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Dear [redacted]

Re: Single Technology Appraisal – Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkins lymphoma [ID414]

The Evidence Review Group BMJ Group and the technical team at NICE have now had an opportunity to take a look at submission received on the 28 November 2012 by Cell Therapeutics Inc. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm, Wednesday 16 January 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted] – Technical Lead ([redacted]). Any procedural

questions should be addressed to [redacted] – Project Manager ([redacted]) in the first instance.

Yours sincerely

[redacted]
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

EXECUTIVE SUMMARY

The responses in this document and the attached appendices address the clarification questions from NICE and the ERG, which relate primarily to additional analyses for the subgroup of participants in the PIX301 study who had aggressive B-cell lymphoma determined on retrospective consensus by the study pathologists, and further subgroup analyses for those patients with consensus-agreed aggressive B-cell lymphoma who received third or fourth-line therapy as part of PIX301.

Our analyses have demonstrated that the conclusions from our original submission relating to the efficacy, safety and cost-effectiveness of pixantrone in patients with multiply-relapsed or refractory, aggressive non-Hodgkin's lymphoma are still valid for the subpopulation covered by the UK marketing authorisation. In particular:

- Confirmed clinical response occurred in significantly more patients with HITT B-cell lymphoma receiving pixantrone overall or as combined third or fourth-line therapy, than those receiving physician's choice of chemotherapy (Tables A1-1, A1-4)
- Progression-free survival was significantly longer in patients with HITT B-cell lymphoma receiving pixantrone overall (Table A1-1), and in patients undergoing third-line therapy (Table A1-2) or combined third or fourth-line therapy (Table A1-4) than those receiving physician's choice of chemotherapy.
- Improvement in progression-free survival was particularly seen in patients receiving pixantrone overall (Table A1-6) or as third or fourth-line therapy (Table A1-8), who had no prior exposure to rituximab.
- Overall response rate, at both the end of treatment and at the end of the study, was significantly higher in patients with consensus-agreed HITT B-cell lymphoma receiving pixantrone overall, as third-line, or as combined third and fourth-line therapy, compared with physician's choice (Table A1-2, A1-4)
- There were too few patients in the consensus-agreed HITT B-cell group receiving fourth-line therapy for differences between groups to be statistically significant, although more patients treated with pixantrone achieved an overall response or confirmed complete response, and a longer mean and median progression-free survival (Table A1-3).
- Kaplan-Meier curves derived for the consensus-agreed HITT B-cell group illustrate the improved progression-free (Figure A11-1) and overall survival (Figure A11-2) with pixantrone.
- Pixantrone resulted in an incremental life-year gained of 0.5 years, and 0.45 incremental quality-adjusted life-years gained compared with Physician's choice of chemotherapy for the consensus-agreed HITT B-cell group, with an overall ICER per QALY of £32,728/QALY (Table B1-5).

Pixantrone fulfils the criteria for end of life medicines as it is indicated for patients with life expectancy less than 24 months (relapsed or refractory aggressive B-cell non-Hodgkin lymphoma patient have less than 1-year expected survival), and extended life by more than 3 months in the subgroup with consensus-agreed aggressive B-cell lymphoma, in a small patient population who have no licensed treatment option. We ask therefore that the innovation provided by pixantrone be recognised by approving the drug as an end of life medicine.

SECTION A – Clarifications of the clinical data

A1 Priority question.

In light of the disease characteristics covered by the UK marketing authorisation for pixantrone (multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas), please provide the information depicted in the table that follows for each of the subgroups of patients listed below (i.e., 6 tables of information):

- *histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review);*
- *histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review) and receiving pixantrone or physician's choice of chemotherapy as third- or fourth-line chemotherapy, both as individual subgroups and as a combined subgroup analysis (i.e., 3 tables of information);*
- *separate data for patients with histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review) and based on prior treatment with rituximab (i.e., yes versus no).*

PIX301 was designed for the central independent pathological review to identify whether or not patients had one of the aggressive NHL histologies identified in the protocol, rather than to determine the exact histology of their disease. Site-determined histology was utilised for patient entry criteria and randomisation. As such, the requested subgroup reanalyses have been conducted post-hoc, and necessitated the implementation of an algorithm to identify the patients with aggressive B cell lymphoma.

The design of PIX301 required two independent pathologists to review each baseline sample, as described in section 9.1.1 of the PIX301 Clinical Study Report (CSR). If the pathologists did not agree on the diagnosis of aggressive NHL, the specimen was assessed by a third pathologist, with the majority opinion prevailing. The Case Report Form (CRF) used to collect this data is included in the accompanying CD to this response. To determine consensus for the histologically-confirmed aggressive B-cell lymphoma (HITT B-Cell) analysis set for this re-analysis, the following algorithm was used for those patients classified by the central independent pathological review as having aggressive NHL:

- If there were results for a particular patient from only one reviewer, then that assessment was used. If this result was recorded as DLBCL, Follicular Grade III Lymphoma, or Transformed Indolent Lymphoma, the patient was selected for the HITT B-Cell analysis set.
- If there were results for a particular patient from two reviewers, the first reviewer's assessment was used to determine inclusion in the analysis set. If this result was DLBCL, Follicular Grade III Lymphoma, or Transformed Indolent Lymphoma, the patient was selected for the HITT B-Cell analysis set.
- If there were results from three reviewers, the assessment of the third reviewer was used, since that reviewer was the adjudicator for the determination of aggressive NHL. If the third reviewer's recorded judgment was DLBCL, Follicular Grade III Lymphoma, or Transformed Indolent Lymphoma, the patient was selected for the HITT B-Cell analysis set.
- In all cases, patients with diagnoses other than DLBCL, Follicular Grade III Lymphoma, or Transformed Indolent Lymphoma were excluded from the HITT B-cell analysis.

Using these criteria, consensus for aggressive histology was reached on 54 (77%) of patients who received pixantrone and 50 (71%) of patients receiving physician's choice of chemotherapy.
Non-aggressive histology was agreed on for 2(3%) of patients on pixantrone and 3 (4.5%) of the physician's choice group.
Low-grade histology was agreed on for 6 (9.3%) of patients receiving pixantrone and 7 (10%) of those receiving physician's choice.
These results are consistent with the published literature[1].

This algorithm identified the following:

- 97 patients with consensus-determined aggressive B-cell lymphoma; data summarised in Table A1-1;
- 42 patients who received third-line therapy during the PIX301 study; data summarised in Table A1-2;
- 36 patients who received fourth-line therapy during the PIX301 study; data summarised in Table A1-3;
- 78 patients who received either third- or fourth-line therapy during the PIX301 study; data summarised in Table A1-4;
- 56 patients who had received rituximab therapy prior to recruitment into PIX301; data summarised in Table A1-5; and
- 41 patients who had not received rituximab prior to recruitment into PIX301; data summarised in Table A1-6.

These tables are all reported in Appendix X on the accompanying CD, and show that:

- Confirmed clinical response occurred in significantly more patients with HITT B-cell lymphoma receiving pixantrone overall or as combined third or fourth-line therapy, than those receiving physician's choice of chemotherapy (Tables A1-1, A1-4)
- Progression-free survival was significantly longer in patients with HITT B-cell lymphoma receiving pixantrone overall (Table A1-1), and in patients undergoing third-line therapy (Table A1-2) or combined third or fourth-line therapy (Table A1-4) than those receiving physician's choice of chemotherapy.
- Improvement in progression-free survival was particularly seen in patients receiving pixantrone overall (Table A1-6) or as third or fourth-line therapy (Table A1-8), who had no prior exposure to rituximab.
- Overall response rate, at both the end of treatment and at the end of the study, was significantly higher in patients with consensus-agreed HITT B-cell lymphoma receiving pixantrone overall, as third-line, or as combined third and fourth-line therapy, compared with physician's choice (Table A1-2, A1-4)
- There were too few patients in the consensus-agreed HITT B-cell group receiving fourth-line therapy for differences between groups to be statistically significant, although more patients treated with pixantrone achieved an overall response or confirmed complete response, and a longer mean and median progression-free survival (Table A1-3).

As the efficacy of pixantrone has not previously been determined in patients with four or more prior lines of therapy, we have analysed the effect of prior rituximab therapy on patients in the consensus-determined HITT B-cell subgroup who received third or fourth-line therapy as part of PIX301, who had prior exposure to rituximab, data

[1] Available at:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM204335.pdf

summarised in Table A1-7; and those without prior rituximab therapy, summarised in Table A1-8. These additional tables are also reported in Appendix X. These tables show that the time to complete response was shorter, and the mean and median duration of response in this subgroup was longer with pixantrone than with physician's choice for those with prior rituximab therapy, although the small numbers mean that the hazard ratio could not be evaluated.

A2

For the results presented in response to A1 for the subgroup of patients with histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review), please indicate the number of patients censored for the outcomes listed.

According to the protocol described in the SAP, all patients in a given population or analysis are analysed for the response rate analyses. For patients who were not definitely known to have died at the time of analysis, survival was censored at the time of last contact or last date when the patient was seen alive. The number of patients censored for several endpoints is summarised in Table A2-1. As there were more patients still alive or progression-free at the end of the study in the pixantrone group than the physician's choice group, there was a correspondingly slightly higher number of patients who were censored in pixantrone group for both overall and progression-free survival.. All seven of the patients in the pixantrone group were censored in the PFS analysis because they were progression-free at the end of the study. One of the two physician's choice group was progression-free at the end of the study while the other patient was censored due to withdrawal of consent. Thus the censoring for the PFS analysis was non-informative.

