone group and 18 patients in the TPC group. For clarity, the ERG presents both sets of results (Table 3).

The ERG notes that, based on data in Table 5 of the ACD response, the median OS gain in HITT patients receiving pixantrone as a third or fourth line treatment and prior rituximab is longer than 3 months (4.1 months), but the difference between treatment groups does not reach statistical significance. By contrast, the median OS gain in this group of patients based on the data provided during clarification was 2.1 months, with a mean OS gain of 2.0 months.

The ERG has updated the tables provided by the manufacturer to incorporate the p values provided by the manufacturer either in the original submission or as part of the clarification process.

Table 2. Clinical effectiveness for subgroup analyses based line of therapy in patients with retrospectively histologically confirmed aggressive B-cell NHL, irrespective of prior rituximab treatment (Tables 2 and 3 from the ACD response augmented with data from Tables 9–12 of ERG report)

	All lines of treatment			Pixantrone as a third or fourth line		
Outcome	**Pixantrone (N = 50)**	**TPC (N = 47)**	**Measure of effect (p value or HR with 95% CI)**	**Pixantrone (N = 39)**	**TPC (N = 39)**	**Measure of effect (p value or HR with 95% CI)**
CR/CRu (end of study)	9 (18%)	4 (8.5%)	0.236	9 (23.1%)	2 (5.1%)	0.047
CR (end of study)	7 (14.0%)	0	0.013	7 (17.9%)	0 (0%)	0.012
ORR (end of study)[a]	18 (36.0%)	8 (17.0%)	0.041	17 (43.6%)	5 (12.8%)	0.005
Median PFS, months	5.6 (0.7 to 24.0)	2.5 (0.0 to 24.0)	0.51 (0.33 to 0.78)	5.7 (0.7 to 24.0)	2.8 (0.0 to 13.5)	0.44 (0.27 to 0.71)
Mean PFS (SD), months	7.7 (7.75)	3.7 (4.10)	–	8.3 (8.07)	3.4 (2.94)	–
Median OS, months	8.1 (0.8 to 24.0)	6.3 (0.1 to 24.0)	0.72 (0.45 to 1.13)	11.9 (1.1 to 24.0)	7.0 (0.2 to 24.0)	0.67 (0.40 to 1.12)
Mean OS (SD), months	11.3 (8.80)	8.9 (7.91)	–	12.1 (8.78)	9.3 (7.92)	–

[a] Includes patients with a partial response.

Abbreviations used in table: ACD, Appraisal Committee Document; CR, complete response, CRu, unconfirmed complete response; 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.

Table 3. Clinical effectiveness for subgroup analyses based line of therapy in patients with retrospectively histologically confirmed aggressive B-cell NHL and who have received previous rituximab treatment (Tables 4 and 5 from the ACD response augmented with data from Tables 14 and 16 of the ERG report)

	All lines of treatment			**Pixantrone as a third or fourth line (from ACD response)**			**Pixantrone as a third or fourth line (from ERG report)**		
Outcome	**Pixantrone (N = 30)**	**TPC (N = 26)**	**Measure of effect (p value or HR with 95% CI)**	**Pixantrone (N = 25)**	**TPC (N = 25)**	**Measure of effect (p value or HR with 95% CI)**	**Pixantrone (N = 20)**	**TPC (N = 18)**	**Measure of effect (p value or HR with 95% CI)**
CR/CRu (end of study)	6 (20.0%)	3 (11.5%)	0.481	6 (24%)	1 (4%)	Reported as not significant	5 (25.0%)	1 (5.6%)	0.184
CR (end of study)	5 (16.7%)	0 (0%)	0.055	5 (20%)	0	p <0.05	5 (25.0%)	0 (0%)	0.048
ORR (end of study)[a]	9 (30.0%)	5 (19.2%)	0.537	11	3	Reported as not significant	9 (45.0%)	2 (11.1%)	0.033
Median PFS, months	3.5 (0.7 to 24.0)	2.3[b] (0.0 to 24.0)	0.66 (0.38 to 1.14)	4.3	2.8	0.83 (0.46 to 1.50)	5.4 (0.7 to 24.0)	2.8 (0.0 to 10.3)	0.52 (0.26 to 1.04)
Mean PFS (SD), months	5.9 (6.2)	3.6 (4.78)	–	–	–	–	6.4 (6.19)	3.2 (2.71)	–
Median OS, months	6.0 (0.8 to 24.0)	4.6 (0.1 to 24.0)	0.85 (0.48 to 1.50)	10.2	6.1	0.90 (0.47 to 1.75)	7.5 (1.1 to 24.0)	5.4 (0.2 to 22.5)	0.76 (0.38 to 1.55)
Mean OS (SD), months	8.9 (7.9)	7.7 (7.8)	–	–	–	–	9.9 (8.15)	7.9 (7.85)	–

[a] Includes patients with a partial response.

