National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma

Response to consultee and commentator comments on the draft remit, draft scope (pre-referral) and provisional matrix

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	CSAS	This is an appropriate topic as currently only palliative care options are available for people with aggressive NHL who have failed two lines of treatment.	Comment noted. No action required.
	NHS Heywood Middleton and Rochdale	This topic is appropriate for consideration as the organisations need to have the appropiate evidence in making funding decisions for chemotherapy. NHL accounts for 4% of all cancers, so although the incidence at PCT level will be small the costs can be potentially high. Further information is needed to outline the proportion of NHL that is relapsed or refractory aggressive. It may be that given the relative rareness of the condition that this appraisal would not be prioritised against more expensive therapies or those for more common conditions.	Comment noted. The scope has been updated to include an estimate of the proportion of people with NHL who have aggressive disease, and of those patients how many are expected to experience relapsed or refractory disease.
	Roche Products	None.	Comment noted. No action required.
	Royal College of Pathologists and British Society for Haematology	Yes.	Comment noted. No action required.
Wording	CSAS	Yes.	Comment noted. No action required.
	NHS Heywood Middleton and Rochdale	Clinical and cost effectiveness wording appropriate	Comment noted. No action required.

Section	Consultees	Comments	Action
	Roche Products	None.	Comment noted. No action required.
	Royal College of Pathologists and British Society for Haematology	No - there is no wording about specific clinical outcome measures and no wording about cost effectiveness in relation to other comparator costs.	Comment noted. Specific clinical outcome measures are not included in the remit. An extensive assessment of the clinical and cost-effectiveness of pixantrone compared to routine best practice will be conducted during an appraisal of pixantrone, and specific outcome measures for assessment will be outlined in the decision problem for this appraisal. No change to the remit has been made.
	Cell Therapeutics Life Sciences	Agree	Comment noted. No action required.
Timing Issues	CSAS	The marketing company is expected to submit an application for marketing authorisation to the EMEA in the third quarter of 2010.	Comment noted. No action required.
	NHS Heywood Middleton and Rochdale	Timescale appropriate would not require escalation from the perspective of the PCT. However the marketing company is expected to submit an application for marketing authorisation to the EMEA in the third quarter of 2010.	Comment noted. No action required.
	Roche Products	None.	Comment noted. No action required.
	Royal College of Pathologists and British Society for Haematology	Yes *[in response to question "is the suggested timing for submission of evidence appropriate"?].*	Comment noted. No action required.
	Cell Therapeutics Life Sciences	Agree	Comment noted. No action required.

Section	Consultees	Comments	Action
Additional comments on the draft remit	Roche Products	No.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	CSAS	This appears complete and accurate This appears complete and accurate.	Comment noted. No action required.
	NHS Heywood Middleton and Rochdale	Additional information is required on the proportion of NHL cases that are classifed as relapsed or refractory aggressive NHL and also the relationship with staging. A population incidence rate in addition to UK registrations would be preferred.	Comment noted. The scope is intended to provide a brief overview of the condition and current treatment options. It has been updated to include an estimate of the proportion of people with NHL who have aggressive disease, and of those patients how many are expected to experience relapsed or refractory disease. More detailed estimates of the incidence of aggressive relapsed or refractory NHL will be requested and considered during the appraisal of pixantrone.
	Roche Products	Treatment for relapsed DLBCL includes combination chemotherapy with or without rituximab, however there is no evidence for single agent rituximab use in the treatment pathway. According to Genactis CAF Patient Record Survey in DLBCL in 2010, 54% of relapsed DLBCL patients received rituximab in combination with chemotherapy however there was no usage of single agent rituximab in any line of therapy. Therefore, we suggest removing single agent rituximab from comparators.	Comment noted. During the scoping workshop the clinical specialists confirmed that rituximab monotherapy is rarely used in the UK for relapsed or refractory aggressive NHL. As a result, rituximab monotherapy has been removed from the list of comparators.