Table A2-1 Censoring of patients in the consensus-determined HITT B-Cell analysis set

Outcome	Number of patients censored				p value
	Pixantrone		Physician's choice		
	n	N	n	N	
Primary outcome					
CR/CRu (end of treatment)	0	50	0	47	NE
CR/CRu (end of study)	0	50	0	47	NE
Secondary outcomes					
PFS	7[a]	50	2[b]	47	0.161
OS	14	50	8	47	0.231
ORR (end of treatment)	0	50	0	47	NE
ORR (end of study)	0	50	0	47	NE

Abbreviations used in table: CR, complete response; CRu, unconfirmed complete response; n, number of patients with outcome; N, number of patients in subgroup; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival..

[a] All 7 patients were progression-free at the end of the study.

[b] One patient was progression-free at the end of the study and the other withdrew consent.

A3

The submission presents patient characteristics for the overall trial population (intention-to-treat population). Please provide patient details for the subgroup of patients with histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review) for:

- *patient baseline demographic characteristics (as in Table 14 [pg 63] of the submission);*
- *patient baseline history (as in Table 15 [pg 64] of the submission);*
- *patient baseline disease characteristics (as in Table 16 [pg 64] of the submission);*
- *prior NHL treatment (as in Table 17 [pg 65] of the submission).*

The patient characteristics for the consensus-determined HITT B-Cell analysis set, for all lines of therapy, are displayed as follows:

- Patient baseline demographic characteristics; shown in Table A3-1;
- Patient baseline history; shown in Table A3-2;
- Patient baseline disease characteristics; shown in Table A3-3; and
- Prior NHL treatment; shown in Table A3-4.

These tables are all reported in Appendix X. There were no significant baseline differences between the pixantrone and physician's choice groups for any of the characteristics evaluated. The patient characteristics for the consensus-determined HITT B-Cell patients receiving third or fourth line of therapy are included in Appendix Z on the accompanying CD.

A4

For the subgroup of patients with histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review), please complete the table that follows to indicate the duration of treatment and the number of cycles of therapy received during PIX301 in each group.

Table A4-1 shows the duration of treatment and the number of cycles of therapy received during PIX301 in each treatment group for the HITT B-Cell analysis set for all lines of therapy. We have presented the mean dose intensity for patients receiving just third or fourth-line therapy, with and without prior rituximab therapy, in Tables A1-7 and A1-8 in Appendix X.

Please note that the PIX301 study protocol permitted a maximum of six cycles of therapy, so no patients received 7 or 8 cycles. These rows have therefore been deleted from the ERG table template.

Table A4-1 Duration of treatment in the consensus-determined HITT B-Cell analysis set

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

Abbreviations used in table: N, number of patients in subgroup; SD, standard deviation.

*Fisher exact test was used to compare proportions between the group and a two-sided student's t-test was used in the comparison of means between treatment groups.

Table A4-2 shows the duration of treatment and the number of cycles of therapy received during PIX301 in each treatment group for the label population (HITT B-cell patients receiving their 3rd or 4th line of therapy analysis set).

Table A4-2 Duration of treatment in the consensus-determined HITT B-cell patients receiving third or fourth-line therapy analysis set

Outcome	Pixantrone N=39	Physician's choice N=39	p value
Duration of study therapy in PIX301, months			
Number of patients who received study drug	39	38	
Median (range)	3.1 (0.0-7.4)	1.9 (0.0 - 4.9)	
Mean (SD)	3.3 (2.03)	2.0 (1.53)	0.003
Number of cycles of therapy given during PIX301			0.420
0	0 (0.0%)	1 (2.6%)	1.000
1	6 (15.4%)	8 (20.5%)	0.769
2	7 (17.9%)	9 (23.1%)	0.780
3	4 (10.3%)	8 (20.5%)	0.347
4	6 (15.4%)	4 (10.3%)	0.737
5	2 (5.1%)	0 (0.0%)	0.494
6	14 (35.9%)	9 (23.1%)	0.321
Median number of cycles (range)	4.0 (1-6)	3.0 (0-6)	

Mean (number of cycles (SD)	3.8 (1.94)	3.1 (1.88)	0.080
Abbreviations used in table: N, number of patients in subgroup; SD, standard deviation; Fisher exact test was used to compare proportions between the group and a two-sided student's t-test was used in the comparison of means between treatment groups.			

A5

For the subgroup of patients with histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review), please complete the table that follows to indicate the breakdown of treatments received in the physician's choice group.

Table A5-1 shows the treatments received in the physician's choice group for the consensus-determined HITT B-Cell analysis set, for all lines of therapy. The treatments received in the consensus-determined HITT B-Cell patients receiving third or fourth line of therapy were similarly distributed, and are included in Appendix Z on the accompanying CD.

Table A5-1 Treatment received in the physician's choice group in the consensus-determined HITT B-Cell analysis set

Treatment	Physician's choice N=47
Vinorelbine	10 (21.3%)
Oxaliplatin	15 (31.9%)
Ifosfamide	9 (19.1%)
Etoposide (intravenous)	3 (6.4%)
Etoposide (oral)	4 (8.5%)
Mitoxantrone	3 (6.4%)
Gemcitabine	1 (2.1%)
Rituximab	0
Not Dosed	2 (4.3%)
Abbreviations used in table: N, number of patients in subgroup	

A6

Data on post-progression therapies in the PIX301 trial have not been provided. Please provide a breakdown of the post-progression treatments given to patients in each group of the trial and the number of patients in each group who received the treatment for:

- *the overall trial population;*
- *the subgroup of patients with histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review).*

Table 2.4.7 in Appendix 1 summarises the post-progression therapies in the PIX301 ITT population. In both the pixantrone and physician's choice treatment groups, 25 patients (36%) received post-progression therapy.

Table 2.4.8 in Appendix 1 summarises the post-progression therapies in the PIX301 HITT B-Cell analysis set. In the pixantrone treatment group, 21 patients (42%) received post-progression therapy compared to 14 patients (30%) in the physician's choice treatment group.

A7

Please provide mean (with accompanying SDs) PFS and OS data for the full intention-to-treat analysis, and the histologically confirmed intention-to-treat analysis (i.e., mean PFS and OS in each arm, together with mean difference [and SDs] between groups in PFS and OS).

As documented in Table A2-1, 14 patients from the pixantrone group and 8 from the physician's choice group were censored as still alive at the end of the follow-up period of the PIX301 study, and 7 patients from the pixantrone group and 2 from the physician's choice were still alive and without disease progression.

To enable the estimation of the mean, the prediction of long-term survival and extrapolation beyond the trial period is crucial. Thus Kaplan-Meier data of PFS and OS from the PIX301 trial were fitted with parametric distributions, as described in section 7.3 of the original submission (pg132). Among all distributions, the lognormal provided the best and the most clinically reasonable fit. Use of this distribution was confirmed by clinical experts. The mean PFS and OS for the intention-to-treat population and the consensus-determined aggressive B-cell population are presented in Table A7-1, below.

Table A7-1. Mean PFS and OS for ITT and consensus-determined aggressive B cell populations

	Pixantrone	**Physician's choice**	**Incremental survival with Pixantrone vs Physician's choice**
Intention-to-treat population			
PFS, months Mean (SD)	14.9 (3.8)	6.6 (1.4)	8.2 (4.2)
OS, months Mean (SD)	28.6 (7.1)	20.0 (4.7)	8.6 (8.4)
Histologically-confirmed aggressive B-cell population			
PFS, months Mean (SD)	14.3 (3.6)	5.2 (1.2)	9.0 (3.8)
OS, months Mean (SD)	22.6 (6.2)	15.2 (4.1)	7.2 (7.4)
Abbreviations used in table: OS, overall survival; PFS, progression-free survival; SD, standard deviation			

A8

The submission reports that various post-hoc subgroup analyses were carried out (pg 56) in the full trial population but subgroup data are not reported within the submission. Subgroups evaluated were:

- *effect of rituximab on the efficacy of pixantrone;*
- *aggressive B-cell lymphoma;*
- *patients who had previously received stem cell transplant;*
- *European patients;*
- *older adults;*
- *women.*

For the subgroup of patients with histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review), please complete the table that follows for the outcomes of (i.e., 4 tables):

- *complete response/unconfirmed complete response (end of treatment and end of study);*
- *overall response rate (end of treatment and end of study);*
- *progression-free survival;*
- *overall survival.*

The following tables provide the data requested for the consensus-determined aggressive B cell lymphoma (HITT B cell) subgroup across all lines of therapy:

- Confirmed response/unconfirmed response at end of treatment; data summarised in Table A8-1;
- Confirmed response/unconfirmed response at end of study; data summarised in Table A8-2;
- Overall response rate at end of treatment; data summarised in Table A8-3;
- Overall response rate at end of study; data summarised in Table A8-4;
- Progression-free survival; data summarised in Table A8-5; and
- Overall survival; data summarised in Table A8-6.

These tables are all reported in Appendix X. Similar results were noted among consensus-determined HITT B-Cell patients receiving third or fourth line of therapy and are included in Appendix Z. Both these appendices are on the accompanying CD.