[b] Median duration of PFS taken from manufacturer's response to clarification. In the response to ACD comments (Table 4), the manufacturer reported a median PFS in the TPC group of 4.6 (0.1 to 24.0) months. The ERG notes that this result would favour TPC in median PFS.

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

4. Issues surrounding the economic model

The manufacturer raised the following five points in relation to the statements made in the economic components of the ACD:

1. mean time on treatment from PIX301 was not used to inform the economic model;
2. one-way sensitivity analysis around the effect of treatment on the length of PFS and OS is inaccurately described in the ACD;
3. the manufacturer's cost-effectiveness results were generated deterministically and probabilistically;
4. the utility values used in ERG exploratory analysis were from last line; i.e. from third line upwards therapy, rather than third-line patients;
5. the confidence intervals, surrounding the ICER, estimated by the ERG do not demonstrate uncertainty around the ICER and represent a factual inaccuracy.

The ERG's response to each of these points is detailed in the sections that follow.

4.1. Inclusion of mean time on treatment

Section 3.23 of the ACD states that mean time on treatment was used to inform the manufacturer's economic model. The manufacturer claims that this is factually inaccurate. The ERG notes that Kaplan–Meier data on time to treatment discontinuation are used in the model; however, this is implemented per cycle rather than as a mean estimate. Therefore, the ERG agrees with the manufacturer that mean time on treatment is not used to parameterise the economic model.

4.2. One way sensitivity analyses

The manufacturer asserts that statements, regarding one-way sensitivity into the impact of treatment effect on PFS and OS, made in Section 3.31 of the ACD are factually inaccurate. The statements referred to are:

"The manufacturer noted that when the effect of pixantrone relative to treatment of physician's choice was overestimated using the 2.5% lower CI for progression-free survival, pixantrone dominated treatment of physician's choice (that is, gave a greater benefit at lower cost). Conversely when the effect of pixantrone was underestimated using the 97.5% upper CI, the ICER increased to £90,914 per QALY gained."

The manufacturer highlights that separate distributions, for the pixantrone and TPC groups, are fitted to PFS and OS data. Based on this, the manufacturer states that it was the effect (on the cost-effectiveness results) of changing parameters of the fitted distribution, for each treatment separately, which was assessed in the one-way sensitivity analyses referred to in Section 3.31 of the ACD. Furthermore, the manufacturer implies that this is not equivalent to assessing the "effect of pixantrone relative to the treatment of physician's choice".

The ERG acknowledges the manufacturer's point that the distributions used to inform the effect of each treatment on PFS and OS, rather than the relative effect of treatment were varied in the manufacturer's one-way sensitivity analysis. However, the ERG notes that a consequence of varying the individual distributions is to vary the relative effect of treatment.

4.3. Presentation of results

Within the ERG report, the ERG states that "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" (ERG report, pg 117). This statement is reiterated in Section 3.49 of the ACD. The manufacturer highlights that within the model results are generated deterministically and probabilistically. In addition, the manufacturer states that cost-effectiveness results are presented in the MS in line with the NICE template and methods guide.

As stated in the ERG report, the ERG acknowledges that the manufacturer's model generates deterministic and probabilistic results. However, the ERG notes that Section 7.7 of NICE's template for manufacturer's evidence submission requests "A statement as to whether the results are based on a PSA".[(4)] Therefore, the ERG decided to highlight that the incremental cost-effectiveness results presented in Section 7.7 of the MS, were generated deterministically, rather than probabilistically. Furthermore, for completeness, the ERG decided to present the manufacturer's probabilistically generated cost-effectiveness results alongside those generated deterministically.

In addition to highlighting that both probabilistic and deterministic incremental cost-effectiveness results were available from the manufacturer's model, the manufacturer requests that a full summary of the probabilistic results be given. That is, that the percentage of iterations in each quadrant of the cost-effectiveness plane be reported. The ERG notes that this information has been presented in the ERG report (Tables 47, 52, and 60) but considers that the likelihood of scenarios where pixantrone use could result in fewer QALYs than TPC (i.e., scenarios in the South-West [pixantrone less costly and less effective] or North-East [pixantrone more costly and more effective] quadrants of the cost-effectiveness plane) is an important component of the decision-making process.

