NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Rituximab for the treatment of recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma (Review of TA 37)

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to clarify the therapeutic indications in the marketing authorisation. Clarification was also sought for the search strategies used for both the clinical effectiveness and economics reviews. The manufacturer was asked for clarification to ensure a summary of all randomized patients in the EORTC trial was available, and to clarify the rationale for the methods and assumptions used for survival modeling.

Licensed indication

The following indications from the summary of product characteristics are relevant to this appraisal

Rituximab (MabThera, Roche) is indicated for treatment of patients with stage III–IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

Rituximab maintenance therapy is indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab.

Related NICE guidance for follicular lymphoma

Rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma. NICE technology appraisal guidance 37 (2002). Available from: www.nice.org.uk/TA037.

1.1 The use of rituximab for third-line or subsequent-line, but not 'last-line', treatment of patients with recurrent or refractory stage III or IV follicular lymphoma is not recommended.

1.2 For last-line treatment, rituximab is recommended only in the context of a prospective case series. All patients for whom alternative therapies have been exhausted (that is, those who are either chemo-resistant or chemointolerant – see section 4.1.3) would be appropriate for inclusion in the case series on the basis that data are systematically collected to allow aggregation and analysis at a national level. The Institute's recommendations for data to be recorded for this case series are set out in paragraphs 7.2 and 7.3.

Rituximab for the treatment of follicular lymphoma. NICE technology appraisal guidance 110 (2006). Available from: www.nice.org.uk/TA110..

Rituximab within its licensed indication (that is, in combination with cyclophosphamide, vincristine and prednisolone) is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.

Key issues for consideration

- Clarification on the marketing authorisation: does rituximab hold a marketing authorisation for only induction at first relapse in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP)?
- The pivotal EORTC RCT was conducted in rituximab naïve patients. NICE guidance (TA 110) recommends rituximab as a treatment option at first line. How might this impact on the generalisability of RCT evidence to the NHS population?
- Has the absence of new evidence for the use of rituximab monotherapy at second relapse of follicular lymphoma (FL) been sufficiently demonstrated?
- Are the different fludarabine-containing regimens of equal effectiveness? How does the clinical effectiveness of fludarabine-containing regimens compare with that of CHOP? Can the results of the cost effectiveness based on the CHOP regimen be extrapolated to fludarabine containing regimens?
- Are there difficulties in inference from the two-arm model because it does not account for the impact of rituximab use at induction?
- Are the methods used to extrapolate survival beyond the trial period reasonable (choice of Weibull model and assumption of proportional hazards)?
- Is the modelling approach of no health benefits being attached to treatment at relapse reasonable?
- Are the assumptions that lead to an estimated duration of benefit of rituximab of five years reasonable?
- What is the appropriate duration over which to calculate costs and benefits in the model (1500 days or lifetime)?
- What are the most appropriate assumptions for calculating of costs of treatment at relapse (noting ERG adjustments to manufacturer's model)?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

	Final scope issued by NICE	Decision problem addressed in the MS
Population	**For induction of remission** Adult patients with stage III-IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy **For maintenance therapy** Adults with relapsed/refractory FL responding to induction therapy with chemotherapy with or without rituximab	**For induction of remission using rituximab monotherapy:** Adult patients with stage III-IV FL who are chemoresistant or are in their second or subsequent relapse after chemotherapy **For induction of remission using chemotherapy plus rituximab:** Adult patients with stage III-IV FL who are in relapse after previous chemotherapy, who are still suitable for chemotherapy **For maintenance therapy:** As scope. Responding meaning having achieved at least a partial response
Intervention	Rituximab as induction and as maintenance therapy	**For induction of remission in patients who are chemoresistant or in 2nd or subsequent relapse:** 4 weekly doses of rituximab alone **For induction of remission in relapsed FL patients in conjunction with chemotherapy:** 1 dose of rituximab with each chemotherapy cycle **For maintenance therapy**: 1 dose of rituximab every 3 months for 2 years
Comparator(s)	• Cyclophosphamide, hydroxydaunomycin (doxorubicin), oncovin (vincristine), and prednisone (CHOP) • Fludarabine, as a single agent, or in combination with mitoxantrone and dexamethasone (FMD). • Cyclophosphamide, vincristine, and prednisone (CVP) • Chlorambucil • Best supportive care (BSC)	**For induction of remission using rituximab monotherapy:** BSC, other active treatment options having been exhausted. Chemotherapy would be an option according to Marketing Authorization but not within existing NICE guidance. With no new data this guidance should stand **Rituximab + chemotherapy for induction of remission in relapsed FL:** Chemotherapy alone. As will be explained in Section 4.1, CHOP and, fludarabine-containing chemotherapy are the dominant cytototoxic regimens used in relapsed FL and are the most appropriate comparators. These will be considered. Chlorambucil, BSC alone and CVP are little used in this setting and therefore will not be considered as comparators **Rituximab maintenance:**

