Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal Consultation Document

Pixantrone monotherapy for treating relapsed or refractory aggressive non-Hodgkin's lymphoma [ID414]

Prepared by:

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30 April 2013

Summary

CTI Life Sciences (CTILS) are in receipt of the Appraisal Consultation Document (ACD) for pixantrone and remain committed to working with NICE to ensure that pixantrone can be made available to those patients in England and Wales for whom there is no licensed alternative treatment option at this time.

Following review of the document, we believe that there are four issues to address in the document, broadly separated as:

- Those regarding the patient population (Section 1)
    - Retrospective histological review of disease (Section 1a)
    - Prior use of rituximab (Section 1b)
- Those regarding the trial design of PIX301 (Section 2)
- Those regarding the clinical effectiveness of pixantrone (Section 3)
- Those specifically relating to the model (Section 4)

The clinical aspects of the ACD are addressed in detail in the remainder of this document.

The comments of the Evidence Review Group (ERG) on the model have been noted and where applicable, addressed in a revision of the model submitted with this response.

In addition, CTILS would like to highlight to the Committee that pixantrone has been granted a European Medicines Agency (EMA) licence via the central authorisation process and as such, pixantrone was not subject to a UK Marketing Authorisation (MA) process, therefore reference to a UK MA in the ACD is incorrect.

Furthermore the conditional licence 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. Given the potential for interpretation and the importance that CTILS be responsible in assuring it is promoting only within the licensed population CTILS engaged regulatory counsel to review the SPC and EPAR and CHMP correspondences. That review confirmed that the licensed patient population excludes use in fifth line or beyond. It is for this reason that the model has been developed using the subgroup of patient receiving third or fourth line therapy. CTILS would also like to respectfully point out that research into treatment practices by physicians in England demonstrates physicians do not tend to treat patients beyond fourth line offering such patients participation in clinical trials or palliative care.

CTILS look forward to continue working with the NICE process to gain a positive recommendation for pixantrone and hope that this response document and accompanying model assist the Committee in its review.

Section 1: Population under consideration

The ACD reflected the considerable discussion and debate surrounding the appropriate patient population from the Phase III study PIX301 which should be used to inform the clinical and cost effectiveness of pixantrone. Specific sections of the ACD which refer to this issue are discussed in detail below.

ACD Section 4.5 Licensed indication

The Committee noted that, although the UK marketing authorisation is for multiply relapsed or refractory disease and states that the benefit of pixantrone treatment in fifth-line or later treatment has not been demonstrated, this did not necessarily restrict use of pixantrone to third- and fourth-line treatment. It was aware that the intention-to-treat population included patients whose tumour histology would make them ineligible for treatment with pixantrone according to the terms of the UK marketing authorisation, and that these ineligible patients accounted for around 10% of the total trial population. The Committee concluded that, although the PIX301 study included a high proportion of patients eligible for treatment under the terms of the UK marketing authorisation, the intention-to-treat population of PIX301 was not appropriate for evaluation and decision-making.

CTILS would like to highlight a part of the European Public Assessment Report (EPAR) for pixantrone [1,2] to the Committee. The latter part of this (underlined), we believe clearly limits the use to third or fourth line patients only:

This benefit needs to be further confirmed by a phase III study. <u>The indication has been reworded with the statement "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". This proposed indication reflects the available data and is considered acceptable</u>

CTILS would also contend that the patient population presented is applicable to the decision problem as patients failing four prior lines of therapy for aggressive B-cell NHL are not offered further therapy but rather are considered for clinical trials or palliative care, this is noted below:

1. It is highly unusual for patients with diffuse large B-cell lymphoma (DLBCL) to be treated beyond 4 lines of therapy in the UK at the current time.
2. To the best of my knowledge I am unaware of any licensed agent for use in the 3rd and 4th line setting. [3]

Section 1a: Histological confirmation of disease

The question of the disease status of patients in the PIX301 trial is mentioned multiple times:

ACD Section 3.50

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

ACD Section 3.10

"The manufacturer considered the first of these groups, the post-hoc subgroup of patients with aggressive B-cell lymphoma confirmed by onsite pathological review, to be similar to the population eligible for treatment according to pixantrone's UK marketing authorisation, and indicated that this formed the basis of population in the base case of its cost-effectiveness analysis (however, it should be noted that the manufacturer stated that its economic evaluation focused on those who had received 2 or 3 previous therapies; see section 3.19 for details)."