4.4. Inclusion of Quality of Life

Section 4.16 of the ACD states that the utility values selected by the ERG, for use in exploratory analysis, were for patients receiving third-line treatment. However, the manufacturer highlights that these utilities were in fact for last line of treatment, that is, from third-line upwards. As outlined in Table 28, pg 98 of the ERG report, the ERG notes that the utility values used in the ERG exploratory analyses are those elicited from patients receiving "final-line therapy" for chronic lymphocytic leukaemia, reported in Ferguson *et al.*[(5)]

4.5. Issues surrounding confidence intervals

In response to statements made in Sections 3.49 and 3.53 of the ACD, regarding confidence intervals around the ICER, presented in the ERG report, the manufacturer asserts that "the confidence intervals surrounding the incremental cost-effectiveness ratio (ICER) do not demonstrate uncertainty around the ICER and thus the numbers present a factual inaccuracy" (manufacturer's response to ACD, pg 18). The manufacturer's rationale for this assertion is based on the fact that:

- "no consensus has been reached on the most appropriate methodology to calculate credible intervals around the ICER" (manufacturer's response to ACD, pg 18);
- "the CEAC is a more appropriate way of representing uncertainty around the ICER than CIs" (manufacturer's response to ACD, pg 18);
- "Both in the NICE and ISPOR modelling guidelines a confidence interval around ICER is not considered an appropriate method to demonstrate uncertainty due to the issues around the different interpretation of the four quadrants" (manufacturer's response to ACD, pg 19);
- NICE methods guide[(6)] recommends the presentation of confidence ellipses, scatter plots on the cost-effectiveness plane, cost-effectiveness acceptability curves, and the probability that the treatment is cost effective at maximum acceptable ICERs of £20,000–£30,000 per QALY gained.

The ERG agrees that, in isolation, confidence intervals around the ICER do not accurately represent uncertainty. However, the ERG notes that confidence intervals have not been presented in isolation; scatter plots in the cost-effectiveness plane, cost-effectiveness acceptability curves and tabulated probabilities of cost-effectiveness have also been presented in the ERG report. Furthermore, the ERG notes that neither NICE[(6)] nor ISPOR[(7)] modelling guidelines state that the use of confidence intervals around the ICER is inappropriate. Rather, confidence intervals around the ICER are not mentioned in the most recent NICE methods guide.[(6)] Furthermore, the only mention, in the ISPOR modelling guidance, of confidence intervals around the ICER is as follows:

"*The outputs from a PSA may inform several different forms of analysis, including confidence intervals, cost-effectiveness planes (showing the distributions of costs and effects for each evaluated technology or service), cost-effectiveness acceptability curves (showing the probability of cost-effectiveness for each option), and value of information analyses.*"[(7)]

In addition to the comments made regarding the appropriateness of confidence intervals around the ICER, the manufacturer asserts that the method used by the ERG to estimate the confidence intervals is inappropriate. The manufacturer's rationale for this assertion is that the same weight is applied to ICERs in the South-West (where pixantrone is less costly and less effective than the comparator) and North-East (where pixantrone is more costly and more effective than the comparator) quadrants. The ERG agrees that the method used to estimate confidence intervals around the ICER places the same weight on positive ICERs, regardless of quadrant; however, the ERG considers it important to highlight that the aim of the confidence interval is to present the magnitude of the uncertainty. In

addition, the ERG notes that the presentation of confidence intervals in the ERG report is accompanied by a tabular summary of the percentage of iterations in each quadrant.

To conclude, the ERG considers that the confidence intervals presented in the ERG report provide additional information regarding the uncertainty associated with the ICERs. The ERG recommends that this information be considered alongside tabulated and diagrammatic summaries of the probabilistic results.

Manufacturer's revised cost-effectiveness analyses

In relation to the economic evaluation originally submitted by the manufacturer, the Appraisal Committee raised the following key points:

4.15 "The Committee concluded that the subgroup with aggressive B-cell lymphoma confirmed by central independent pathological review for all lines of treatment in the PIX301 trial was the most appropriate for decision-making and that therefore this population should inform the cost-effectiveness analyses";

4.16 "The Committee agreed that the manufacturer's utility values were likely to overestimate the quality of life for patients receiving third- or fourth-line treatment for relapsed or refractory aggressive non-Hodgkin's lymphoma. Conversely, it decided that the ERG's utility values were likely to underestimate the quality of life for this population";

4.17 "The Committee concluded that the structural uncertainty associated with the manufacturer's economic model had been satisfactorily explored but that there was still considerable uncertainty about the cost-effectiveness estimates for pixantrone in patients previously treated with rituximab";

As part of the response to the ACD, the manufacturer submitted a revised model which considers the following population subgroups:

- HITT patient populations with patients starting 3rd/4th line according to the MA;
- HITT patient populations with patients who had prior rituximab treatment and were starting on 3rd/4th line;
- HITT patient populations on any line of treatment for sensitivity analyses;
- HITT patient populations with patients who had prior rituximab treatment and were starting on any line of treatment for sensitivity analysis.