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	Royal College of Pathologists and British Society for Haematology	Yes.	Comment noted. No action required.
	Cell Therapeutics Life Sciences	Agree	Comment noted. No action required.
The technology/ intervention	CSAS	This is accurate.	Comment noted. No action required.
	NHS Heywood Middleton and Rochdale	Not able to assess.	Comment noted. No action required.
	Roche Products	None.	Comment noted. No action required.
	Royal College of Pathologists and British Society for Haematology	Yes *[in response to question "is the description of the technology accurate?"]*	Comment noted. No action required.
	Cell Therapeutics Life Sciences	Pixuvri (pixantrone) is only a weak inhibitor of topoisomerase II. Unlike other related agents such as doxorubicin or mitoxantrone, pixantrone is a DNA alkylator. Unlike the related agents, pixantrone does not bind iron or form alcohol metabolites resulting in minimal production of free radicals and a resultant decrease in cardiac toxicity in animal models.	Comment noted. No action required.
Population	CSAS	Yes, assuming that the treatment is suitable for all types of aggressive lymphoma	Comment noted. No action required.
	NHS Heywood Middleton and Rochdale	Population is appropriately defined however there is no definition of what is classified as adult. NHL diagnoses can occur in adolescents although the incidence is very low. It may also be useful to consider bulky disease.	Comment noted. Adults are considered to be individuals aged 18 years or older. This definition is consistent with the clinical trial population for pixantrone. All types of aggressive NHL will be considered during the appraisal of pixantrone.
	Roche Products	None.	Comment noted. No action required.
	Royal College of	Yes *[in response to question "is the population defined appropriately?"]*	Comment noted. No action required.

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	Pathologists and British Society for Haematology		
	Cell Therapeutics Life Sciences	Agree.	Comment noted. No action required.
Comparators	CSAS	Comparators are appropriate.	Comment noted. No action required.
	NHS Heywood Middleton and Rochdale	This is best addressed by clinical opinion; however the comparators appear to be appropriate.	Comment noted. During the scoping workshop the clinical specialists confirmed that all the comparators in the clinical trial except rituximab (that is, vinorelbine, oxaliplatin, ifosfamide, etoposide mitoxantrone and gemcitabine) reflect current UK clinical practice and are appropriate treatment options for relapsed or refractory aggressive NHL.
	Roche Products	Treatment for relapsed DLBCL includes combination chemotherapy with or without rituximab, however there is no evidence for single agent rituximab use in the treatment pathway. According to Genactis CAF Patient Record Survey in DLBCL in 2010, 54% of relapsed DLBCL patients received rituximab in combination with chemotherapy however there was no usage of single agent rituximab in any line of therapy. Therefore, we suggest removing single agent rituximab from comparators.	Comment noted. During the scoping workshop the clinical specialists confirmed that rituximab monotherapy is rarely used in the UK for relapsed or refractory aggressive NHL. As a result, rituximab monotherapy has been removed from the list of comparators.
	Royal College of Pathologists and British Society for Haematology	The comparators are reasonable, but typically they are used as part of a regimen and rarely on their own as single agents. In this context as single agent use would be for symptomatic palliative control.	Comment noted. The clinical specialists advised that single agent chemotherapy is a part of standard practice in the UK as either a second line treatment option for people with a low performance status or who are unable to be

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			treated with combination chemotherapy regimens, or as subsequent lines of therapy. They confirmed that all the comparators in the clinical trial except rituximab (that is, vinorelbine, oxaliplatin, ifosfamide, etoposide mitoxantrone and gemcitabine) reflect current UK clinical practice and are appropriate treatment options for relapsed or refractory aggressive NHL. No action required.
	Cell Therapeutics Life Sciences	Physicians were allowed to chose what they felt was the most appropriate comparator agent from the attached list. The choice was made based on prior therapy. It is of note that the median number of prior regimens was 3, most were multiagent, and all patients had received at least one doxorubicin or equivalent-containing regimen.	Comment noted. No action required.
Outcomes	CSAS	Complete response (CR) and unconfirmed response (CRu) have been the primary outcomes of trials. The outcomes currently listed (ORR, OS, PFS) have been secondary outcomes so far, but are to be major outcomes in new phase III trial recruiting this year.	Comment noted. The consultees agreed that 'response rate' reflected the outcome measure collected in the pivotal trial (CR/CRu). They acknowledged that the list of outcomes in the draft scope was not exhaustive and other outcome measures could be included in a sponsor's submission to NICE. It was agreed that the listed outcomes in the draft scope were appropriate and no changes to the scope were required.
	NHS Heywood Middleton and Rochdale	Seem appropriate assuming that disease regression would be included in response rate. Complete response (CR) and unconfirmed response (CRu) have been	Comment noted. The consultees agreed that 'response rate' was intended to include disease