ACD Section 4.6

The Committee heard from the clinical specialists that this was not representative of UK clinical practice, in which multidisciplinary team review is routine and specimens are examined by 2 or 3 pathologists

It noted that the Evidence Review Group (ERG) had also been advised by clinical specialists that a population with disease confirmed by central independent pathological review was more relevant to UK clinical practice. It also noted that a considerable proportion of patients were excluded after the central independent pathological review (for example, if indolent disease had been confirmed)

ACD Section 4.11

The Committee recalled the clinical specialists' and ERG's opinion that the central independent pathological review mirrored clinical practice in the UK more closely than onsite pathological review. It noted that the retrospective central independent pathological review had excluded a sizeable proportion of patients originally included in the trial but later found not to have aggressive disease. In light of the breadth of the UK marketing authorisation (see section 2.1), it agreed that that it was more appropriate to evaluate all lines of treatment in the PIX301

ACD Section 3.40

The ERG viewed the data from the post-hoc subgroup of patients with aggressive B-cell non-Hodgkin's lymphoma that was histologically confirmed by central independent pathological review to be more relevant to the marketing authorisation and the decision problem in the NICE scope than the other 2 subgroups categorised

The ERG noted that retrospective central independent pathological review revealed 23% of patients receiving pixantrone and 29% of patients receiving a comparator in the intention-to-treat population had disease that was subsequently determined not to be aggressive.

ACD Section 3.43

The ERG considered that an important limitation of the manufacturer's base-case analysis was that it used data from patients whose disease had not been histologically confirmed as aggressive. The ERG indicated that the subgroup of patients with aggressive B-cell non-Hodgkin's lymphoma confirmed by central independent pathological review for all lines of treatment in the PIX301 trial was the most informative to the decision problem because it excluded patients who were later found to have disease

However, the ERG noted that the manufacturer's estimate of cost-effectiveness in this patient population was highly uncertain because it used post-hoc subgroup data and because the subgroups were not powered to detect a difference in efficacy between treatment with pixantrone and the comparators.

ACD Section 4.18 Plausibility of ICER

The Committee therefore agreed that, based on currently available evidence, the most plausible ICER would be for pixantrone compared with treatment of physician's choice in people who had aggressive B-cell lymphoma confirmed by central independent pathological review. Having agreed this, it decided that the population should not be restricted to third- or fourth-line treatment, in line with the UK marketing authorisation

The retrospective review of histology (HITT) was included in the PIX301 protocol as a sensitivity analysis. In PIX301 consensus for aggressive histology was reached in 77% and 71% of patients in pixantrone and comparator arm respectively.

The difficulty of categorising patients retrospectively is well described in literature [4-6], with a consistent pattern of disagreement between experts with a discordance rate reported between 21% and 42% of cases reviewed. The results noted above in the PIX301 study are consistent with these findings in the scientific literature.

The Committee appears to be mistaken in the belief that the retrospectively determined (HITT) B-cell subgroup is one of the relevant patient population subsets, due to 36 patients in the ITT population subsequently being identified as having low grade NHL.

The pathologic review panel only reached consensus on 13 patients as having low grade or indolent NHL (recognising that in transformed indolent disease tissue samples can have areas of indolent NHL and not contain samples of transformed aggressive histology).

For the remaining 23 patients, the panel could not reach consensus on the histologic subtype with one pathologist noting DLBCL another renal cell and the third Hodgkins as a single example. Again consistent with that reported in the scientific literature.