In addition, the manufacturer's revised model uses:

- utility data (for the health states of progression free survival [PFS] and progressive disease [PD]) from renal cell carcinoma patients receiving second-line treatment;
- disutilities associated with adverse events recommended in the ERG report;
- drug prices taken from the eMIT database.

ERG assessment of the manufacturer's revised cost-effectiveness analyses

As discussed in Section 3, there is some uncertainty in the nomenclature used to inform the patient populations considered in the manufacturer's response to the ACD. In particular, the ERG notes that, based on the patient numbers and clinical efficacy results presented in Tables 2 to 4 of the manufacturer's ACD response, the patient population originally called "aggressive B-cell" is now called "ITT". Furthermore, the patient population named "retrospectively histologically confirmed aggressive B-cell" in the manufacturer's clarification response is now referred to as "HITT". In addition, it appears that the population of patients entitled "HITT population all lines of therapy, **without prior rituximab**" in Table 2 actually corresponds to HITT (originally called retrospectively histologically confirmed aggressive B-cell) patients, all lines of therapy **regardless of rituximab**. Similarly, it appears that the population of patients entitled "HITT population third or fourth lines of therapy, **without prior rituximab**" in Table 3 actually correspond to HITT (originally called retrospectively histologically confirmed aggressive B-cell) patients, third or fourth lines of therapy **regardless of rituximab**.

The uncertainty regarding the patient populations considered in the economic analyses submitted as part of the manufacturer's response to the ACD resulted in difficulties validating the manufacturer's revised model. However, a validation exercise was undertaken which reversed the model changes listed in the manufacturer's written response to the ACD. This validation exercise resulted in an ICER (£33,607.03; inc. costs: £18,680.26; inc. QALYs: 0.56) for the "ITT, 3rd and 4th line" patient population that was identical to the manufacturer's original base case for patients with "aggressive B-cell, 3rd and 4th line".

In addition, the ERG carried out cross checks to verify the implementation of:

- health state (PFS and PD) utility values;
- disutilities associated with adverse events;
- drug prices sourced from the eMIT database.[8]

The ERG notes that the updated utilities/disutilities are appropriate and have been implemented correctly. However, the ERG identified a few minor errors in the updated costs used; although, correction of these resulted in a negligible change in the ICER (See Appendices 1 and 2 for details of the changes made). In addition, the ERG notes that the some of the adverse event costs continued to include missing data in the cost calculation and carried out a sensitivity analysis to remove these data (see Appendix 3 for details of changes). Table 4 summarises the impact of this additional sensitivity analysis on the manufacturer's revised deterministic cost-effectiveness results. As a consequence of errors in the manufacturer's revised model, it was not possible for the ERG to generate probabilistic

results. The ERG was unable to rectify these errors, as a result of time constraints. However, the ERG notes that the level of uncertainty, present in the cost-effectiveness results presented in the manufacturer's response to ACD, is likely to be higher than the level of uncertainty present in the cost-effectiveness results presented in the manufacturer's original submission. This is because the clinical data used to inform the manufacturer's revised model were associated with wider confidence intervals, with respect to effectiveness, than the clinical data used in the manufacturer's original model.

Table 4. Summary of deterministic results from the manufacturer's revised economic model (adapted from manufacturer's response to ACD; Table 1; pg 8)

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	43,398	1.10	0.78	–	–	–	–	–
	Pixantrone	62,073	1.77	1.31	18,675	0.67	0.53	27,720	35,326
ERG[a]	TPC	43,646	1.10	0.78	–	–	–	–	–
	Pixantrone	62,582	1.77	1.31	18,937	0.67	0.53	28,108	35,820
HITT all lines with prior rituximab									
Manufacturer's	TPC	38,669	1.00	0.71	–	–	–	–	–
	Pixantrone	40,913	1.01	0.75	2,244	0.01	0.04	151,951	52,178
ERG[a]	TPC	38,898	1.00	0.71	–	–	–	–	–
	Pixantrone	41,320	1.01	0.75	2,422	0.01	0.04	164,025	56,324
HITT 3rd or 4th line prior rituximab									
Manufacturer's	TPC	38,437	0.94	0.66	–	–	–	–	–
	Pixantrone	47,607	1.17	0.87	9,170	0.23	0.20	39,243	45,282
ERG[a]	TPC	38,665	0.94	0.66	–	–	–	–	–
	Pixantrone	48,059	1.17	0.87	9,394	0.23	0.20	40,203	46,389
HITT all lines without prior rituximab									
Manufacturer's	TPC	43,800	1.13	0.80	–	–	–	–	–
	Pixantrone	59,331	1.64	1.20	15,531	0.50	0.40	30,882	38,937
ERG[a]	TPC	44,030	1.13	0.80	–	–	–	–	–
	Pixantrone	59,790	1.64	1.20	15,761	0.50	0.40	31,340	39,514