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		the primary outcomes of trials. The outcomes currently listed (ORR, OS, PFS) have been secondary outcomes so far, but are to be major outcomes in new phase III trial recruiting this year.	regression. They acknowledged that the list of outcomes in the draft scope was not exhaustive and other outcome measures could be included in a sponsor's submission to NICE. It was agreed that the listed outcomes in the draft scope were appropriate and no changes to the scope were required.
	Roche Products	None.	Comment noted. No action required.
	Royal College of Pathologists and British Society for Haematology	Yes *[in response to question "will these outcomes measures capture the most important health related benefits and harms of the technology?"]*	Comment noted. No action required.
	Cell Therapeutics Life Sciences	No quality of life data is available however meaningful increases in durable complete responses and progression free survival with a 21% improvement in overall survival was observed compared to other available therapies.	Comment noted. No action required.
Economic analysis	CSAS	None.	Comment noted. No action required.
	NHS Heywood Middleton and Rochdale	The time horizon is not specified.	Comment noted. No action required.
	Roche Products	The proposed economic analysis and time horizon is appropriate.	Comment noted. No action required.
Equality and Diversity	CSAS	None.	Comment noted. No action required.
	NHS Heywood Middleton and Rochdale	Ethnicity recording of patients may be useful	Comment noted. Ethnicity is not considered to be a factor which would restrict an individual's access to this technology. No action required.
	Roche Products	None.	Comment noted. No action required.
Innovation		No comments on innovation were received from consultees or commentators	No action required.
Other	CSAS	Subgroups could be considered according to type of aggressive NHL	Comment noted. During the scoping

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considerations		(assuming use is not restricted by type, e.g. diffuse large B cell), stage, and by prior chemotherapy regimen and whether HSCT was used	workshop the clinical specialists advised that there are no prospectively defined subgroups in the pivotal clinical trial. They further emphasised that the trial population was small and it would not be possible to produce an adequately powered sample of patients from the trial to allow a robust analysis of the suggested subgroups. There was agreement that no subgroups need to be specified in the draft scope.
	NHS Heywood Middleton and Rochdale	Subgroups could be considered according to type of aggressive NHL (assuming use is not restricted by type, e.g. diffuse large B cell), stage, and by prior chemotherapy regimen and whether HSCT was used	Comment noted. During the scoping workshop the clinical specialists advised that there are no prospectively defined subgroups in the pivotal clinical trial. They further emphasised that the trial population was small and it would not be possible to produce an adequately powered sample of patients from the trial to allow a robust analysis of the suggested subgroups. There was agreement that no subgroups need to be specified in the draft scope.
	Roche Products	None.	Comment noted. No action required.
	Cell Therapeutics Life Sciences	Achieving a complete remission is rare in multiply relapsed aggressive NHL and is associated with improvement in lymphoma-related symptoms, reduces the need for additional therapy, and was associated with substantial prolongation of progression free survival, all clinically beneficial outcomes. These factors should be associated with favorable cost of care measures although these were not directly assessed in the current trial	Comment noted. No action required.

Section	Consultees	Comments	Action
Questions for consultation	CSAS	Consideration should be given to whether this appraisal should be deferred until after the results of this years planned phase III trial are known.	Comment noted. The consultees discussed the design of the planned Phase III trial and agreed that the choice of comparators (that is either rituximab monotherapy or gemcitabine in combination with rituximab) did not reflect current clinical practice in the UK, and therefore it would be unlikely that results from this trial would add any additional value to an assessment of pixantrone in the UK. Consequently, it was agreed that the proposed timing of the appraisal was appropriate and that a delay to wait for results from the planned Phase III trial was unnecessary.
	NHS Heywood Middleton and Rochdale	Consideration should be given to whether this appraisal should be deferred until after the results of this years planned phase III trial are known.	Comment noted. The consultees discussed the design of the planned Phase III trial and agreed that the choice of comparators (that is either rituximab monotherapy or gemcitabine in combination with rituximab) did not reflect current clinical practice in the UK, and therefore it would be unlikely that results from this trial would add any additional value to an assessment of pixantrone in the UK. Consequently, it was agreed that the proposed timing of the appraisal was appropriate and that a delay to wait for results from the planned Phase III trial was unnecessary.