Section 1b: Prior use of rituximab

The prior use of rituximab in patients enrolled in the PIX301 trial is mentioned multiple times:

ACD Section 3.35

The ERG had concerns about the generalisability of the PIX301 trial population to clinical practice in England and Wales. It noted that only 7 out of 140 patients in the trial were recruited from the UK. The remaining patients were recruited from North America (n=8), Western Europe (n=31) and the rest of the world (n=94). It further noted that patients from Western Europe were heavily pretreated and may have had more severe disease than patients typically eligible for treatment with pixantrone in the UK.
3.36: The ERG had concerns about the potential effect of previous rituximab treatment on the response to pixantrone in UK clinical practice because rituximab is given as part of standard first-line treatment in the UK

ACD Section 3.36

"The ERG noted that about 50% of patients had previously received treatment with a biological agent (for example, rituximab)"

ACD Section 4.8

The Committee then discussed more specifically the impact of previous rituximab treatment on response to any subsequent treatment. It again noted the clinical specialists' opinion that patients with relapsed or refractory non-Hodgkin's lymphoma who have previously received rituximab are less likely to respond to later lines of treatment than those who have not. The Committee noted the results of the manufacturer's subgroup analyses, which showed a reduced benefit in patients who had previously received rituximab. It was also aware of the specific obligation to the European Medicines Agency in pixantrone's UK marketing authorisation, which stipulated that an additional trial was required to confirm the clinical benefit in patients who have previously received rituximab. The Committee concluded that there was considerable doubt over the clinical benefit of pixantrone in patients who had previously received rituximab, and that this applied to virtually all patients with relapsed or refractory aggressive B-cell lymphoma in England and Wales.

CTILS have noted the concerns raised by the Committee and have submitted a revised model both with and without prior use of rituximab, alongside this response. The key results from this model are shown in the economic response document. CTILS would also like to draw attention to the EPAR[1,2] for pixantrone which specifically commented on the prior use of rituximab.

While it was noted in the (EPAR) that:
"There is limited data in patients previously treated with rituximab (38 patients in the Pixuvri arm and 39 patients in the comparator arm)."

The EPAR stated that:
"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)."

Further, the conclusions drawn by the CHMP were:
"Modern treatment strategies of aggressive lymphoma generally include rituximab upfront and the consideration of high dose chemotherapy followed by a stem cell transplant in eligible patients. This means that almost all patients suffering from a second or later relapse in Europe have been exposed to rituximab, and eligible patients also to a stem cell transplant. In the PIX301 study, only approximately 55% of patients were previously treated with rituximab and 15% had undergone transplantation, with a marked geographically skewed distribution as the corresponding fractions in the Western Europe/US and Rest of world regions are 91% vs. 37% and 28% vs. 8%, respectively.

Response rates to pixantrone were superior to comparator irrespective of prior rituximab use (32% vs. 18%, 50% vs. 10% pixantrone vs. comparator, with and without prior rituximab respectively).

An evaluation of these data by the number of regimens patients had received prior to study entry showed small impact of prior rituximab therapy on the treatment effect in patients who received 2 prior lines of therapy (50% vs. 0%, 50% vs. 13.3%, pixantrone vs. comparator with and without prior rituximab use). Similar results were observed with patients who received 3 prior lines of therapy (40% vs. 18.8%, 44.4% vs. 6.3%, and pixantrone vs. comparator, with or without prior rituximab use)."

Although the outcome was not as favourable as in the patients without prior rituximab the PFS was still more favourable in the pixantrone arm versus the comparator arm regardless of prior rituximab use, particularly in patients with only two prior regimens. These data support the efficacy of pixantrone in patients that have received prior rituximab and up to 3 prior treatment regimens.

The subgroup analysis data show that the advantage of pixantrone over comparator detected in the ITT population is lower in the group of patients pre-treated with rituximab and diminishes further with increasing number of prior regimens. The results seen for Western European patients are explained partly by more heavily pre-treated patients and, importantly, by a higher prevalence of prior rituximab therapy. Still, in the group of pre-treated patients with rituximab, pixantrone shows a numerically better effect than the comparator in patients pre-treated with up to 3 regimens. This benefit needs to be further confirmed by a phase III study. The indication has been reworded with the statement "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". This proposed indication reflects the available data and is considered acceptable

The latter point clearly indicates that it is not the intention of the CHMP to recommend pixantrone for use as fifth line or later.

