NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (review of technology appraisal guidance 37)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (October 2007)

Consultee or commentator	Comment	Institute response
Roche	For full details of manufacturer's response to the ACD, including the further analyses and clarifications requested in the preliminary recommendations please see separate document. **Alternative survival analysis provided by Roche in response to the ERG clarification letter** Several of the questions raised in section 4.14 of the ACD can be addressed through reference to the further analysis provided by Roche within our response to the ERG clarification letter. For example, the ACD fails to acknowledge the analysis presented in tables 1 and 2 of the Roche clarification letter. This analysis illustrates that the selected Weibull curve by Roche generated the smallest incremental clinical benefit for rituximab dual therapy, thus utilizing any other curve would lead to increased clinical benefit and a reduced ICER for rituximab dual therapy. The ACD fails to give reference to this important evidence when evaluating the appropriateness of the Roche estimates of the long term	See below for responses to detailed comments The Committee wanted further analysis which took into account the event-free period when fitting the model (see FAD sections 3.14, 4.7 and 4.11).

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	clinical benefits of rituximab.	
	Actual RCT reported post progression treatments / costs Section 4.7 of the ACD states how the Appraisal Committee: "thought that it was appropriate to calculate costs at progression by aggregating treatments into categories, and it agreed with the ERG's assumptions as to how these would vary across the treatment strategies". Roche consider this a step down in the hierarchy of evidence presented to the Appraisal Committee. The original Roche submission made available the actual treatments received post progression within the EORTC study for each arm. Costing data captured from within the RCT of interest is traditionally seen as the optimum source of resource use and costing evidence. Had Roche not utilised this evidence and adopted the more arbitrary non-evidence based approach, undoubtedly this would have raised criticism by the Appraisal Committee.	The Committee accepted the approach of aggregating costs to minimise the effect of widely varying costs between strategies. (See FAD 4.6)
	Inaccurate representation of event-free period within Roche economic model Section 4.8 of the ACD states: "It noted that there was no initial zero-hazard period modelled, but there was a protocol-driven event-free period in the data. The Committee agreed that including an event-free period could change the goodness-of-fit of any distribution fitted to trial data and influence the outcome of the cost-effectiveness	

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	analysis” The Roche economic model, as outlined in the original Roche submission (page 98, Roche STA submission) utilises the actual Kaplan Meier data direct from the EORTC study for the first 2 years of the model. The extrapolated curves are only utilised beyond this time horizon. Consequently for the ACD to state that an event-free period was not modelled is both incorrect and misleading. This event-free period was also included when estimating the extrapolated curves in the original Roche economic model. However for sensitivity analysis, the extrapolated curves have since been estimated and subsequent ICER reported when this event-free (zero hazard) period is excluded. The analysis in section one above confirms that the significance of this event-free period is very small when estimating both the extrapolated curves and the ICER for dual therapy rituximab.	The Committee wanted to know the effect of excluding the event-free period on model fitting and resulting changes in extrapolated costs and benefits.
	Inaccurate representation of assumed treatment benefit within Roche economic model Section 4.9 of the ACD reports that: “the Committee considered that assuming proportional hazards from data over the RCT follow-up period and then extrapolating parametric models beyond the trial period, would assume that the treatment benefit observed in the trial would persist over the duration of the extrapolation. The Committee concluded that the manufacturer’s approach to survival	

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	modelling could overestimate the clinical and cost effectiveness of rituximab” The ACD fails to give reference to the fact the Roche economic model assumes no treatment benefit for rituximab after 5 years (with further sensitivity analysis further curtailing this to 2 years). As evidence within the Roche response to the ERG clarification letter clearly indicates, firstly alternative parametric curves generated a higher incremental clinical benefit than the selected curve and secondly the treatment benefit was not assumed over the entire duration of the economic model. Consequently Roche considers the above statement within the ACD both incorrect and misleading in relation to the survival analysis by Roche. The under-estimation of clinical benefits could equally apply based upon the evidence presented to the committee.	The Committee was aware that limiting the duration of treatment benefit or limiting the time horizon would underestimate the cost-effectiveness of the intervention and requested further analysis addressing concerns with the survival modelling. See FAD 4.9)
	Inaccurate representation of relationship between post progression treatments and outcomes One of the main reasons that the Appraisal Committee rejected the trial-based evidence of drug treatment upon disease progression relates to the claim that the economic model does not capture the subsequent outcomes related to these specific treatment distributions. Considering the Kaplan Meier overall survival data utilised within both the economic model and for the purposes of curve estimation will reflect the treatments actually utilised within the	The Committee was concerned that the points raised here would not apply over the entire duration of the extrapolation and requested further analysis.

