National Institute for Health and Clinical Excellence

Multiple Health Technology Appraisal (MTA)

Follicular lymphoma - rituximab (review of TA110)

Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Lymphoma Association	Staging of advanced follicular lymphoma can be more complicated than the draft scope suggests. Some people will have what appears to be stage II disease but may have other test results suggesting the need for treatment as advanced disease. Early stage disease is relatively rare. Most patients have advanced disease at the time of diagnosis. The section discussing treatment could do with a shift in emphasis and some clarification. The aim of treatment for advanced disease is to achieve the best quality remission possible, for as long as possible, with as good a quality of life as possible. Prolonging survival is a clearly a desirable outcome, but perhaps not the first thing on the list of treatment objectives. First line treatment options for advanced disease are: watchful waiting, immuno-chemotherapy (R-chemo) or oral single agent chemotherapy for people who cannot tolerate intravenous chemotherapy regimens. Some patients will be ineligible for treatment with rituximab, in which case they will be offered combination therapy without rituximab. Currently used regimens include steroids.	Comments noted. The draft scope has been updated. Please note the scoping document is only intended to provide a brief summary of the condition and its management.

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	Institute for Cancer Research	With respect to the comment about prognosis it would be important to include that prognosis of Follicular lymphoma and therefore management, is variable and dependent on histological grade (WHO classification grades I, II, IIIA, IIIB) and a prognostic score (FLIPI). An explanation of these would be useful. Despite a long median survival, Follicular lymphoma is generally considered incurable with the aim of treatment being a durable remission (disease free interval).	Comment noted. Information on the treatment of follicular lymphoma has been updated in the scope. Please note the scoping document is only intended to provide a brief summary of the condition and its management.
	Royal College Pathologists	This information is accurate. Follicular lymphoma is the second most frequent non-Hodgkin Lymphoma (NHL). Approximately 80 % present with stage III or IV disease. Previous studies have demonstrated no survival benefit in treating asymptomatic follicular lymphoma patient with advanced disease. Patients are therefore managed with an expectant approach with active surveillance until they develop symptoms requiring treatment.	Comment noted.
	NHS North of Tyne on behalf of North Tyneside PCT	The information appears accurate	Comment noted.
	Roche Products	For accuracy, Roche suggests amending sentence in 5th paragraph to "First-line treatment options for stage III or IV follicular lymphoma include single-agent or combination (immuno-) chemotherapy regimens based on alkylating agents, with or without steroids"	Comment noted. The scope has been amended accordingly.
The technology/ intervention	Lymphoma Association	The Lymphoma Association welcomes the expansion of the product license to include any chemotherapy regimen. This allows individual clinicians and patients to choose therapy based on individual tolerance, co-morbidity, options for future treatment, and patient choice.	Comment noted

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	Institute for Cancer Research	Yes	Comment noted.
	Royal College Pathologists	The description of the technology is accurate. R-CVP is recommended in NICE guidance TA110 as a front line treatment (Marcus, Blood 2005). The rituximab UK marketing authorisation for this indication has now been extended from R-CVP to rituximab in combination with any chemotherapy regimen. This application seeks to extend the NICE guidance accordingly. There are no details of possible alternative chemotherapy regimens used in combination with rituximab. The addition of rituximab to chemotherapy has shown to be beneficial in terms of response rate and progression free survival in a number of phase III studies. Other chemotherapy regimens used in these studies include CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), FCM (fludarabine, cyclophosphamide, mitozantrone), FM (fludarabine and mitozantrone) (Hiddenmann Blood 2005, Forstpointner, Blood 2004, Zinzani,J Clin Oncol 2004). Rituximab in combination with single chemotherapy agents (chlorambucil, bendamustine or fludarabine) might be appropriate for older individuals with co-morbidities although phase III data is often lacking. The most appropriate first-line treatment for follicular lymphoma patients should be risk adapted and individualised taking into account co-morbidities. Extending the NICE guidance for front line treatment of follicular lymphoma to allow other R-chemotherapy combinations will allow physicians to use their clinical acumen and evidence based approach to treatment where possible.	Comment noted.
	NHS North of Tyne on behalf of North Tyneside PCT	The description of the technology is accurate	Comment noted.