	Final scope issued by NICE	Decision problem addressed in the MS
		• No treatment (patients in remission currently get no treatment until relapse)
Outcomes	The outcome measures to be considered include: • Partial response (PR)/complete response (CR) rates • Duration of response/remission • Health related quality of life • Event-free survival • Time to new anti-lymphoma treatment/ time to progression • Overall survival (OS) • Adverse effects (AE) of treatment, including serious infection/ immunologic competence	The endpoints appropriate to rituximab use vary according to the way in which rituximab is employed: **All situations** • Health related quality of life (seldom collected in lymphoma interventional studies and dealt with by reference to general evidence of the quality of life benefit to patients of being in remission and off chemotherapy) • Adverse events of treatment **Rituximab maintenance after induction** • Event-free survival/progression-free survival/disease-free survival • Time to new anti-lymphoma treatment/progression • Overall survival **R-CHOP as part of induction therapy prior to maintenance** • Response rate • Event-free survival/progression-free survival/disease-free survival • Overall survival
Extracted from Table 3-1, page 20 of ERG report and amended by authors		

1.2 Evidence Review Group comments

1.2.1 Population

The ERG considered the appropriateness of the population identified in the manufacturer's submission (MS) would depend on the interpretation of the marketing authorisation. In addition the main clinical trial (European organisation for research and treatment of cancer, EORTC) identified by the manufacturer included only rituximab–naïve patients. The application for a marketing authorisation for the maintenance indication was supported by additional trials as detailed in the EMEA scientific discussion (Mabthera-H-C-259-II-44 Scientific Discussion). As NICE technology appraisal guidance 110 currently recommends rituximab as an option at first line in FL the trial

population may not represent patients in routine clinical practice. The efficacy of rituximab in patients with relapse who have already received rituximab is unknown.

1.2.2 Intervention

The ERG agreed with the intervention, provided that the marketing authorisation was clarified regarding the licensing status of rituximab in combination with chemotherapy for induction of remission at first relapse.

1.2.3 Comparators

For rituximab as monotherapy for induction the manufacturer's submission states that the comparator is best supportive care but no further evidence is presented for this indication.

For rituximab as combination therapy for induction the MS states that CHOP and fludarabine-based regimens (for example, fludarabine, cyclophosphamide, mitoxantrone [FCM] and FMD) are the comparators. Other comparators are specified in the scope as being little used and are rejected in the MS. The ERG confirmed with clinical experts that this was appropriate.

For maintenance therapy the ERG agrees with the MS that the comparator is observation as is usual clinical practice.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer conducted a systematic review of the literature for relevant studies of rituximab. Of 155 papers identified, 13 publications from two randomised controlled trials (RCTs) (EORTC and GLSG-FCM) were included as relevant. The two studies are described in some detail in the

manufacturer's submission although fewer details were available from the second study (tables on page 36 and 37 of ERG report). Both studies included patients of an average age lower than that of patients in whom follicular lymphoma is normally diagnosed (54 years in the EORTC and 60 years in the GLSG trial). The EORTC trial included a few patients at stages I and II of the disease and a majority of patients in the trial had been treated with just one previous chemotherapy regimen. The German lymphoma study group (GLSG) study included patients with indolent lymphomas other than of the follicular type and results for follicular lymphoma were not reported separately.