Section 2: Trial design

A number of comments referred to the trial design of the Phase III study PIX301 and these are addressed in the section below.

ACD Section 3.38 Power of the study

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

Power is normally used for the planning of the study under certain assumptions. When a study reached results, it is the p-value that determines the probability of success and power is no longer relevant. The study was originally powered under a conservative assumption (i.e. 10% difference of CR/Cru between the treatments).[7] At the time of primary analysis PIX301 demonstrated a statistically significant (p=0.021) higher CR/CR rate of 17% (22% in pixantrone vs. 5% in comparator), i.e. there is only 2.1% chance that this result is not true.

ACD Section 3.24 Patient reported outcomes

There were no patient-reported outcomes in the PIX301 trial and the manufacturer did not identify any utility data for any line of treatment in aggressive non-Hodgkin's lymphoma in its systematic literature review for studies on health-related quality of life

Patient reported outcomes have not been collected in this disease area to date. However, recognising the need for such data, CTI Life Sciences are considering a potential amendment to the post marketing commitment trial protocol Phase III study (PIX306) such that newly enrolled patients will complete the EORTC QLQ-C30. This will enable their quality of life to be quantified and converted into a health related quality of life value through the use of the EORTC-8D. [8]

ACD Section 3.37 and 4.9 Comparators

3.37 The ERG considered whether the treatments of physician's choice in the PIX301 trial represented UK clinical practice. Following input from its clinical specialists, the ERG noted that there is no consensus on which chemotherapy regimens should be used after second-line treatment fails and that there is a lack of comparative data on their clinical effectiveness. The ERG concluded that this meant the choice of treatment in the comparator arm of the PIX301 trial was unlikely to be a key issue. It also concluded that the small number of patients receiving each treatment meant that the choice of treatment in the comparator group could not be reliably analysed.

4.9 The Committee discussed whether the comparator arm (treatment of physician's choice) in the PIX301 trial was relevant to clinical practice in England and Wales. It heard from clinical specialists that apart from the PIX301 trial, there was no evidence base for

selecting a third- or fourth-line treatment for multiply relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma and that there was wide variation in UK clinical practice. The Committee noted that 45% of patients in the comparator arm of PIX301 had received oxaliplatin but heard from the clinical specialists that oxaliplatin was rarely used in this setting in the UK and was aware that the cost of oxaliplatin would be overestimated by the British National Formulary (BNF). The Committee further heard that gemcitabine was now routinely used in this setting in the UK but that only 1 patient in PIX301 had received it. Nevertheless, the Committee concluded that although there was some uncertainty in the proportions, all of the comparators used in the treatment of physician's choice arm in the PIX301 trial were clinically relevant, and the comparator arm was therefore acceptable for decision-making.

Unlike pixantrone, the benefit of gemcitabine or other agents either alone or in combination with rituximab has never been studied in a randomised clinical comparative trial rendering data limited to small single arm studies which produced results similar to that of the comparator arm of PIX301 and inferior to the results achieved with pixantrone monotherapy.

Because of the lack of standard of care in the third and fourth line treatment setting, physicians in the UK utilise a variety of agents including gemcitabine (14%), bendamustine (15%) lenalidamide (5%), bortezomib (3%), fludarabine/cyclophosamide (9%), gemcitabine/oxaliplatin (7%). None of which are approved therapies in this disease and have the evidenced based results of a randomised clinical trial like pixantrone. Due to the lack of effective agents 19% of UK physicians offer no therapy for this patient population.[9]

ACD Section 4.4 CRu as an endpoint

The Committee heard from the clinical specialists that although this end point would have been acceptable when the trial began in 2004, positron emission tomography (PET) scans have made unconfirmed complete response obsolete.

