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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

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).

Outcome	**Pixantrone**		**Physician's choice**		**p value**
	n	N	n	N	
Primary outcome (end of treatment)					
CR/CRu					
CR					
CRu					
Primary outcome (end of study)					
CR/CRu					
CR					
CRu					
Secondary outcomes					
ORR (end of treatment)					
CR					
CRu					
Partial response					
ORR (end of study)					
CR					
CRu					
Partial response					
Proportion of patients achieving a response (CR/CRu or partial response) that lasted ≥4 months					
Relative dose intensity					
	Result (end of study)	**N**	**Result (end of study)**	**N**	**HR (95% CI) (end of study)**
PFS (months)					
Median, range					
Mean (SD)					

OS (months)					
Median, range					
Mean, SD					
Time to response (months)					
Median, range					
Mean, SD					
Time to complete response (months)					
Median, range					
Mean, SD					
Duration of response (months)					
Median, range					
Mean, SD					
Abbreviations used in table: CR, complete response; CRu, unconfirmed complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation.					

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.

	Number of patients censored				
Outcome	**Pixantrone**		**Physician's choice**		**p value**
	n	N	n	N	
Primary outcome					
CR/CRu (end of treatment)					
CR/CRu (end of study)					
Secondary outcomes					
PFS					
OS					
ORR (end of treatment)					
ORR (end of study)					
Abbreviations used in table: CR, complete response; CRu, unconfirmed complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.					

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).

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.

Outcome	**Pixantrone**	**Physician's choice**	**p value**
	N	N	
Duration of study therapy in PIX301, months			
Median (range)			
Mean (SD)			
Number of cycles of therapy given during PIX301			
1			
2			
3			
4			
5			
6			
7			
8			
Median number of cycles (range)			
Mean (number of cycles (SD)			

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.

Treatment	**Physician's choice N**
Vinorelbine	
Oxaliplatin	
Ifosfamide	
Etoposide (intravenous)	
Etoposide (oral)	
Mitoxantrone	
Gemcitabine	
Rituximab	

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).

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).

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.

Subgroup	**Outcome**		
	Pixantrone	**Physician's choice**	**% difference 95% CI**
	N	N	
Prior stem cell transplant			
Yes			
No			
Patient location			
North America			
Western Europe			
Rest of the World			
Age			
≥65[a]			
<65[a]			
Gender			
Male			
Female			
[a] Age cut offs taken from full publication of PIX301.			

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?

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.

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).

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.

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.

A14
Please provide reference details to support the data on cardiotoxicity reported for the PIX203 trial.

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.

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.

	Values in submission	**Values in model**
Grade 3–4 adverse events		
Abdominal pain	0.070	–0.069
Anaemia	–0.069	–0.254
Anorexia	–0.254	–0.371
Asthenia	–0.371	–0.115
Back pain	–0.115	–0.069
Bronchitis	–0.069	–0.371
Dehydration	–0.371	–0.103
Dyspnoea	–0.103	–0.050
Ejection fraction decreased	–0.050	–0.371
Fatigue	–0.371	–0.115
Febrile neutropenia	–0.115	–0.150
Hypotension	–0.150	–0.371
Nausea	–0.371	–0.048
Neutropenia	–0.048	–0.090
Pain in extremity	–0.090	–0.069
Platelet count decreased	–0.069	–0.108
Pleural effusion	–0.108	–0.371

Pneumonia	–0.371	–0.200
Pyrexia	–0.200	–0.110
Renal failure	–0.110	–0.273
Thrombocytopenia	–0.273	–0.108
Vomiting	–0.108	–0.048
Weight decreased	–0.048	–0.117

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).

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.

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.

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.

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.

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.

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.

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).

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.

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).

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.

B14
Please provide a confirmed UK list price (per vial).

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).

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).

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.

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).

C5
Please provide reference details to support the algorithm for treatment of aggressive NHL presented in Figure 1 (pg 24) of the submission.

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.