ITT 3rd and 4th line									
Manufacturer's	Comparator	66,209	1.71	1.20	–	–	–	–	–
	Pixantrone	84,703	2.42	1.76	18,494	0.71	0.56	26,093	33,272
ERG[a]	Comparator	66,446	1.71	1.20	–	–	–	–	–
	Pixantrone	85,126	2.42	1.76	18,680	0.71	0.56	26,356	33,607

[a] ERG analysis excludes missing data for adverse event costs.

Abbreviations used in table: ERG, Evidence Review Group; HITT, histological intention-to-treat (thought to be the retrospectively histologically confirmed aggressive B-cell patient population); ICER, incremental cost-effectiveness result; ITT, intention-to-treat; LYG, life years gained; QALYs, quality adjusted life years.

1 APPENDICES

Appendix 1. Drug procurement costs changes between the manufacturer's original and revised economic models

Drug	Concentration	Tablet or vial size	Price (£)	
			Original submission	Response to ACD
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]
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
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
	20 mg/mL	25 mL	£ 60.75	£ 7.98
Gemcitabine[c]	200 mg	200 mg	£ 32.00	£ 3.22
	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]
	25 mg/mL	2 mL	£ 3.00	£ 1.34[e]
	25 mg/mL	20 mL	£ 30.00	£ 4.77[f]
	100 mg/mL	10 mL	£ 78.33	£ 17.15[g]
	100 mg/mL	50 mL	£ 380.07	£ 84.90[h]
Mitoxantrone[i]	2 mg/mL	10 mL	£ 100.00	£ 26.06
	2 mg/mL	13 mL	£ 152.33	£ 26.96
Oxaliplatin[j]	50 mg	50 mg	£ 150.00	£ 12.23
	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
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, Appraisal Committee Document.

Appendix 2. Adverse event disutility changes between the manufacturer's original and revised economic models

Adverse event	Disutility		
	Original submission	Response to ACD	Used in ERG exploratory analysis
Anaemia (Grade 3 or 4)	–0.25	–0.119	–0.119
Renal failure (Grade 3 or 4)	–0.27	–0.159	–0.159
Vomiting (Grade 3)	–0.05	–0.10	–0.10
Weight decreased	–0.117	–0.37	–0.37
Abbreviations used in table: ACD, Appraisal Committee Document; ERG, Evidence Review Group.			

Appendix 3. Summary of adverse event costs changes between the manufacturer and ERG revised cost-effectiveness results

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
Asthenia	49	147
Pain in extremity	4	11
Fatigue	56	84

Grade 3–4 adverse events		
Abdominal pain	4	11
Anaemia	129	194
Back pain	4	11
Cellulitis	953	1,430
Dehydration	869	1,303
Dyspnoea	265	794
Fatigue	56	84
Hypotension	653	1,958
Neutropaenia	245	736
Pain in extremity	4	11
Platelet count decreased	573	1,718

References

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

(2) European Medicines Agency. CHMP assessment report. EMA. 2012. [last accessed 2013 May]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002055/WC500127970.pdf

(3) 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.

(4) National Institute for Health and Care Excellence. Specification for manufacturer/sponsor submission of evidence. NICE. 2012. [last accessed 2013 May]; Available from: URL: http://www.nice.org.uk/media/D54/6E/SpecificationForManufacturerSponsorSubmissionOfEvidenceJune2012.doc

(5) Ferguson J, Tolley K, Gilmour L, Priaulx J. 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.

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

(7) Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model Parameter Estimation and Uncertainty: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. *Value in Health* 2012; **15**:835-42.

(8) Department of Health. Commercial Medicines Unit (CMU). Department of Health. 2013. [last accessed 2013 May]; Available from: http://cmu.dh.gov.uk/cmu/files/2013/01/NATIONAL_eMIT_WEB_VERSION_201301.xls