The definition for unconfirmed complete response (CRu) is a lesion with >75% reduction in bi-parametal measure but <100%. In that setting it is unclear if the residual radiographic abnormality is in fact residual tumour or scar tissue. In 2007 the IWG criteria added PET scanning to resolve such uncertainties and removed CRu from its classification.

However if one examines the duration of CR or CRu in PIX301 the median duration was 9.5 months with 67% of patients who achieved either a CR or CRu alive at 2 years of study follow-up. Placed in context of these data the change in nomenclature should not render the endpoint results "obsolete".

CTI Life Sciences would like to note that the CRu correlated with OS and this further validates the CRu data.

CRu as stated were generally short in the comparator arm, but CRu and CR were consistent in the pixantrone arm; CRu remained a predictor of prolonged OS and PFS.

Section 3: Clinical effectiveness of pixantrone

The comments addressed previously in Sections 1 and 2 of this response document are relevant to the subsequent conclusions on the clinical effectiveness of pixantrone. Specific comments referring to clinical efficacy demonstrated in the Phase III study PIX301 are addressed in the section below.

ACD Section 3.38 Study end points

However, the observed proportions of patients with a complete or unconfirmed complete response in the intention-to-treat population were 20.0% in the pixantrone group and 5.7% in the comparator group.

This was the primary endpoint of the trial in the intent to treat population and was met with statistical significance (p=0.021) and was the basis of approval by the EMA.

ACD Section 3.38 and 3.39 Clinical efficacy

ERG had reservations about whether pixantrone had been shown to have superior efficacy in the PIX301 trial. Consequently, it felt that results from the full trial population might not reflect the benefit of pixantrone in patients with aggressive B-cell lymphoma

In recognition of the concerns regarding clinical efficacy, CTILS have provided the results from the PIX301 trial for the HITT population for all lines of therapy and for the HITT population third and fourth line only, the latter of which is in line with the license. Both are presented both with and without prior rituximab in a separate document.

In addition, CTILS would like to remind the committee of the procedure preceding conditional marketing authorisation for pixantrone:

Article 14(7) of the EMA Regulation provides that a conditional authorisation may be granted for a medicinal product if related cumulative obligations are met. The purpose of grant of a conditional marketing authorisation is to permit medicinal products to reach patients with unmet medical needs earlier than might otherwise be the case. Conditional authorisation also ensures that additional data on a product are generated, submitted, assessed and acted upon.

The procedure related to grant of a conditional marketing authorisation is provided in Regulation (EC) No 507/2006.[11] Article 4(1) of this Regulation provides that:

"A conditional marketing authorisation may be granted where the Committee finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

(a) the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC , is positive;

(b) it is likely that the applicant will be in a position to provide the comprehensive clinical data;

(c) unmet medical needs will be fulfilled;

(d) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required."

Article 4(2) of the Regulation continues that:

"For the purposes of paragraph 1(c), 'unmet medical needs' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected."

These provisions demonstrate that a conditional marketing authorisation shall only be provided in relation to a medicinal product where the CHMP find that the criteria provided in Article 4(1) of the Regulation have been fulfilled

In the CHMP Assessment Report [1] it is concluded that:

"There is a lack of approved and standard of care pharmacological treatment for patients with multiply relapsed or refractory aggressive NHL and there is a need in this patient population that could be fulfilled with the proposed medicinal product. The CHMP concluded that the product fulfils an unmet medical need due to the lack of available alternative treatments in this population." [3]

In the Assessment Report, the CHMP examined whether the cumulative obligations provided in Article 4.1 of Regulation (EC) No 507/2006 were fulfilled by pixantrone. The Committee concluded that this was the case and, as a result of this assessment, a conditional marketing authorisation was granted for pixantrone in which it was acknowledged that, although additional clinical data was necessary, the product could fulfil an unmet medical need in patients suffering from multiply relapsed or refractory aggressive NHL due to the lack of available alternative treatments in this population.

The conditional marketing authorisation for pixantrone was reviewed and renewed in March 2013 by the EMA who noted that "The CHMP having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Pixuvri"[12]

Section 4: Issues surrounding the economic model

ACD Section 3.23 Inclusion of mean time on treatment

Other data from the PIX301 trial that were used to inform the model were mean dose for the comparator treatments plus sex, body surface area and mean time on treatment.