A9

For the reported adverse events, please clarify the criteria used to define the adverse events listed below:

- *renal failure;*
- *pain;*
    - *How was pain measured? And by whom? Was a validated questionnaire used to record the level of pain experienced by the patient?*
- *decrease in neutrophil count;*
    - *to what extent did neutrophil count decrease to be classified as an adverse event?*
- *decrease in platelet count;*
    - *to what extent did platelet count decrease to be classified as an adverse event?*
- *decrease in weight;*

- *to what extent did weight decrease to be classified as an adverse event?*

In the PIX310 study, adverse events were classified as any noxious and unintended sign, symptom, or disease that occurred while the patient was in the treatment phase of the trial. The study protocol required that the investigator evaluated changes in physical signs, laboratory values and other diagnostic procedures to determine adverse events. In addition, patients reported any adverse event they had experienced. Non-directive questioning of the patient was to be used to identify subjective adverse events. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 (NCI CTCAE[2] (v3)) were used to define and assess the severity of adverse events. Additionally, laboratory results were graded by the sponsor using the CTCAE criteria and summarised.

Renal failure
Renal failure was defined according to CTCAE version 3 criteria: grade 3 is defined as chronic dialysis not indicated; grade 4 is defined as chronic dialysis or renal transplant indicated. No additional criteria were specified in the study.

Renal failure was reported in five patients in the physician's choice group and none of the pixantrone group. The worst CTCAE grade for two of the patients was grade 3 while one patient experienced grade 4 renal failure and one patient had grade 5 renal failure.

Pain
Pain was determined by patient reporting or a physical examination, and not assessed with a questionnaire. One patient in the pixantrone group and two in the physician's choice group had grade 3 adverse events of pain.

Neutropenia
Any decrease in neutrophil count was classified as an adverse event by the investigator. The event was then graded using the CTCAE criteria.

Thrombocytopenia
Any decrease in platelet count was classified as an adverse event by the investigator. The event was then graded using the CTCAE criteria.

Weight loss
Any decrease in weight was classified as an adverse event by the investigator. The event was then graded using the CTCAE criteria. One patient in the pixantrone group and two in the physician's choice group had grade 3 weight loss.

A10
In the submission, it is reported that planned follow-up of PIX301 was 18 months. However, data in Figure 5 (pg 57 of the submission) indicate that, of the patients entering follow-up, 37 and 32 patients in the pixantrone and physician's choice group, respectively, did not complete 18 months of follow-up. Please provide the median (with accompanying range) and mean (with accompanying SD) duration of follow-up in each group.

Figure 5 in the original submission indicates that 52 patients in the pixantrone treatment group and 43 patients in the physician's choice treatment group entered

[2] Available from: http://www.eortc.be/services/doc/ctc/ctcaev3.pdf

the 18-month follow-up. The median, range, mean, and standard deviation of the duration of follow-up in months is displayed in Table A10-1.

Table A10-1 Duration of follow-up (ITT population)

Outcome	Pixantrone	Physician's choice
	N=70	N=70
Duration of follow-up, months		
Number of patients entering follow-up	52	43
Median, months (range)	9.6 (0.2 - 18.0)	8.2 (0.8 - 18.0)
Mean. months (SD)	9.8 (7.06)	10.1 (6.59)

A11

Please provide revised Kaplan–Meier plots for progression-free survival and overall survival in the full trial intention-to-treat population, indicating the number of patients at risk at the time points specified in the plots (Figures 8 and 9).

The requested Kaplan-Meier plots are displayed in the following two figures:

- Progression-free survival curves for the full intent-to-treat population; displayed in Figure A11-1;
- Overall survival for the full intention-to-treat population; displayed in Figure A11-2.

Figure A11-1 displays the updated Kaplan-Meier plot for progression-free survival, determined by the Independent Assessment Panel (IAP), in the intention-to-treat population, with the number of patients at risk reported at the specified time points, In this figure, the pixantrone group is represented by "BBR 2778", and the physician's choice group by "Chemotherapeutic Agent".

Figure A11-1. Progression-free survival per IAP assessment (ITT population)

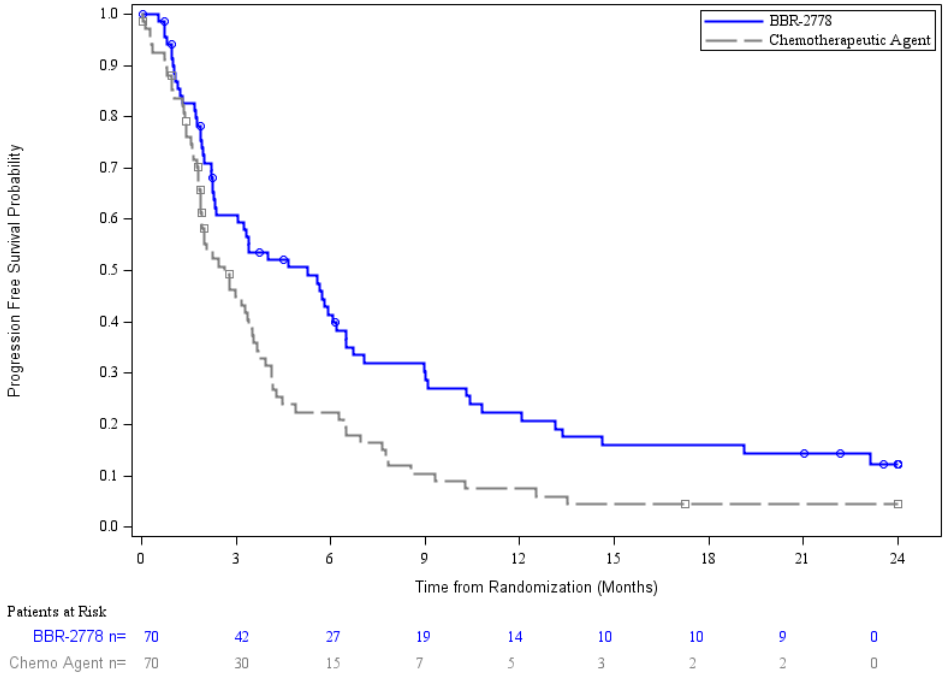
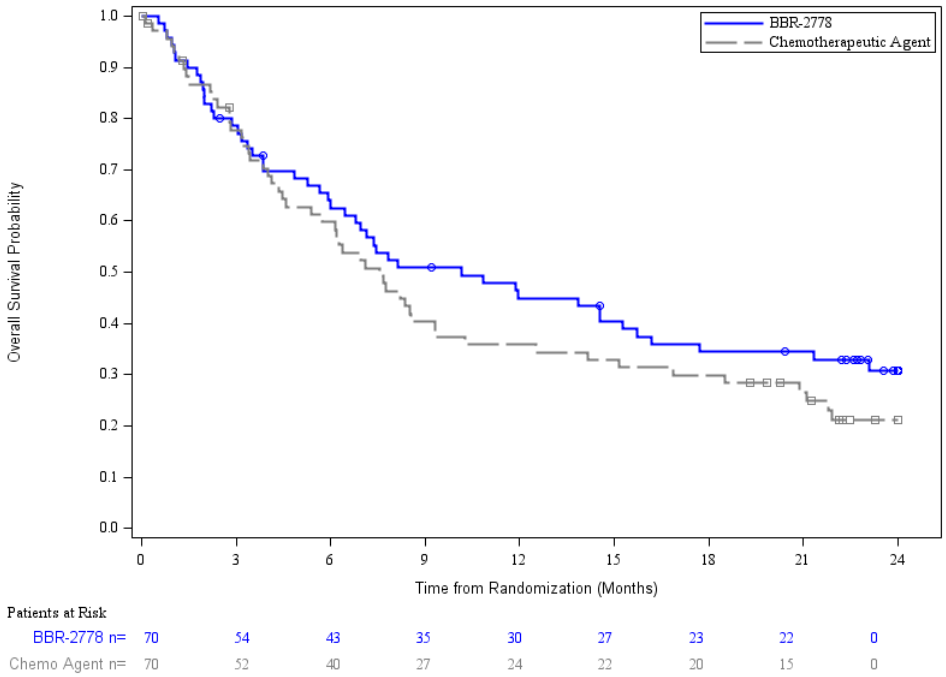


Figure A11-2 displays the updated Kaplan-Meier plot for overall survival in the intention-to-treat population with the number of patients at risk reported at the specified time points, In this figure, the pixantrone group is represented by “BBR 2778”, and the physician’s choice group by “Chemotherapeutic Agent”.

Figure A11-2. Overall survival (ITT population)



A12

In the submission, it is stated that “patients were followed up for 18 months after last treatment for disease progression and survival” (pg 60). The Kaplan–Meier plots for progression-free survival and overall survival in the full trial intention-to-treat population (Figures 8 and 9) include a time point of 24 months. For those patients

alive at 24 months in each group, please provide a breakdown of their disease status at baseline (i.e., proportion of patients with the baseline histories given in Table 15 [pg 64] of the submission). In addition, please indicate the number of patients in each group whose disease was histologically confirmed as aggressive B-cell lymphoma.

The disease status for the 20 patients alive at 24 months (13 patients in the pixantrone group and 7 patients in the physician's choice group) are displayed in Table A12-1.