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	trial post progression, this reasoning for rejecting the trial based costs appears flawed.	
	Reasons why £43,000 ICER is uncertain are incompletely reported within ACD As illustrated in the introduction to section 1 above, the main reason the ICER for rituximab dual therapy exceeds £30,000 in the ERG's analysis is through the use of Kaplan Meier data only and the rejection of any curve extrapolation, a conventional requirement in order to estimate the lifetime costs and benefits of an intervention as set out in the Guide to Methods of Technology Appraisal. However section 4.12 of the ACD reports that: "the committee thought this high ICER could indicate that this strategy is not cost effective, but was aware that the limited availability of data for the ERG's probabilistic sensitivity analysis comparing the cost effectiveness of multiple strategies made this analysis uncertain". The ACD implies that the absence of suitable PSA is the reason for uncertainty around the high ICER, when the ERG selection of survival data is clearly the primary reason for the high ICER and subsequent uncertainty.	The Committee noted the concerns with the survival modelling and also the limitations of analysis based on K-M data. (See FAD 4.8 and 4.9) The Committee requested further analysis to include a PSA so as to indicate the probability that the strategy of induction was cost-effective when compared to the strategy of maintenance that it had recommended.
	Firstly they currently fail to recommend the most clinically effective treatment strategy for follicular lymphoma patients, despite this being demonstrated to be cost effective compared to current standard of care, as confirmed within the conclusion	The Committee took the view that, following the recommendation of maintenance, that this would become the

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	of the ERG report. The only rationale presented for ignoring this fact is the assertion in section 4.11 of the ACD that maintenance therapy was considered the clinical priority and therefore will become standard of care following this appraisal. However one could equally argue that following this appraisal dual therapy should become the new standard of care as it is cost effective compared to current standard of care (no rituximab use). Secondly the current guidance being based inappropriately upon an estimated ICER of £43,000 for dual therapy, does not take a lifetime time horizon and thus adequately consider the potential longer term benefits of rituximab. Consequently, current guidance is based on utilizing analyses which are inconsistent with NICE's own Guide to Methods of Technology Appraisal and its reference case methods.	appropriate comparator for induction. (See FAD 4.8) The Committee was aware of the limited time horizon and requested further analysis. (See FAD 4.9)
British Society for Haematology, Royal College of Physicians/Royal College of Pathologists Intercollegiate Committee in Haematology	I do believe all the appropriate evidence has been reviewed in this document and I am pleased that the original recommendation of Rituximab mono-therapy for patients when all alternative treatment options have been exhausted remains. This is a small group of patients but nonetheless in those with no chemotherapy options or particularly those without the haematological reserve to continue with chemotherapy, this is an extremely useful and active treatment modality.	Noted.
	…recommendation 1.3 first which is that the ACD does not recommend the use of Rituximab in combination with	The Committee was aware of the higher response rates when rituximab was