The mean time on treatment was not among the data used from the PIX301 trial that were used to inform the model. It should be deleted from this section.

ACD Section 3.31 Sensitivity analyses

The manufacturer tested the robustness of the model using one-way sensitivity analyses and reported that the key drivers of the cost-effectiveness estimates produced using its economic model were the parametric fitting methodology for progression-free survival and overall survival, the utility estimate for the stable or no progression health state, the time horizon and the cost of pixantrone. 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 distributions fitted to progression-free and overall survival were fitted separately to the pixantrone and the comparator arm, since the hazard curves crossed each other multiple times and the shape of the hazard functions was different in the two treatment arms, suggesting the use of treatment as predictor was not appropriate. Thus in the one-way sensitivity analyses, it was not the "effect of pixantrone relative to the treatment of physician's choice" that was estimated, but the effect of changing the parameters of the fitted distribution using the Cholesky decomposition separately for each treatment arm. The set of one-way sensitivity analyses (depicted on the tornado diagram) do not represent a potential lower and upper value of the ICER due to the overly simplistic nature of the analyses. For example, in this case the progression-free survival curve for pixantrone is unlikely to change without the same curve changing for the comparator arm also.

ACD Section 3.49 Presentation of results

The ERG stated that the manufacturer's base-case cost-effectiveness results were generated deterministically rather than probabilistically (that is, mean values rather than distributions were used to inform the value of each parameter). However, the ERG noted that probabilistic cost-effectiveness results could be assessed using the manufacturer's model. It noted that the mean probabilistic ICER of £28,846 per QALY gained (incremental costs £17,900; incremental QALYs 0.62) was highly consistent with the manufacturer's deterministic ICER of £28,423 per QALY gained (incremental costs £17,638; incremental QALYs 0.62). Nevertheless, the ERG considered the wide 95% confidence interval, which ranged from pixantrone dominating treatment of physician's choice (that is, it was more effective and less costly) to £308,681 per QALY gained, to show substantial uncertainty in the manufacturer's cost-effectiveness results. The ERG also noted that pixantrone was less effective than treatment of physician's choice in approximately 9% of the 5000 simulations, and pixantrone was dominated in 0.22% of simulations (that is, it was less effective and more expensive).

The results were generated both deterministically and probabilistic in the model, and were reported according to the NICE STA template, i.e. deterministic results were reported in sections 7.7.4-7.7.6, and probabilistic results in section 7.7.8. Probabilistic results are

depicted with scatterplot and cost-effectiveness acceptability curves as required by the template and the NICE Methods guideline.[13]

To report the full results, beside the scenarios that were not advantageous for pixantrone, all the scenarios should be included, such as:

- Pixantrone was less costly in 29% of simulations vs. less effective in 9% of simulations
- Pixantrone was more effective and more costly in 70% of simulations
- Pixantrone was dominant, i.e. more effective and less costly in 20% of simulations vs. dominated in 0.22% of simulations

ACD Section 4.16 Inclusion of Quality of Life

The Committee discussed how quality of life had been incorporated into the manufacturer's model. It heard from the clinical specialists that patients with multiply relapsed or refractory aggressive non-Hodgkin's lymphoma (who are generally aged over 60 years) would have reduced quality of life compared with people of a similar age who were otherwise healthy. The Committee then heard from the ERG that the manufacturer's utility values for patients receiving first-line treatment for aggressive non-Hodgkin's lymphoma were higher than those for healthy older adults in the UK. The Committee then reviewed the utility values selected by the ERG for its exploratory analyses, which were for patients receiving third-line treatment for chronic lymphocytic leukaemia. The Committee heard from the clinical specialists that although these patients might have a similar quality of life to those receiving third- or fourth-line treatment for aggressive non-Hodgkin's lymphoma, there were differences between the 2 conditions (such as increased infections with chronic lymphocytic leukaemia) that could mean these utility values were too low. 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. The Committee therefore concluded that, because of the utility values used, the manufacturer's cost-effectiveness estimates for any given population would be too low and the ERG's too high, and that the true cost effectiveness estimate would lie somewhere in the range between the two.