Table A12-1 Disease status at baseline for patients alive at 24 months (ITT population)

Outcome	Pixantrone	Physician's choice
	N=70	N=70
Number of patients alive at 24 months	13	7
Histology by site assessment		
Transformed Indolent Lymphoma	2 (15.4%)	3 (42.9%)
Diffuse Large B-cell Lymphoma	10 (76.9%)	4 (57.1%)
Anaplastic large cell lymphoma/null cell/primary systemic	1 (7.7%)	0
HITT B-Cell		
Yes	9 (69.2%)	2 (28.6%)
No	4 (30.8%)	5 (71.4%)
Abbreviations used in this table: HITT B-cell, histologically-confirmed aggressive B cell lymphoma; N, number of patients in the subgroup		

A13

Please provide Kaplan–Meier plots for progression-free survival and overall survival in the subgroup of patients with histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review), indicating the number of patients at risk at the time points.

The requested Kaplan-Meier plots are displayed in the following two figures:

- Progression-free survival curves for the consensus-determined aggressive B-cell lymphoma group; displayed in Figure A13-1;
- Overall survival for the consensus-determined aggressive B-cell lymphoma group; displayed in Figure A13-2.

Figure A13-1 displays the updated Kaplan-Meier plot for progression-free survival per IAP assessment in the HITT B-cell analysis set, with the number of patients at risk reported at the specified time points, In this figure, the pixantrone group is represented by "BBR 2778", and the physician's choice group by "Chemotherapeutic Agent".

Figure A13-1. Progression-free survival per IAP assessment (consensus-determined HITT B-cell analysis set)

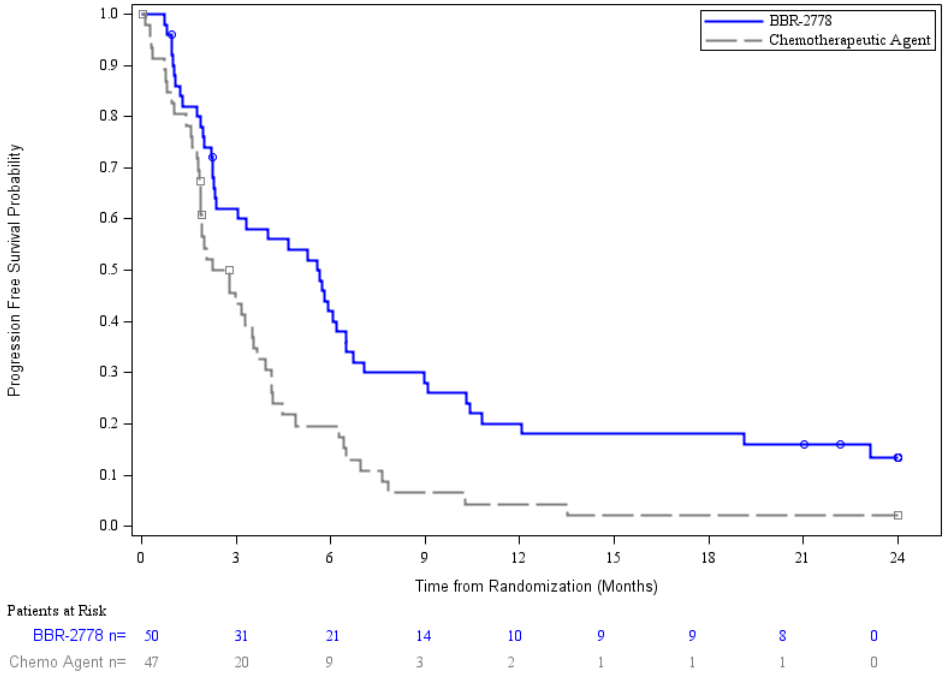
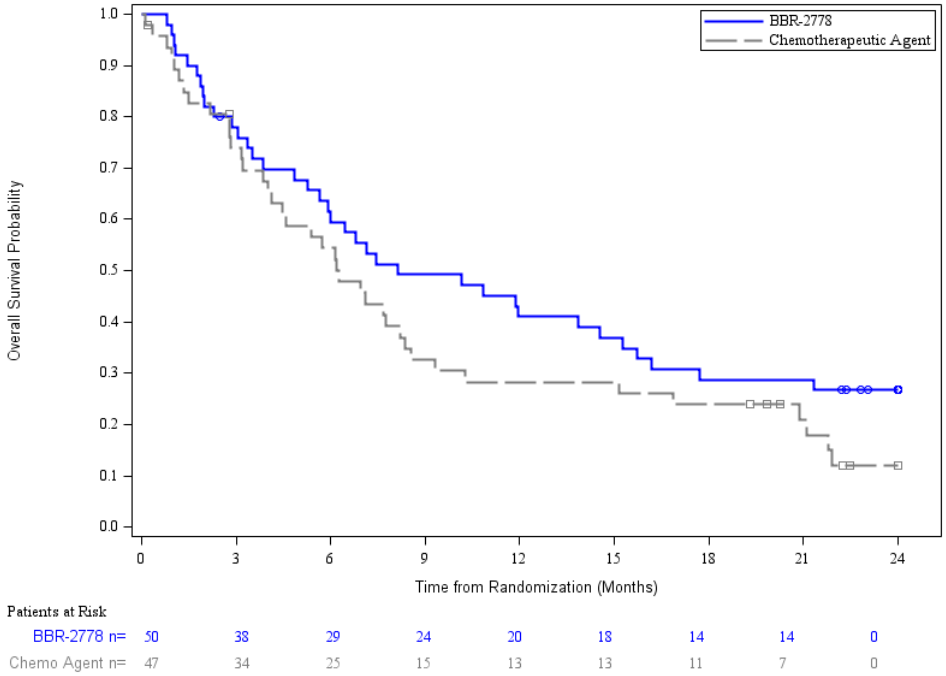


Figure A13-2 displays the updated Kaplan-Meier plot for overall survival in the consensus-determined aggressive B-cell lymphoma analysis set, with the number of patients at risk reported at the specified time points, In this figure, the pixantrone group is represented by “BBR 2778”, and the physician’s choice group by “Chemotherapeutic Agent”.

Figure A13-2. Overall survival (consensus-determined HITT B-cell analysis set)



A14

Please provide reference details to support the data on cardiotoxicity reported for the PIX203 trial.

Two references were used to support the data on cardiotoxicity:

Herbrecht, R., MacDonald, D., Weissinger, F., Wilhelm, M., Holaday, C.,Dang, NH., et al. CPOP-R Versus CHOP-R as First-line Therapy for Diffuse Large B-cell Lymphoma (DLBCL): A Phase 2, Randomized, Open-label, Multicenter Study. Presented at 53rd ASH Annual Meeting and Exposition, Decembere 10-13, 2011. Available from: https://ash.confex.com/ash/2011/webprogram/Paper40334.html

Salvatorelli, E., Menna, P., Gonzalez Paz, O., Chello M., Covino, E., Singer, JW., *et al.* The novel anthracenedione, pixantrone, lacks redox activity and inhibits doxorubicinol formation in human myocardium: Insight to explain the cardiac safety of pixantrone in doxorubicin treated patients. *Pharmacol Exp Ther.* 2012 Dec 3

Both these papers are saved on the accompanying CD.

SECTION B – Clarifications of the economic data

B1 Priority question.

Please clarify whether the patient level data used to calculate overall survival and progression-free survival are based on the histologically confirmed aggressive B-cell lymphoma population.

If data in the model are not based on patients with histologically confirmed aggressive B-cell lymphoma (as determined by the radiological panel), please provide:

- *a scenario analysis with an updated model and incremental cost-effectiveness ratio in which only data from patients whose aggressive B-cell disease was confirmed histologically are used;*
- *a replica of Table 40 in the submission comparing clinical trial and model results from patients with histologically confirmed aggressive B-cell lymphoma;*
- *Kaplan–Meier data similar to that provided in the "Efficacy inputs" worksheet in the economic model for patients whose disease was confirmed histologically for both the pixantrone and physician's choice treatment groups.*

Data in the originally submitted model were not based on the histologically-confirmed aggressive B-cell lymphoma population. Additional statistical analyses were conducted on this subpopulation using the same methods described in sections 7.3.1 and 7.3.7 of the original submission. The results of the analyses presented below are as follows:

- Kaplan-Meier data of all efficacy inputs for consensus-determined aggressive B-cell subgroup; data reported in Table B1-1 in Appendix X

- Parametric fitting for overall survival for consensus-determined aggressive B-cell subgroup provided in Appendix X;

    - Data for parametric fittings for Overall Survival are reported in Table B1-2, in Appendix X;

    - Parametric fittings for Overall Survival with pixantrone for duration of trial are shown in Figure B1-1, in Appendix X;

    - Parametric fittings for Overall Survival with pixantrone with long-term projection are shown in Figure B1-2, in Appendix X;

    - Parametric fittings for Overall Survival with physician's choice for duration of trial are shown in Figure B1-3, in Appendix X;

    - Parametric fittings for Overall Survival with physician's choice, with long-term projection are shown in Figure B1-4, in Appendix X;

    - Kaplan-Meier curves for Overall Survival with pixantrone and physician's choice are shown in Figure B1-5, in Appendix X;

    - Negative log of estimated survivor functions for overall survival are shown in Figure B1-6, in Appendix X;

    - Epanechnikov Kernel-smoothed hazard functions for Overall Survival are shown in Figure B1-7, in Appendix X.