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	chemotherapy for induction of remission of patients with relapsed stage 3 or 4 follicular non-Hodgkin's lymphoma. This seems a somewhat strange decision as the evidence for the combination of Rituximab with chemotherapy in the two trials that you have reviewed extensively, shows a significant increase in response rates in those patients receiving the combination and those response rates translate into significant improvements in progression free survival. There is every likelihood that these improvements will translate into overall survival benefits as is being seen with the similar trials for newly diagnosed patients.	included in induction therapy. Following further analysis rituximab is recommended for induction. (See FAD 4.3 and 4.11)
	There is an assumption through this document that patients at relapse will have received Rituximab as part of induction therapy following on from the recent recommendation to Rituximab in combination with CVP chemotherapy for newly diagnosed patients requiring therapy. The vast majority of patients requiring treatment for relapse over the next few years are going to be Rituximab naive and so this cohort of patients is going to be refused access to this drug as a consequence of when they were diagnosed. It is also clear, although in a limited number of patients, that the addition of Rituximab to chemotherapy derives an equal benefit with regards response, whether those patients relapse following chemotherapy or following immuno-chemotherapy.	The Committee was aware of the concerns regarding the efficacy of rituximab in patients who had already received it previously as the trial was conducted in rituximab-naïve patients. (See FAD 4.4) Rituximab is recommended for induction.
	With regards recommendation 1.2, the use of Rituximab mono-therapy as maintenance. The addition of Rituximab to chemotherapy for follicular lymphoma produces significant	The Committee was aware of the higher response rates when rituximab was included in induction therapy. Following

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	increases in overall response rates thereby limiting Rituximab maintenance to those patients that have had a response (which I assume you define as a complete remission together with a partial remission) will mean that significantly fewer patients will be eligible to receive Rituximab. Using CHOP as an example approximately 13% of patients will not get a response by failing to have the addition of Rituximab to the chemotherapy and these patients will then not be eligible for Rituximab by way of maintenance. So what you have done here is reduce the likelihood of people getting response by limiting access to Rituximab with chemotherapy and those patients then fail a second time because they will not be eligible for Rituximab in a maintenance setting.	further analysis rituximab is recommended for induction. .
NCRI Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Joint Collegiate Council for Oncology, Association of Cancer Physicians	We welcome the review and agree that the relevant evidence of clinical benefit has been considered. We agree that the review of guidance 37 relating to use of Rituximab as a single agent in second or subsequent relapse has reached the appropriate conclusion, as expressed in recommendation 1.1. We also agree with the recommendation that Rituximab be available as maintenance therapy following successful treatment of recurrence with chemotherapy, but would also recommend maintenance Rituximab be given after treatment with chemotherapy-Rituximab in combination.	Noted
	We do not concur with the view that chemotherapy alone (without Rituximab) should be recommended for the treatment of recurrent follicular lymphoma, as put forward in	Rituximab is recommended for induction

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	recommendation 1.3. This conclusion is not sound and would not constitute a suitable basis for preparation of guidance to the NHS.	
	We were not persuaded by the ERG calculation of cost per QALY decreasing the duration of treatment benefit to 2 years. No logical argument was advanced for this limitation of benefit which appears to artificially inflate the cost. An equally good clinical argument could be made for a benefit horizon of 3, 5 or 10 years.	The Committee was aware of the effect on cost-effectiveness estimates of assuming varying durations of treatment benefit. (See FAD 4.11)
	The assertion that Rituximab will be generally given as day-case rather than out-patient therapy owing to the duration of infusion (para 3.9) is incorrect. The practice of rapid (90 minute) administration is now widespread following description of its safety in the literature (Sehn et al., Blood. 2007 May 15; 109(10):4171-3).	Noted.
	The most important consideration in denying patients access to chemotherapy-Rituximab combination for re-induction of remission is that the response rate has been consistently shown to be lower for chemotherapy alone. Since patients will only receive maintenance therapy if they have shown a response to re-induction therapy, the lower response rate would deny a significant proportion of patients access to maintenance therapy, which the appraisal committee has already indicated should be made available. The net effect would be to contradict the committee's own recommendation in 13%-24% of patients: this is the difference	See above

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	in response rates with or without Rituximab in the EORTC and German Low Grade Lymphoma Study Group trials respectively. It is therefore the proportion of patients who would go on to receive maintenance Rituximab after Rituximab-chemotherapy, but not after chemotherapy alone. It would be perverse to recommend a treatment, and simultaneously make a recommendation which would deny that treatment to around 20% of those who would benefit from it.	
The Royal College of Pathologists	Do you consider that all the relevant evidence has been taken into account? No. The assumption has been made that the benefit of rituximab would end at 1500 days. This would have been the case if the survival curves had come together at the end of this time, which they do not. Clinical experience is that the benefits of rituximab extend beyond this time and evidence from other trials of rituximab in lymphoma demonstrates that this is so.	The Committee was aware of the effect on cost-effectiveness of assuming varying durations of treatment benefit. (See FAD 4.9 and 4.11)
	Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate? No. The use of 1500 days as an end point for benefit inflates the cost of rituximab so that it falls outside the range normally regarded as acceptable. A longer supposed benefit would bring the cost down. At present maintenance rituximab is recommended, but inclusion of rituximab as part of the	The Committee did consider further analysis which varied the duration of treatment benefit assumed.