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	Roche Products	As noted above, there is no evidence of usage of single agent rituximab in the treatment of relapsed DLBCL in the UK (Genactis, CAF Patient Record Survey, Q2 2010), therefore, single agent rituximab in not appropriate comparator.	Comment noted. During the scoping workshop the clinical specialists confirmed that rituximab monotherapy is rarely used in the UK for relapsed or refractory aggressive NHL. As a result, rituximab monotherapy has been removed from the list of comparators.
	Royal College of Pathologists and British Society for Haematology	*Question: What do you consider to be the relevant clinical outcomes and other potential health related benefits of the technology particularly when compared with other currently avaialble treatment options?* Overall survival, progression-free survival, response rate, toxicity of the agent, health-related quality of life. *Question: Please identify the nature of the data which you understand to be available to enable the Committee to take account of these benefits.* Results of clinical trials , publications in peer reviewed journals needed.	Comment noted. No action required.
	Cell Therapeutics Life Sciences	The pivotal trial achived statistical significance for Complete Response and Unconfirmed Complete Response Rates (`p=0.009 at end of study); Overall Response Rate (p=0.001); Progression Free Survival (HR=0.56; p = 0.002); and a trend (21% improvement) toward improvement in Overall Survival (HR=0.79;p=0.215) Question 2: Pixantrone may ultimately prove to be a safer alternative for doxorubicin in patients with aggressive NHL at high risk for cardiac toxicity such as patients with intrinsic cardiac disease, severe hypertension, and the elderly. This attribute may also be of significant importance in pediatric malignancies where anthracyclines based therapies, while often curative, can lead to late onset severe cardiac toxicity. Question 4: Data to be available to the committee include the clinical	Comment noted. No action required.

Section	Consultees	Comments	Action
		trial report or the Summary or Clinical Safety and Efficacy.	
Additional comments on the draft scope.	NHS Heywood Middleton and Rochdale	None.	Comment noted. No action required.
	NCRI/RCP/RCR/ACP/JCCO	The NCRI/RCP/RCR/ACP/JCCO are grateful for the opportunity to comment on this draft scope. We do not believe there is any data currently available that would make for a meaningful appraisal by NICE. We are aware that the US FDA advisory panel recently voted unanimously to reject the application by Cell Therapeutics for accelerated approval of its drug pixantrone dimaleate (Pixuvri) on the basis of results of the EXTEND trial.	Comment noted. It was agreed that modest data was available from the EXTEND trial and that the comparators in this trial (except rituximab monotherapy) were relevant to standard practice in the UK. The consultees noted that the FDA had rejected the accelerated approval of pixantrone in the US based on the EXTEND trial because the trial included comparators that did not necessarily reflect current practice in the US (and instead better reflected practice in the UK and EU), and therefore further studies were required. No action required.
	Roche Products	None.	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Lymphoma Association
Macmillan Cancer Support
Welsh Government
NHS Quality Improvement Scotland
Public Health Wales NHS Trust
Royal College of Nursing
Sanofi-aventis
Medicines and Healthcare products Regulatory Agency (MHRA)
Department of Health

Comment 3: the provisional matrix

Version of matrix of consultees and commentators reviewed: **Provisional matrix of consultees and commentators sent for consultation**					
Summary of comments, action taken, and justification of action:					
	Proposal:	**Proposal made by:**		**Action taken: Removed/Added/Not included/Noted**	**Justification:**
1.	Remove British National Lymphoma Investigation from relevant research group consultees.	NICE Secretariat		Removed	British National Lymphoma Investigation has now closed, and therefore been removed from the matrix.
2.	Add Allied Health Professionals Federation to general group commentators.	NICE Secretariat		Added	Allied Health Professionals Federation meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general group commentator.
3.	Remove Sue Ryder Care from patient/carer group consultees.	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. Sue Ryder Care has not been included in the matrix of consultees and commentators.