- Parametric fitting for progression-free survival for consensus-determined aggressive B-cell subgroup provided in appendix x:

    - Data for parametric fittings for Progression-free survival are reported in Table B1-3, in Appendix X;

    - Parametric fittings for Progression-free Survival with pixantrone for duration of trial are shown in Figure B1-8, in Appendix X;

    - Parametric fittings for Progression-free Survival with pixantrone with long-term projection are shown in Figure B1-9, in Appendix X;

    - Parametric fittings for Progression-free Survival with physician's choice for duration of trial are shown in Figure B1-10, in Appendix X;

    - Parametric fittings for Progression-free Survival with physician's choice, with long-term projection are shown in Figure B1-11 in Appendix X;

- Kaplan-Meier curves for Progression-free Survival with pixantrone and physician's choice are shown in Figure B1-12, in Appendix X;
- Negative log of estimated survivor functions for Progression-free survival are shown in Figure B1-13, in Appendix X;
- Epanechnikov Kernel-smoothed hazard functions for Progression-free Survival are shown in Figure B1-14, in Appendix X.

The same methods were employed as described in sections 7.3.1 and 7.3.7 of the submission.

For overall survival, since the hazard curves crossed each and the shape of the hazard functions was different in the two treatment arms, analysing both arms together and using treatment as predictor was not appropriate. Therefore, separately fitted distributions were chosen. As the hazard curves were not monotonic, the Weibull distribution was not appropriate, as indicated by the parametric fits. Based on visual goodness-of-fit estimations during the two-year trial period and AIC/BIC criteria comparisons, generalised gamma, log-normal and log-logistic distributions provided the best fit (see Appendix X for details). As the fits were good, piecemeal fittings were not considered. . Clinical experts from England suggested that the generalised gamma distribution overestimated long-term survival, and the log-normal distribution provided a realistic estimation consistent with observations in clinical practice. Thus the separately fitted lognormal distribution was selected. Progression-free survival was defined as time to progression or death in the base case. Although, according to AIC/BIC in addition to log-normal and log-logistic distributions for the physician's choice arm Weibull distribution provided a good fit instead of generalized gamma, for similar reasons as for overall survival, lognormal distribution was chosen as the base case (see Appendix X for details).

The modelled medians for overall and progression-free survival are similar to the ones reported in the PIX301 trial. For overall survival, the model overestimates the median with pixantrone, while slightly underestimating the median for the physician's choice arm. For progression-free survival, the model overestimates the median for the pixantrone arm while slightly underestimating it for the physician's choice arm. These data are displayed in Table B1-4,below. The differences are because of the steps seen in the Kaplan-Meier curves at the median. These steps have been smoothed out for the model to reduce the effect of the trial assessment schedule.

Table B1-4. Summary of model results compared with clinical data (based on Table 40 of the submission)

Outcome	**Pixantrone**		**Physician's choice**	
	Clinical trial result (median)	**Model result (median)**	**Clinical trial result (median)**	**Model result (median)**
Progression-free survival	5.9 months	6.8 months	3.0 months	2.7 months
Overall survival	8.2 months	9.2 months	6.2 months	6.1 months

In the economic model analysis, from an incremental perspective, there is an overall ICER of £32,728/QALY with pixantrone compared with physician's choice of chemotherapy. This is demonstrated in Table B1-5, below.

Table B1-5 Cost-effectiveness summary results for consensus-determined aggressive B-cell population

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)/QALY
Pixantrone	60,918	1.64	1.22	14,809	0.50	0.45	32,728
Physician's choice	46,109	1.13	0.77				
Abbreviations used in this table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B2

Please clarify the potential discrepancies between values cited for utilities in the submission (Table 34; pg 159) and those used in the model, which are summarised in the table below. Please clarify which are the correct values.

In Table 34 of the submission, the values slipped one row from row 10. We apologise for this error. The correct values were, however, used in the model. Table B2-1, below, represents the revised table for Table 34 in P159 of the original submission. Please note that the PIX301 study reported separate outcomes for reduced platelet count and thrombocytopenia. Both were used in the model.

Table B2-1: Summary of disutility values for cost-effectiveness analysis – adverse events (Table 34 in section 7.4.9 of the original submission)

Adverse Events	Duration of Adverse Events (days)*	Utility Decrement	Reference	Justification
Grade 2				
Neuropathy	35.3	-0.115	-	Assumed to be the same as for fatigue and asthenia, assumed to be the same as for grade ¾
Abdominal pain	17.0	-0.069	Doyle et al., 2008 374 – 380. Table 2[67]	Assumed to be the maximum disutility of all the other grade 2 adverse events, assumed to be the same as for grade 3/4
Vomiting	2.3	-0.103	Lloyd et al 2006, 683 – 690. Table 3[68]	Assumed to be the same as for grade ¾

Adverse Events	Duration of Adverse Events (days)*	Utility Decrement	Reference	Justification
Asthenia	35.3	-0.115	Lloyd et al 2006, 683 – 690. Table 3[68]	Assumed to be the same as for grade ¾
Pain in extremity	3.0	-0.069	Doyle et al., 2008 374 – 380. Table 2[67]	Assumed to be the same as for grade ¾
Fatigue	31.5	-0.115	Lloyd et al 2006, 683 – 690. Table 3[68]	Assumed to be the same as for grade ¾
Grade 3/4				
Abdominal Pain	17.0	-0.069	Doyle et al., 2008 374 – 380. Table 2[67]	
Anaemia	16.1	-0.254	Swinburn et al, 2010, 1091–1096 Table 1[72]	
Anorexia	35.0	-0.371	-	Assumed to be the maximum disutility of all the other grade 3/4 AEs
Asthenia	35.3	-0.115	Lloyd et al 2006, 683 – 690. Table 3[68]	
Back Pain	18.0	-0.069	Doyle et al., 2008 374 – 380. Table 2[67]	
Bronchitis	24.0	-0.371	-	Assumed to be the maximum disutility of all the other grade 3/4 AEs
Cellulitis	12.5	-0.371	-	Assumed to be the maximum disutility of all the other grade 3/4 AEs
Dehydration	8.0	-0.103	Lloyd et al 2006, 683 – 690. Table 3[68]	
Dyspnoea	12.7	-0.050	Doyle et al., 2008 374 – 380. Table 2[67]	
Ejection Fraction	11.5	-0.371	-	Assumed to be the maximum disutility of all the

Adverse Events	Duration of Adverse Events (days)*	Utility Decrement	Reference	Justification
Decreased				other grade 3/4 AEs
Fatigue	31.5	-0.115	Lloyd et al 2006, 683 – 690. Table 3[68]	
Febrile Neutropenia	7.1	-0.150	Lloyd et al 2006, 683 – 690. Table 3[68]	
Hypotension	8.0	-0.371	-	Assumed to be the maximum disutility of all the other grade 3/4 AEs
Leukopenia	14.0	-0.371	-	Assumed to be the maximum disutility of all the other grade 3/4 AEs
Lymphopenia	34.0	-0.371	-	Assumed to be the maximum disutility of all the other grade 3/4 AEs
Malignant Neoplasm Progression	11.0	-0.371	-	Assumed to be the maximum disutility of all the other grade 3/4 AEs
Mucosal Inflammation	4.0	-0.371	Swinburn et al, 2010, 1091–1096 Table 1[72]	
Nausea	6.0	-0.048	Nafees B, et al, 2008. 84 Table 2[69]	
Neutropenia	15.1	-0.090	Nafees B, et al, 2008. 84 Table 2[69]	
Pain In Extremity	3.0	-0.069	Doyle et al., 2008 374 – 380. Table 2[67]	
Platelet Count Decreased	16.5	-0.108	Tolley K, 2010 (A273-A274)[73]	
Pleural Effusion	3.0	-0.371	Swinburn et al, 2010, 1091–1096 Table 1[72]	
Pneumonia	14.9	-0.200	Beusterien 2010 p50.	

Adverse Events	Duration of Adverse Events (days)*	Utility Decrement	Reference	Justification
			Table 1[66]	
Pyrexia	12.3	-0.110	Beusterien 2010 p50. Table 1[66]	
Renal Failure	29.8	-0.273	Poole et al 2009 (A203)[70]	
Thrombocytopenia	23.2	-0.108	Tolley K, 2010 (A273-A274)[73]	
Vomiting	2.3	-0.048	Nafees B, et al, 2008. 84 Table 2[69]	
Weight Decreased	55.3	0.117	Sinno H, et al, 2011	
* Duration of AE taken from PIX301 trial CSR PIX301 CSR 2010				

The reference for grade 3-4 decrease in weight was omitted in error from table 34 of the original submission document due to the slipping of rows. We apologise for this error. The full citation is:

Sinno H, Thibaudeau S, Tahiri Y, Mok E, Christodoulou G, Lessard L, Williams B, Lin SJ. Utility assessment of body contouring after massive weight loss. *Aesthetic Plast Surg.* 2011 Oct;35(5):724-30. Epub 2011 Apr 13.