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	reinduction regimen is not as it appears too costly. This would likely be changed by considering a more extended benefit.	
	Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance for the NHS? No, for the above reasons. Also extra information has been asked for from the manufacturer. This information may well change the thrust of the review.	Following further analysis rituximab is now recommended for induction.
	Are there any equality related issues that need special consideration that are not covered in the ACD? Possibly. If rituximab is not used as part of the reinduction regimen then fewer patients will be eligible for maintenance rituximab. Those denied rituximab because they failed to achieve CR might be considered to have a legitimate grievance.	Noted. Following further analysis rituximab is now recommended for induction.
Clinical specialist	I think all the relevant evidence has been taken into account. The summaries are reasonable and views appropriate. The provisional recommendations are reasonable. There are no special equality related issues.	Noted
	There is good clinical evidence that rituximab, given with 'induction' chemotherapy, does give added benefit but I acknowledge that the best cost-effectiveness may be achieved with maintenance only.	Noted.
Web response	I am concerned by recommendation 1.3. It is now standard	Rituximab is recommended for induction

Consultee or commentator	Comment	Institute response
NHS Professional	practice to use rituximab in combination with chemotherapy for induction of remission in patients with relapsed follicular lymphoma in the UK and the rest of the world. Without Rituximab there is a significant reduction in response rate and consequently outcome.	in the FAD
Web response NHS Professional	Although Rituximab has frequent mild side effects, especially with first infusion it is extremely uncommon to see severe reactions. It is by cancer therapy standards an incredibly safe agent.	Noted
Web response NHS Professional	Both the trials submitted show clinically highly important improvements in response when rituximab is added to chemotherapy. Without the benefit of rituximab some 15% of patients will have been exposed to a pointless course of chemotherapy. This is likely to increase the resistance of their disease to future treatment and they will not be in a position to benefit from the clear advantage of Rituximab maintenance therapy. The cost of rituximab administration is not 500. When given at the same time as chemotherapy it will not attract an additional day case admission charge. Indeed when the chemotherapy tariffs are introduced in the near future it will all be bundled together with the cost of CHOP and although it would be very nice I do not believe that anyone will suggest giving us an extra 500.	The Committee was aware of the increased rate of response when rituximab is added to chemotherapy for induction. Administration costs for rituximab were not assumed to be additional when given with chemotherapy but only when given alone for maintenance. Rituximab is recommended for induction with chemotherapy in the FAD
Web response NHS Professional	I am not at all convinced that the method NICE has applied of accepting the benefit of maintenance therapy and then separating out the use of rituximab with induction is valid in the current model. The trials were not designed to support this	The Committee was of the opinion that the two uses of rituximab could be considered separately, and that the four-arm economic model provided a basis for

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	type of analysis and the costs of therapy will change in those that do not respond to chemotherapy alone. These patients will be a difficult group to treat. They will need to be exposed to rituximab, either as a single agent (NICE) or probably in combination with an alternate chemotherapy. If they then respond then the trial evidence submitted would suggest that they should then receive maintenance treatment to sustain this response. The cost calculations therefore will be entirely different for this group and this will alter the QALY. Undoubtedly some of these patients will have lost their chance to respond to therapy by this point as their disease will have progressed to the point where therapy is difficult to deliver or their lymphoma will have been made resistant due to exposure to ineffective therapy. I do not believe that depriving 15% of patients a response is clinically or economically justifiable.	considering the appropriate comparisons for the appraisal (see FAD sections 3.6, 4.8 to 4.10). Rituximab is recommended for use in induction in the FAD.
No Comments	MacMillan Cancer Fund	
	Royal College of Nursing	
	Department of Health	