The ACD mentions, that the utility values selected by the ERG were for patients receiving third-line treatment. However these utilities were for last line of treatment, i.e. from third line upwards.

The clinical specialists thought, that CLL patients have different quality of life to those with aNHL, partly due to the different symptoms associated with infection. At the ACD Committee meeting clinical specialists also mentioned, that the quality of life in aNHL depends more on the response than on the treatment line.

Furthermore, CTI Life Sciences recognised, that the utility values selected for base case in the Manufacture's submission is potentially an overestimation. As a result a range of values for sensitivity analysis ranging from 0.47-0.85 were provided.

Based on the opinion of clinical experts at the NICE Committee Meeting renal cell carcinoma has been deemed to have the most similar quality of life implications. Thus utilities used in second-line and subsequent treatment of advanced and/or metastatic renal cell carcinoma has been incorporated in the revised model as base case.

ACD Section 3.49 and 3.53 Issues surrounding confidence intervals

The ERG undertook probabilistic sensitivity analyses in the population of patients with aggressive B-cell lymphoma confirmed by retrospective central independent pathological review and found that the mean probabilistic ICER was £62,000 per QALY gained. It noted that the ICER had a 95% chance of falling between pixantrone dominating treatment of physician's choice and £373,454 per QALY gained. The ERG observed that the wide confidence interval associated with the probabilistic ICER reflected the uncertainty about the data used in the manufacturer's economic evaluation. The ERG also noted that these analyses do not account for treatment potentially being less effective in patients previously treated with rituximab.

The numbers quoted from the Evidence Review Group (ERG) report for 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.

As previously noted to the ERG no consensus has been reached on the most appropriate methodology to calculate credible intervals around the ICER[14] due to the inherent complexity of the ratio having alternative interpretations when falling in different quadrants of the scatterplot[15]. Various methods have been proposed and challenged. However the consensus remains, that due to the limitations of CIs, or credible intervals[15] for ICERs, the CEAC is a more appropriate way of representing uncertainty around the ICER than CIs.[14,15,16]

The ERG seemed to have estimated the CIs with the following steps:

- Setting ICERs indicating that pixantrone is dominant over treatment of physician's choice to an extreme negative value;
- Setting ICERs indicating that pixantrone is dominated by TPC to an extreme positive value;
- The ICERs were then ordered smallest to largest;
- And the 2.5% and 97.5% percentiles selected; that is, the 125th and 4,875th ICERs in the list.

The ERG has attempted to address the difference in interpretation of ICERs in the different quadrants of the scatterplot by using extreme negatives for simulations falling in the north-west quadrant (pixantrone is dominant) and extreme positives in the ICERs falling in the south-east quadrant (pixantrone is dominated). However by using the abovementioned approach ICERs falling in the north-east quadrant (pixantrone is more costly and more effective) and ICERs falling in the south-west quadrant (pixantrone is less costly and less effective) have been grouped together. Whilst both ICERs in the south-west and north-east quadrant carry a positive sign their interpretation is very different. Values in the north-east quadrant represent the ICERs that, depending on the threshold, support pixantrone whilst those in the south-west quadrant represent the ICERs supporting the comparator.

Yet the same magnitude of importance has been given to simulations falling in the north-east and south-west quadrants resulting in the "upper confidence level" calculated to be from a simulation in the south-west quadrant as displayed in Appendix 1 and Figure 1 below.