B3

Please clarify whether the highest disutility taken from the publication by Swinburn et al. was obtained by subtracting the utility of nausea Grade 1–2 from perfect health (1 – 0.635) for Grade 3–4 adverse event. If so, please update the model results and sensitivity analysis to:

- *use the utility of nausea Grade 3–4 reported in the publication by Swinburn et al.;*
- *apply the method used in Doyle et al. to generate the disutility for adverse events (i.e., subtract the utility of adverse event from the stable disease utility).*

The correct disutilities from the publication by Swinburn et al.(2010) have been reported in Table B2-1, above. The model in the submission used these correct utilities.

B4

The Evidence Review Group was unable to verify the utility values for renal failure and decrease in weight from the references provided with the submission. Please

clarify whether the provided references are correct. If not, please provide additional references in support of the cited utility values.

The correct utility values for renal failure and weight loss, and references to support these, have been reported in Table B2-1, above.

B5

Please provide the reference from which data on duration of adverse events were taken. The reference is cited within the model as follows:
EXTEND trial; Pixantrone (BBR 2778) versus other chemotherapeutic agents for third-line single agent treatment of patients with relapsed aggressive non-Hodgkin's Lymphoma: a randomized, controlled, phase III comparative trial. Secondary analysis.

The duration of adverse events were estimated based on the post-hoc analysis of the patient-level data from the PIX301 trial as described in section 7.3.1 of the submission. This analysis was based on data on file and has not yet been reported in any publication.

Table B5-1 below presents the duration of adverse events from the post-hoc analysis, measured in days. Data is only presented for the treatment groups where each adverse event was experienced by one or more patients. The weighted average duration from the pixantrone arm and the physician's choice arm were calculated and used in the model. The final input values can be found in the [Utilities] tab columns M and O in the economic model and Table 34 of section 7.4.9 in the original submission.

Table B5-1. Summary of duration of adverse events with pixantrone and physician's choice.

Adverse Events	Treatment arm	n	Mean	Standard Error
Abdominal pain	Pixantrone	5	21.20	12.64
	Physician's choice	3	10.00	8.54
Anaemia	Pixantrone	4	29.25	27.62
	Physician's choice	12	11.67	19.93
Anorexia	Pixantrone	3	44.00	14.00
	Physician's choice	1	8.00	.
Asthenia	Pixantrone	4	39.00	25.86
	Physician's choice	2	28.00	24.04
Back pain	Pixantrone	1	18.00	.
Bronchitis	Pixantrone	1	24.00	.
Cellulitis	Pixantrone	2	12.00	8.49
	Physician's choice	4	12.75	11.53
Dehydration	Pixantrone	3	8.00	5.20
Dyspnoea	Pixantrone	4	12.75	12.50
	Physician's choice	3	12.67	8.33

Adverse Events	Treatment arm	n	Mean	Standard Error
Ejection fraction decreased	Pixantrone	2	11.50	4.95
Fatigue	Pixantrone	2	31.50	7.78
Febrile neutropaenia	Pixantrone	5	8.20	3.83
	Physician’s choice	2	4.50	2.12
Hypotension	Pixantrone	2	4.50	3.54
	Physician’s choice	1	15.00	.
Leukopenia	Pixantrone	23	15.52	13.01
	Physician’s choice	6	8.00	6.96
Lymphopenia	Pixantrone	2	34.00	38.18
Malignant neoplasm progression	Physician’s choice	1	11.00	.
Mucosal inflammation	Physician’s choice	1	4.00	.
Nausea	Physician’s choice	1	6.00	.
Neutropenia	Pixantrone	62	13.21	14.20
	Physician’s choice	24	19.96	35.87
Pain in extremity	Physician’s choice	1	3.00	.
Platelet count decreased	Pixantrone	2	16.50	17.68
	Physician’s choice	2	16.50	10.61
Pleural effusion	Pixantrone	1	6.00	.
	Physician’s choice	1	0.00	.
Pneumonia	Pixantrone	4	14.00	5.29
	Physician’s choice	3	16.00	5.20
Pyrexia	Pixantrone	3	10.67	15.04
	Physician’s choice	7	13.00	13.84
Renal failure	Physician’s choice	4	29.75	9.64
Thrombocytopenia	Pixantrone	9	28.33	30.62
	Physician’s choice	8	17.50	27.38
Vomiting	Physician’s choice	3	2.33	2.52
Weight decreased	Pixantrone	1	32.00	.
	Physician’s choice	2	67.00	63.64
Abbreviations used in this table: n, number of patients experiencing the adverse event				

B6

On page 124 of the submission, it is reported that patients with complete response after treatment with pixantrone or physician's choice "have the potential to receive stem cell transplantation and would discontinue initial treatment upon the determination of CR". The Evidence Review Group's clinical advisor indicated that stem-cell transplantation would be given after response to second line treatment. This is in agreement with the treatment algorithm outlined in Figure 1 of the manufacturer's submission (pg 24). Given that patients in PIX301 had to have had at least two prior regimens of chemotherapy to be eligible for randomisation, please provide a rationale for asserting that patients who have a complete response to third line or later therapy would be eligible for stem-cell transplantation.

CTI's clinical experts also agree that stem cell transplants are currently given only to patients with complete response after second-line therapy. As such, this intervention was not incorporated into the economic model used in the submission.

The reasons for limiting stem cell transplant to second-line responders relate at least partly to the low likelihood of a complete response to third and subsequent-line therapy. However, the results of PIX301 suggest that a complete response can be achieved as a result of third-line pixantrone therapy. The comment about the potential for patients to receive stem cell therapy was included as acknowledgement that eligibility criteria might change in the future, such that patients who demonstrate a complete response to third-line pixantrone and have a good physical status might be offered stem cell therapy.

B7

On page 124 of the submission, it is reported that "stem cell transplant would have additional costs, but at the same time could increase overall survival significantly". It is asserted that "due to the significantly fewer patient achieving complete response or unconfirmed complete response in the chemotherapeutic agents arm compared to the pixantrone arm (24.3% vs. 7.1%, p=0.009), not taking the potential stem cell transplant into account was a conservative assumption".
Please clarify for what reasons the exclusion of stem-cell transplantation from the model would be considered a conservative assumption. Please provide details of the expected costs and expected survival for patients who receive stem-cell transplantation.

As explained in the response to question B6, stem cell transplant was not included in the economic model as it is not currently available to patients in whom second-line therapy has failed. The issue about whether or not inclusion of stem cell transplantation is a conservative assumption is therefore purely theoretical.

The comment was made in the submission in acknowledgement of the fact that the current criteria for receiving stem cell therapy could change over time, since third-line therapy with pixantrone can lead to complete response. There is, for example, evidence discussed in one review (Pettengell et al., 2002), that relapse-free survival after stem cell transplant may be similar after second-line and third-line therapy, and that patients who have previously responded to chemotherapy have similar overall and progression-free survival whether they undergo transplantation during their first remission or after recurrence of chemosensitive disease.

An economic evaluation of the use of high-dose chemotherapy to support stem cell transplantation in the treatment of relapsed Hodgkin's and non-Hodgkin's lymphoma in the UK used data from a systematic review to calculate the cost per life-year

gained with high dose chemotherapy (Beard et al., 2000). Two clinical trials reported in that review found a survival benefit of 0.8 (BNLI trial) and 1.1 life-years (PARMA trial) with high-dose chemotherapy compared with standard chemotherapy, and calculated the cost per life-year gained at £12,636 (PARMA trial) and £17,375 (BNLI trial). An accompanying editorial concluded that, in relapsed disease, there could be a substantial cost-effectiveness advantage to stem cell transplantation with high-dose chemotherapy, compared with conventional treatment (Sweetenham, 2000). Furthermore, this editorial reports an earlier economic evaluation, that found the cost per life-year gained with stem cell transplant was $26,000 when used in the second relapse, compared with $400,000 when used at first relapse. For these reasons, and given the higher number of responders with pixantrone than physician's choice, the use of stem cell transplant in responders could, although increasing total costs, lead to substantial health benefit, that would outweigh the additional costs, resulting in a decreased ICER.

Additional references for this reply:

Pettengell R. Autologous stem cell transplantation in follicular non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 2002 Feb;29 Suppl 1:S1-4.

Beard SM, Lorigan PC, Sampson FC. The cost-effectiveness of high dose chemotherapy in the treatment of relapsed Hodgkin's disease and non-Hodgkin's lymphoma. *Br J Cancer*. 2000 Jan;82(1):81-4.

Sweetenham JW. Economics of stem cell transplantation for lymphoma: counting the cost of living. *Br J Cancer*. 2000 Jan;82(1):4-6.

B8

Pre-progressed patients face the competing risks of progression, death from disease and death from other causes. Please clarify how these competing risks were accounted for in the model. If competing risks were not considered, please clarify the rationale for not considering competing risks.

In the model, progression was modelled using progression-free survival instead of time to progression. Time to death from any cause was modelled using overall survival. In cases where time to death happened before progression-free survival due to the use of parametric survival curves, time to death took priority.

B9

The ERG notes that there is a potential inconsistency in the "Utilities" worksheet of the economic model, where patients with Grade 2 vomiting have a higher disutility (–0.103) compared with those with Grade 3/4 vomiting (–0.048). If this is an error, please correct and provide a scenario analysis with an updated model and incremental cost-effectiveness ratio.