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	Roche Products	Yes	Comment noted.
	School of Health and Related Research (ScHARR), University of Sheffield	a) The technology is described as rituximab in combination with chemotherapy. We note that there are a number of chemotherapies used in the treatment of follicular lymphoma. It would be helpful to define a list of the chemotherapies administered with Rituximab. b) Whilst the scope clearly defines first-line use treatment, the most cost-effective intervention may be dependent on subsequent treatments, i.e. treatment algorithms may well need to be considered. It is unclear at present if this is the intention of the scope and further clarification is required. Does the scope intend that the output be an 'optimum overall ordering' of treatments? If so, this needs to be made clear in the final scope. c) We note there is a closely related Single Technology Appraisal (STA) going ahead: Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy. A potential issue could arise if the results from the maintenance STA were dependent on an assumed first line treatment option that was not estimated to be the most cost-effective option within this appraisal (review of TA110) or alternatively in assessing the subsequent treatment options we arrive at a different conclusion than the maintenance STA. If so, would we expect the results of the STA to be invalidated?	Comments noted. Advice on specific chemotherapy regimens relevant to this appraisal will be sought during the course of the appraisal.
Population	Institute for Cancer Research	This should extend to Stage II patients with poor risk features deemed to require systemic chemotherapy. (for example, higher histological grade, higher FLIPI score, bulky disease)	Comment noted. Guidance will only be issued in accordance with the marketing authorisation.

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	Royal College Pathologists	Yes the population is appropriately defined	Comment noted.
	NHS North of Tyne on behalf of North Tyneside PCT	The population is accurate. Subgroup analyses could consider people with indolent and aggressive forms, and people with HIV or AIDS.	Comment noted. Only subgroups in whom rituximab is expected to be more clinical effective and cost-effective will be considered.
	Roche Products	For clarity, Roche suggests to please amend this section to read: “Adults with stage III-IV follicular lymphoma who are symptomatic and have not received previous chemotherapy”	Comment noted. The population in the scope has been amended accordingly.
	School of Health and Related Research (ScHARR), University of Sheffield	The population is appropriately defined. We do not believe there are any groups within the population that should be considered separately	Comment noted.

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Comparators	Lymphoma Association	It is difficult to stipulate comparators, as there are no real comparators for eligible patients. R-chemo has been standard first line therapy for some years, combining rituximab with CVP, CHOP and fludarabine-based regimens. The only people offered an alternative to R-chemo are those who cannot tolerate or would not choose intravenous chemotherapy – for reasons of frailty or co-morbidity, for example – or those with B-cells that do not produce CD20. Single agent oral chemotherapy is useful for many patients, especially those in later life. Recent research suggests that R+bendamustine might be a valuable first line treatment for advanced follicular lymphoma. A study that compared R-B with R-CHOP was presented at the American Society for Haematology conference in November 2009 (Rummel et.al.). However, it does not have a product license for first line treatment, and is currently only licensed for relapsed or refractory disease, so is perhaps a comparator for future revision of this guidance.	Comments noted. Advice on specific chemotherapy regimens relevant to this appraisal will be sought during the course of the appraisal.
	Institute for Cancer Research	Yes	Comment noted.
	Royal College Pathologists	Yes, although it would be helpful if a summary of trial data and meta-analyses are provided for the appraisal to facilitate an informed decision.	Comment noted.
	NHS North of Tyne on behalf of North Tyneside PCT	Yes. Chemotherapy regimens could be specified, and comparison also made to nucleoside analogues, alkylating agents and chemo-immunotherapy. Chemotherapy may also be supplemented by radiation therapy. Autologous or allogeneic BMT or PSCT is being evaluated for treatment of patients at high risk of relapse.	Comment noted. Advice on specific chemotherapy regimens relevant to this appraisal will be sought during the course of the appraisal.

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	Roche Products	Yes	Comment noted.
	School of Health and Related Research (ScHARR), University of Sheffield	a) Is treatment sequencing intended to be included in the scope? (See previous comments relating to the technology/intervention). Is it expected that a hierarchy of chemotherapy with Rituximab would be established within this appraisal? We note that there are a number of chemotherapies used in the treatment of follicular lymphoma, including those that are not given in combination with Rituximab e.g. Ibritumomab tiuxetan. In the Single Technology Appraisal in preparation: Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy, Ibritumomab tiuxetan is listed as a comparator for Rituximab maintenance therapy. b) Is Ibritumomab tiuxetan a comparator in this appraisal? c) It would be helpful to define a list of all comparators for the intervention.	Comments noted. Advice on specific chemotherapy regimens relevant to this appraisal will be sought during the course of the appraisal.
Outcomes	Lymphoma Association	Would suggest that quality of remission and duration of remission, and health related quality of life, are the outcome measures of principle interest to patients, with overall survival as a desirable consequence. Some clinicians will also seek to treat patients with a view to high dose therapy and stem cell transplant in first remission. Consideration of quality of remission is important in this context.	Comment noted. The outcomes in the scope have been amended accordingly.