For observations falling in the south-west quadrant (i.e. pixantrone more costly and less effective) the incremental QALY for the comparator versus pixantrone is very small, resulting in a large ICER. As expected, due to this most of these simulation will fall in the in the 90th percentile and above when conducting a simple ranking exercise as above (Figure 1). As these values have a different interpretation, combining the results with different implications

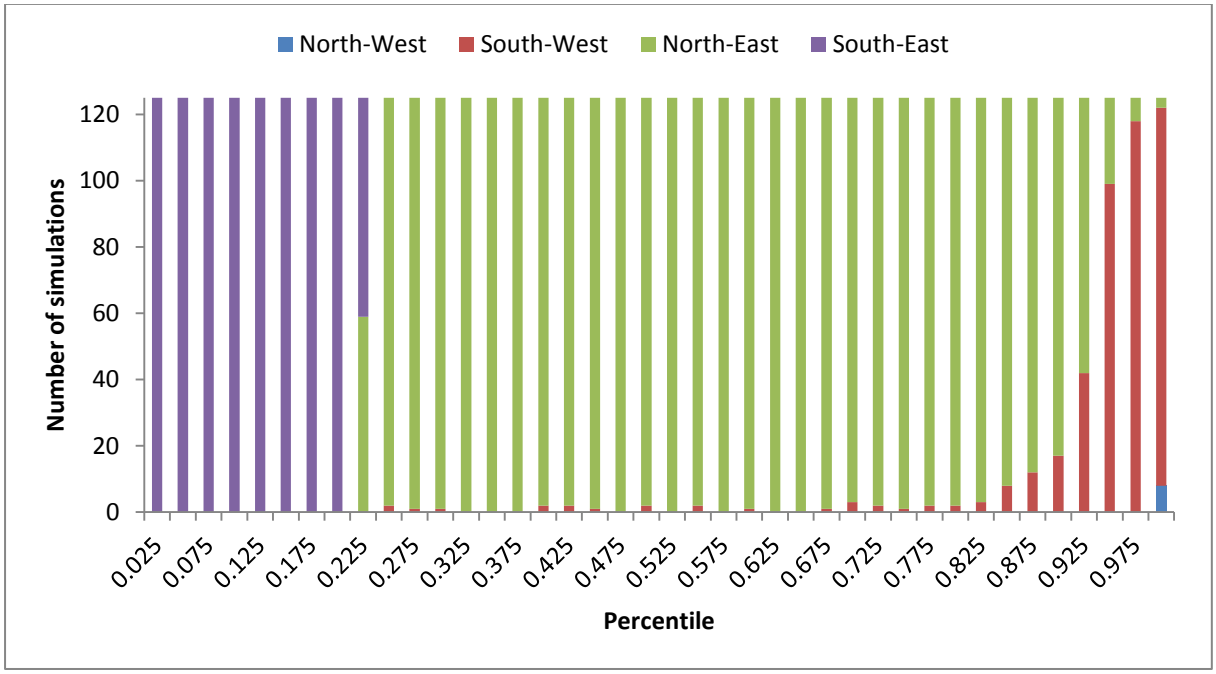
for decision represents a biased picture around the uncertainty of the cost-effectiveness of pixantrone.

For example if only the ICERs from the north-east quadrant (where pixantrone is more effective and more costly) were ranked in the same manner described by the ERG then the estimated 95% CI of the ICER of pixantrone versus standard of care would be £3,945-£84,563. If only the ICERs from the south-west quadrant (where pixantrone is less costly and less effective) were ranked in the same manner then the estimated 95% CI of the ICER of standard of care versus pixantrone would be £34,279-£4,692,844.

Consequently the confidence intervals presented in the report around the ICER derived from the probabilistic analysis are misleading and should be removed.

Both in the NICE[13] and ISPOR[17] 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. In the most recent NICE methods guidance it is noted that "appropriate ways of presenting uncertainty in cost-effectiveness data parameter uncertainty include confidence ellipses and scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves. The presentation of cost-effectiveness acceptability curves should include a representation and explanation of the cost-effectiveness acceptability frontier. Uncertainty should also be presented in tabular form. In addition to details of the expected mean results (costs, outcomes and ICERs), the probability that the treatment is cost effective at maximum acceptable ICERs of £20,000–£30,000 per QALY gained and the error probability (that the treatment is not cost effective) should also be presented, particularly when there are more than 2 alternatives."

Figure 1 Distribution of quadrants falling in each percentile as ordered by the ERG



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