The estimates of the two disutilities were obtained from two different literature sources. The disutility of grade 2 vomiting was estimated based on the disutility estimate of diarrhoea and vomiting in breast cancer from Lloyd et al.'s study (Lloyd et al., 2006). The disutility of grade 3-4 vomiting was estimated based on the estimated disutility of nausea and vomiting in non-small-cell lung cancer from Nafees et al.'s study (Nafees et al., 2008).

Scenario analyses were conducted to test the impact of a range of disutility estimates of vomiting on the incremental cost-effectiveness ratio. The results show that the impact of disutility estimates of vomiting on ICER is minimal.

Table B9-1. Scenario analyses on disutility of vomiting

Scenario	Disutility inputs of grade 2 vomiting	Disutility inputs of grade 3 vomiting	ICER (£)
Base case	0.103	0.048	28,423.41
Scenario 1	0.103	0.103	28,423.33
Scenario 2	0.048	0.048	28,423.45
Scenario 3	0.048	0.103	28,423.38

B10

Please provide a scenario analysis with an updated model and incremental cost-effectiveness ratio that uses costs listed in the current version of the British National Formulary (number 64).

We checked the drug prices against the British National Formulary Number 64 (December 2012) for any update. The only update identified was for epirubicin at a concentration of 2mg/mL and vial size of 100 ml. The price dropped from £386.16 in BNF 62 to £306.20 in BNF 64. The updated prices for all chemotherapy agents are presented in Table B10-1, reported in Appendix X. There was no change to the prices of medication that could be used to manage adverse events that were included in table 14 in appendix F of the original submission.

Updating the cost of epirubicin does not change the ICER: the base case ICER remains at £28,423.41, the same to two decimal places as the original base case ICER.

B11

Please clarify the potential discrepancy in the figures cited in the submission for the base case parameters for progression-free survival; numbers presented in Table 31 (pg 139) differ from those provided in the model and Appendix C (Table 9; pg 48).

Intervention	***Table 31 (pg 139)***		***Table 9 (pg 48) / Appendix C***	
	Intercept	***Scale***	***Intercept***	***Scale***
Pixantrone	*3.2826*	*1.3184*	*3.5423*	*1.3397*
Physician's choice	*2.4763*	*0.9964*	*2.6811*	*1.0624*

In addition, please clarify whether the figures in Table 39 of the submission are for the DLBCL population.

The values provided in table 31 (page139) of the submission were for the DLBCL population but not the wider base case aggressive B-cell population. Table B11-1 below provides a correction to the version of table 31 in the original submission . The values provided in table 9 (page 48) and Appendix C of the submission correctly reflected the base case parameters for progression-free survival, and were also consistent with the model.

Table B11 -1: Summary of variables applied in the economic model (Table 31, pg139 of the original submission)

Variable	Value	CI (distribution)	Reference to section in submission
Time horizon	Lifetime		Section 7.2.6.
Percentage male	61.4%	Standard error 4.1% (Beta)	Section 6.3.4
Cycle length	Weekly cycles to capture the 4-week treatment cycles of pixantrone and 3-week treatment cycles of comparator treatments.	--	Section 7.2.3
Overall survival	Lognormal parameters for pixantrone: Intercept 4.0486, scale 1.4910 Lognormal parameters for standard care: Intercept 3.6986, scale 1.4051	Variance-covariance tables for the lognormal parametric fitting (using Cholesky decomposition)	Appendices B, C, N and P
Progression-free survival	Lognormal parameters for pixantrone: Intercept 3.5423, scale 1.3397 Lognormal parameters for standard care: Intercept 2.6811, scale 1.0624	Variance-covariance tables for the lognormal parametric fitting (using Cholesky decomposition)	Appendices B, C, N and P

Variable	Value	CI (distribution)	Reference to section in submission
Utilities	Stable, no progression 0.81 Progressive/relapsed disease 0.60	Standard error: Stable, no progression 0.08 Progressive/relapsed disease 0.06 (Beta)	Section 7.4.9 Appendix N and P
Adverse events (AE)	Pixantrone: Grade 3 and 4 AE weekly rate 0.136 Grade 2 AE weekly rate 0.0003 Standard care: Grade 3 and 4 AE weekly rate 0.108 Grade 2 AE weekly rate 0.0006	The number of individual AEs were varied instead of the overall rate, using standard gamma distribution	Section 7.3.1 Appendix N and P
Time to treatment discontinuation (TTD)	TTD was incorporated using the Kaplan-Meier estimates for each cycle	A multiplication factor of 1 was varied	Section 7.6.2 Appendix C
Drug costs			Appendix F, N and P
Unit costs for resource use			Appendix F, N and P
Resource use			Appendix G,H,I, M, N and P
Abbreviations used in this table: AE, adverse events; CI, confidence interval			

Table 39 contains no data. Subsequent feedback from NICE has confirmed that this question relates to Table 31 instead.

B12

Please confirm:

- *whether the pre-progression, post-treatment therapies listed in Table 65 (Appendix M), and also applied within the economic model, were estimated from responses to question 1a, Appendix D: Resource Use Questionnaire;*
- *whether the post-progression therapies listed in Table 66 (Appendix M), and also applied within the economic model, were estimated from responses to question 1b, Appendix D: Resource Use Questionnaire.*

If so, please clarify the rationale for asking for therapies used in third-line treatment, when these patients would be at fourth line or later: "We would like to obtain your estimate of the use of different therapies in the treatment for relapsed or refractory aggressive NHL therapies for third-line treatment" (Appendix D: Resource Use Questionnaire).

For both questions, we can confirm that the estimates were obtained from the Resource Use Questionnaire (questions 1a and 1b), as described in the Appendices (tables 65 and 66).

In the questionnaire we were interested in current treatment practice, so Pixantrone was not incorporated in the treatment pathway. The assumption is, that Pixantrone, used as third-line, would push these current third-line therapies into fourth-line treatment. However, as mentioned, participants in the interview were informed that we were interested in third-line and subsequent therapy, so their answers should be valid for the purposes of the model.

B13

Please clarify the rationale for not costing the adverse events listed below. The ERG considers that the listed adverse events could potentially be more costly than back pain, which was costed in the model:

- *leukopenia;*
- *anaemia;*
- *thrombocytopenia.*

Grade 3-4 anaemia was included in the model, with an estimated cost of £129.27.

Key opinion-leaders we consulted suggested that, because leukopenia and thrombocytopenia are laboratory abnormalities of white blood cell and platelet counts respectively, which are often asymptomatic, they would be treated only when a patient developed symptoms. As such, no costs were considered for uncomplicated leukopenia and thrombocytopenia in the model.

In cases of chemotherapy-induced uncomplicated leukopenia, the usual management is for chemotherapy to be delayed or provided at reduced dose until the white blood cell count is restored. However, patients with leukopenia are at higher risk of infection, resulting in complications such as febrile neutropenia. (Dale et al., 2002) Costs of managing febrile neutropenia, pneumonia and cellulitis have been included in the model.

Thrombocytopenia is a side effect of chemotherapy which leads to increased risk of bleeding. In cases of chemotherapy-induced thrombocytopenia, chemotherapy may be delayed or provided at a reduced dose until the platelet count is improving. This does not incur any additional cost, and so no costs were considered for

uncomplicated thrombocytopenia. In patients who experience bleeding when thrombocytopenic, platelet transfusion may be required.(Elting, et al., 2001)

An additional scenario analysis has been conducted to test the impact of alternative costs for leukopenia and thrombocytopenia on the ICER. The inclusion of costs for thrombocytopenia and leukopenia led to a slightly increased ICER, as shown in Table B13-1, below.

Table B13-1 Scenario analyses on cost of leukopenia and thrombocytopenia

Scenario	**Cost of leukopenia and thrombocytopenia**	**ICER (£)**
Base case	0	28,423.41
Scenario 1	- Cost of leukopenia £0 – Cost of thrombocytopenia £227.45 (cost of platelet transfusion)	28,435.37
Scenario 2	- Cost of leukopenia £1,626.79 (same as febrile neutropenia) - Cost of thrombocytopenia £227.45 (cost of platelet transfusion)	28,983.27

Additional references for this response:

Dale DC. Colony-stimulating factors for the management of neutropenia in cancer patients. Drugs. 2002;62 Suppl 1:1-15.

Elting LS, Rubenstein EB, Martin CG, et al. Incidence, cost, and outcomes of bleeding and chemotherapy dose modification among solid tumor patients with chemotherapy—induced thrombocytopenia. *J Clin Oncol.* 2001;19:1137—1146

B14

Please provide a confirmed UK list price (per vial).

The price of pixantrone is £553.50 per 20ml vial which contain 29mg free base pixantrone (equivalent of 50mg pixantrone dimaleate). The price in the submission was calculated based on cost per administration.

However, in responding to the clarification questions from NICE, **CTI identified an error in the submission regarding the cost of pixantrone in the original submission.** The cost per vial of pixantrone was mistakenly quoted in the submission as £343.80, which was based on the vial size given in pixantrone base instead of pixantrone dimaleate. We contacted NICE to discuss this issue and they advised us to highlight and explain the error in this response, which we have tried to do here. NICE also asked us to keep the error in both models. We have reworked the analyses and presented the health economic data in appendix Y, in the accompanying CD.