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	Institute for Cancer Research	Yes	Comment noted.
	Royal College Pathologists	The outcome measures are appropriate.	Comment noted.
	NHS North of Tyne on behalf of North Tyneside PCT	Yes. Terms could be further extended to include event-free survival and relapse-free survival	Comment noted.
	Roche Products	Yes	Comment noted.
	School of Health and Related Research (ScHARR), University of Sheffield	All outcomes listed appear appropriate. The only comment is that whilst progression-free survival is listed (defined as time from start of treatment to the onset of disease progression), in follicular lymphoma, treatment may not be initiated immediately after disease progression and a 'watch and wait' approach used. Therefore, the time to next treatment and progression free survival times may differ. This may have an impact on the cost-effectiveness of the treatment strategies. As such, time to next treatment may be a worthwhile outcome measure.	Comment noted. The outcomes in the scope have been amended accordingly.
Economic analysis	Institute for Cancer Research	none	Comment noted.
	Royal College Pathologists	Appropriate	Comment noted.
	Roche Products	Yes	Comment noted.

Section	Consultees	Comments	Action
	School of Health and Related Research (ScHARR), University of Sheffield	We have no comments on the economic analysis section.	Comment noted
Equality and Diversity	Institute for Cancer Research	none	Comment noted.
	Royal College of Pathologists	The UK population is an aging population and the incidence of follicular lymphoma increases with age. Therefore, to avoid discrimination of older patients with pre-existing co-morbidities it is important for the NHS to fund effective treatments which may include rituximab. These older patients are often under-represented in clinical trials and less likely to tolerate the more intensive combination chemotherapy regimens.	Comment noted.
	Roche Products	None	Comment noted.
	School of Health and Related Research (ScHARR), University of Sheffield	We don't believe there to be any issues that require special attention in relation to this technology in order to eliminate unlawful discrimination and promote equality.	Comment noted.
Other considerations	Roche Products	None	Comment noted.

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	School of Health and Related Research (ScHARR), University of Sheffield	We have no additional comments	Comment noted.
Questions for consultation	Lymphoma Association	See above re comparators. There are no subgroups of patient to be singled out for this appraisal. Re relevant outcomes, see above. No issues re unlawful discrimination and equality	Comment noted

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	Institute for Cancer Research	1. The most appropriate comparators have been used. 2. Rituximab has shown benefit in all groups of Follicular lymphoma requiring systemic chemotherapy so no subgroup should be excluded. 3. The relevant clinical outcomes are progression-free survival, overall survival, response rate (either radiological or metabolic) Quality of Life and toxicity. 4. The major recent data relating to this appraisal is the release of the PRIMA study results of the benefit of maintenance rituximab after first-line chemotherapy plus rituximab. The PRIMA study results support this review, full results are to be released at the ASCO 2010 conference however the investigators have reported that the study has achieved its primary endpoint of an increase in Progression Free Survival by 45% (ie median PFS 37.2 to 54 months) with the addition of maintenance Rituximab to either R-CVP, R-CHOP or R-FCM chemotherapy in 1019 randomised follicular lymphoma patientspatients with a median follow up of 24 months. This study included maintenance rituximab which was continued every 2 months for 2 years after the 8 cycles given in combination with chemotherapy. 5. No specific issues pertaining to unlawful discrimination or promotion of equality require special attention.	Comments noted.
	Roche Products	Q. Please identify the nature of the data which you understand to be available to enable the Appraisal committee to take account of these benefits A. Several large randomised phase III studies and a meta-analysis plus supportive data from retrospective cohort studies and phase II trials. All other questions have already been addressed in the main body of this document.	Comment noted.

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	School of Health and Related Research (ScHARR), University of Sheffield	Nature of the evidence available: We believe there to be trials relating to rituximab in combination with the following agents: 1) Cyclophosphamide, vincristine and prednisolone (CVP) 2) Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) 3) Bendamustine	Comment noted.
Additional comments on the draft scope.	Lymphoma Association	It is our view that both clinicians and patients are concerned about the constraints that are a potential consequence of NICE guidance. It is important that guidance does not impinge on the careful assessment of factors in each individual case such as the age at presentation, co-morbidities, the patient's views on treatment and what side effects they are prepared to put up with. This is a complex disease, that typically affects those in later life, and its potential complexity demands careful individual assessment.	Comment noted.
	Roche Products	No	Comment noted.
	School of Health and Related Research (ScHARR), University of Sheffield	None	Comment noted.

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

The Public Health Wales NHS Trust
Marie Curie Cancer Care
Royal College of Nursing
Welsh Assembly Government