The MS states that the results of the two trials cannot be combined in a meta-analysis. The MS concludes that the clinical evidence suggests that rituximab induction significantly increases the proportion of patients entering remission and the durability of the remission. In addition rituximab maintenance increases the duration of progression free survival (PFS) regardless of whether patients achieve a complete or partial remission. The MS also concludes that rituximab increases overall survival, that it is generally safe and that treatment toxicity is mostly restricted to acute reactions during drug infusion. The MS states that the patients in the trial were representative of those in routine UK practice and would have been actively treated. It discusses the issue of the trial patients being rituximab naïve and states that the impact of prior rituximab exposure would be minimal because:

- The GLSG–FCM study patients had prior exposure to rituximab and achieved comparable outcomes and a subgroup analysis showed prior exposure to rituximab did not affect outcome at second use
- Rituximab maintenance response was similar regardless of whether the drug was used in induction in the EORTC trial
- Other publications suggest that retreatment with rituximab in responders does not compromise treatment benefit.

- Evidence to suggest that a majority of patients maintain rituximab sensitivity when retreated at relapse post–protocol in the trials.

The MS notes that the GLSG–FCM study used an unlicensed schedule of rituximab for maintenance.

2.2 Evidence Review Group comments

The ERG stated that the review of clinical effectiveness was adequate but noted that the manufacturer's submission did not explicitly state the inclusion and exclusion criteria for study selection. In addition the MS did not distinguish the methods and results for the review of rituximab monotherapy from the overall results. However the ERG was confident that no relevant publicly–available studies were excluded from the review. Both studies included in the manufacturer's submission are of good quality and report appropriate outcome measures. Both trials were open-label and the GLSG–FCM study did not use an intention to treat analysis. While accepting that both studies used appropriate methods of statistical analysis the ERG pointed out that the EORTC study was not powered or designed to allow comparison of the four alternative treatment strategies within the trial. The ERG agreed with the manufacturer that a meta–analysis of the two trials was not appropriate.

The following tables highlight important outcomes from the trials and more details can be found in the tables on pages 38 and 39 of the ERG report. A further summary of the important outcomes is on page 47 of the ERG report.

The exact fludarabine–containing regimen used in the GLSG trial FCM (i.e. fludarabine, cyclophosphamide, mitoxantrone) may not be the only or most common fludarabine–containing regimen in use in the NHS. One alternative regimen recommended by the British Committee for Standards in Haematology is FMD (i.e. fludarabine, mitoxantrone, dexamethasone).

EORTC trial results					
Induction	**EORTC**	**CHOP N=231**	**R-CHOP N=234**	**p-value**	**Risk reduction (95% CI)**
	Primary				
	Overall Response Rate	72.30%	85.10%	<0.0001	-
	Secondary				
	Median OS (months)	Not reached	Not reached		
	Median PFS(months)	20.2	33.1	0.0003	35%
	Three year OS	71.90%	82.5%	0.096	26%
Maintenance		**Observation**	**Rituximab**	**p-value (Log-Rank)**	**Risk reduction (95% CI)**
	Primary				
	Median PFS (months)	14.9	51.5	<0.0001	60%
	CHOP induction	11.6	42.2	<0.0001	70%
	R-CHOP induction	23	51.8	0.0043	46%
		Observation	**Rituximab**	**p-value**	**Hazard ratio (95% CI)**
	Secondary (3 years OS)				
	Overall	77.10%	85.10%	0.011[1]	0.52 (not reported)
Extracted from Table 4-6, page 38 of ERG report and amended by authors					

GLSG trial results				
	GLSG-FCM	**FCM**	**R-FCM**	**p-value**
Induction	**No. evaluable**	**N=30**	**N=35**	
	Primary (response rates)			
	Complete response	23%	40%	-
	Complete response + partial response	70%	94%	0.011
	Secondary			
	Median PFS (months)	21	NR	0.0139
	Median OS (months)	NR	NR	-
	2 year survival	70%	90%	0.0943
Maintenance (All patients)		**Observation**	**Rituximab**	**p-value (Log-Rank)**
	Median duration of response (months) after R-FCM induction (n=81)	17	NR	<0.001
	Three year OS	57%	77%	0.1
Extracted from Table 4-7, page 39 of ERG report and amended by authors				

2.3 Statements from professional/patient groups and nominated experts

It was emphasised the benefit that rituximab confers in terms of progression free survival, remissions and overall survival. PFS was noted as being especially important from a patient's viewpoint.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The MS presents two models based on the EORTC trial:

- The two-arm model for maintenance treatment includes patients responding to induction (with or without rituximab) and who were eligible for rituximab maintenance.
- The four-arm model includes all patients entering at induction (CHOP with or without rituximab) with a second randomisation of responders to maintenance as done in the trial.