The impact of this correction on the estimate of cost-effectiveness is minor after adjusting the single vial size and cost, with an increase in the ICER from £ 28,423.41 to £ 28,503.33. The cost-effectiveness model is primarily driven by the cost of one administration of pixantrone, which, as a consequence, has increased by only 0.3%, and all the other assumptions and calculations remain the same and unchanged. For information purposes, in addition to submitting the original model (with error retained) with the new consensus-determined HITT B-cell subgroup incorporated, we have also added the corrected original submission model and the corrected model with the HITT B-cell subgroup in the appendices. CTI Life Sciences apologises

for this small error and are sorry for any subsequent confusion it may have caused/causes NICE and the ERG group in assessing Pixantrone. We recognise the importance of communicating the error to NICE/ERG and took steps to rectify it as soon as it came to light, in the interests of honesty and transparency.

SECTION C: Minor queries and potential typographical discrepancies

C1

For the subgroup of patients with histologically confirmed aggressive B-cell lymphoma (as retrospectively confirmed by central independent pathological review), please provide plots of the ratio of duration of progression-free survival in PIX301 to the duration of progression-free survival patients experienced on their last chemotherapy prior to enrolment to PIX301 based on individual patient data (one plot for the pixantrone group and one for the physician's choice group).

In PIX301, the date of progression was not captured for prior chemotherapy regimens. Duration of progression-free survival after the last chemotherapy regimen prior to enrolment was estimated as the time from the end date of the last prior regimen to the date of randomisation into PIX301.

Figures C1-1 and C1-2 plot the ratio of PIX301 PFS to the PFS for the last chemotherapy regimen prior to PIX301 for the consensus-determined aggressive B-cell lymphoma analysis set for the pixantrone and physician's choice groups, respectively.

Figure C1-1. Ratio of PIX301 Independent Assessment Panel assessment of PFS time and PFS time on last chemotherapy (consensus-determined HITT B-cell analysis set, pixantrone treatment group)

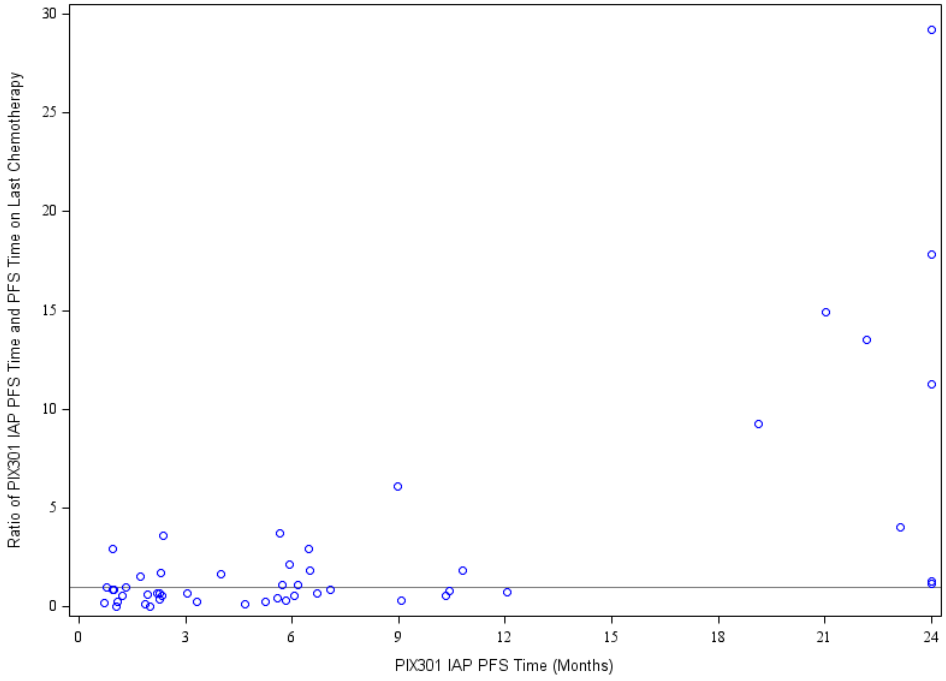
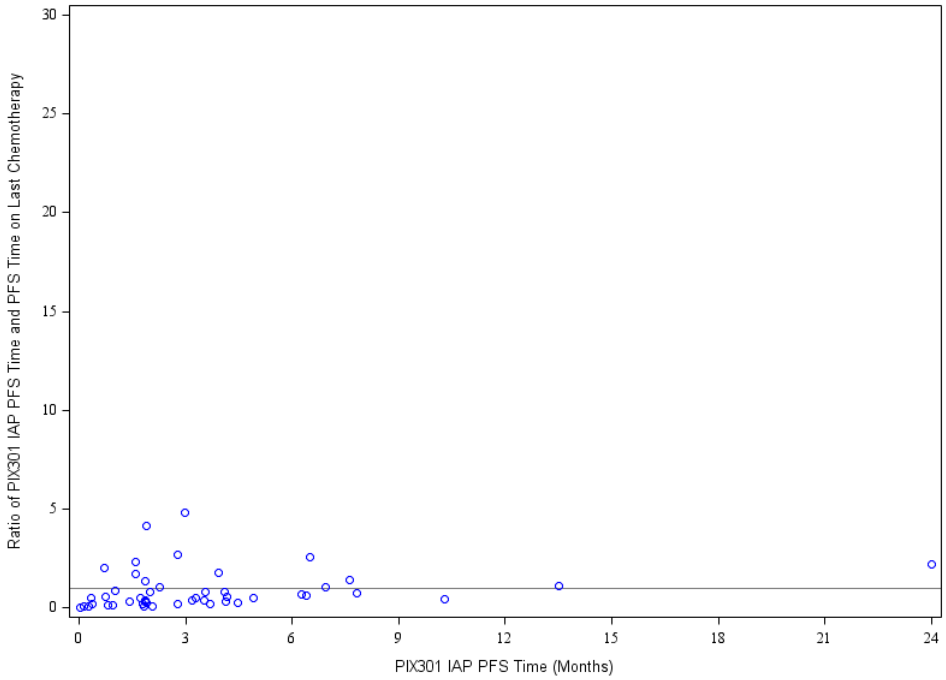


Figure C1-2. Ratio of PIX301 IAP PFS time and PFS time on last chemotherapy (consensus-determined HITT B-cell analysis set, physician's choice treatment group)



C2

Figure 5 presents data on participant flow through PIX301. Data in Figure 5 indicate that, of 70 patients randomised to pixantrone, 50 patients discontinued treatment but 52 patients entered follow-up. In the physician's choice group, of 70 randomised patients, 54 discontinued treatment but 43 patients entered follow-up. Please clarify the reasons for non-continuance (18 patients in the pixantrone group and 27 patients in the physician's choice group).

Most of the patients who did not continue into follow-up died between the end of the last treatment visit and the first follow-up visit 2 months later. The reasons patients did not continue to follow-up are summarised in Table C2-1.

Table C2-1 Reasons for not continuing to follow-up (ITT population)

	Pixantrone	**Physician's choice**
	N=70	N=70
Discontinued treatment without continuing to follow-up	18 (25.7%)	27 (38.6%)
Reason for not continuing to follow-up		
Died prior to first follow-up visit	12 (17.1%)	20 (28.6%)
Progressive/relapsed disease	2 (2.9%)	1 (1.4%)
Withdrew consent	2 (2.9%)	5 (7.1%)
Lost to follow-up or noncompliant	1 (1.4%)	0
Other	1 (1.4%)	1 (1.4%)

C3

In Tables 14, 16, and 17 (pgs 64 to 67), text reported in the table footnote indicates that the statistical significance of differences between the baseline demographics of the groups was carried out for the characteristics presented in the tables. If so, please reproduce Tables 14, 16, and 17 and include the appropriate p values.

Tables 14, 16, and 17 are reproduced below with the appropriate p-values included:

- Table 14 from the original submission is reproduced as Table C3-1;
- Table 16 is reproduced as Table C3-2;
- Table 17 is reproduced as Table C3-3.

All three tables are reported in Appendix X.

C4

Please clarify the differences (if any) between the two documents provided as accompanying documentation and labelled 20121130 Appendices A_B and 20121130 Appendices A_M. The ERG has read the documents and considers that there are no differences between the reports (number of figures and tables, and the section headings are the same in the two documents).

The two documents viewed by the ERG are indeed the same, but there should have been an additional appendices document. We believe that the files must have been corrupted during the download, as discussed with NICE. We have copied the two appendices files on the CD with this response to NICE ("Appendices to Original Submission" and "Numerical Appendices to Original Submission").

C5

Please provide reference details to support the algorithm for treatment of aggressive NHL presented in Figure 1 (pg 24) of the submission.

Figure 1 in the original submission reflects the current standard of clinical practice adopted in the management of both newly-diagnosed and relapsed/refractory aggressive NHL. It is therefore an interpretation of Figure 2 reported in the publication by Friedburg (2011), which was quoted in the submission and in the reference pack:

Friedburg JW. 2011. Relapsed/refractory diffuse large B-cell lymphoma. *American Society of Hematology Education.* December 10; 1:498-505.

C6

The outcome of "time to response" is defined as the time between the date of randomisation and the date of the initial response independent of the duration. Please clarify whether "duration" in this context refers to duration of response.

We confirm that "duration" here refers to the duration of the response.
The time to response is perceived as being independent of the duration of the response. Duration of response is typically calculated from the point at which criteria for complete or partial response are met, to the first date that recurrence or progression of disease is objectively documented.