Model structure

A tabular summary of key model assumptions is on page 53 of the ERG report.

The two-arm (maintenance) model consists of three health states – progression free (PF), progressive disease (PD) and death. All patients enter the model in the PF state and exit only at death. They receive rituximab until progression or for two years, which ever is soonest. The comparator arm is observation only.

The four-arm model (induction and maintenance) consists of five health states – PF in induction setting, PF neither in the induction or maintenance setting, PF in maintenance setting, PD and death. Patients enter the model at induction and responders go on to receive maintenance as specified in the

two-arm model. The comparator arm was CHOP at induction (versus R-CHOP) as this was felt to be a reliable proxy for other possible treatments. Fludarabine–containing regimens were not included. The outcomes from the CHOP–based EORTC trial were said to be a conservative estimate of effectiveness. The outcomes of the GLSG trial, which used fludarabine–containing regimens, were better (bearing in mind that the latter trial included patients with indolent lymphomas other than FL). The comparator for maintenance was as in the two-arm model.

The four-arm model meant there were six outcomes across the four treatment groups:

1. Patients who had received R-CHOP, were eligible for maintenance and were receiving rituximab
2. Patients who had received R-CHOP, were eligible for maintenance and were in the observation group
3. Patients who had received CHOP, were eligible for maintenance and were receiving rituximab
4. Patients who had received CHOP, were eligible for maintenance and were in the observation group
5. Patients who had received R-CHOP, but were not eligible for maintenance
6. Patients who had received CHOP, but were not eligible for maintenance

<u>Perspective, time horizon, cycle length and discounting</u>

For both models the study perspective for costs was that of the NHS in England and Wales and for benefits the health state values came from the general public. A full lifetime horizon of 30 years was used. There were no

subgroup analyses performed as there was no evidence for differential effectiveness in any subgroup of patients in the RCT. The cycle length was one month and half-cycle corrections were applied. Costs and quality-adjusted life years (QALY) were discounted at 3.5%.

Modelling of survival

The EORTC trial provided survival data for the first 24 months and results were extrapolated using a Weibull model on the grounds that this provided the best fit to the trial data and was the most appropriate to reflect the underlying natural history of the disease. In addition the hazards for disease progression and death were assumed to be equivalent in both arms beyond five years.

Utility

The quality of life (QoL) values for each health state were derived from a study of lymphoma patients commissioned by the manufacturers. Accurate descriptions of the health states and adverse events were developed and were then valued by 222 members of the general public using the EQ-5D instrument. The QoL in the PD state remains constant; the manufacturer stated it would not be possible to accurately model this with any other assumptions. In the four-arm model the various types of PF states are not given different QoL values. The health effects of adverse events were not included on the grounds that these were similar in the compared arms of the model and that these would be minor over the course of the patients' lifetime.

Costs

Drug utilisation was as per the EORTC trial. Costs for drug administration were calculated as an out patient appointment. In addition patients were assumed to relapse every two years (as in the trial) and generate further treatment costs. Costs were calculated according to post-protocol treatments received in the trial and an expected cost at relapse calculated as a weighted average of these costs. Patients in the PD state were assumed to incur the

costs of monthly outpatient appointments whereas patients in the PF state incurred the costs of 3-monthly appointments. Costs for treating adverse events were calculated separately for serious and non-serious adverse events and expected cost per patient calculated depending on the number of such events reported in the trial.

Sensitivity analysis

The model parameters were subjected to univariate sensitivity analysis and probabilistic sensitivity analysis.

Results

For the two-arm model the base case showed a gain of 0.89 QALYs at an incremental cost of £6,886 and the incremental cost effectiveness ratio (ICER) per QALY gained was £7,721.

For the four-arm model the most effective intervention was to use rituximab at induction and as maintenance (R-CHOP>R). When compared with the next most effective treatment, rituximab as maintenance only (CHOP>R), the ICER was £16,749 per QALY gained.

Base case results			
Treatment and comparator groups	**Total costs**	**QALYs gained**	**Incremental cost per QALY gained**
Maintenance			
Rituximab	£21,608	4.2250	
'Observation'	£14,722	3.3331	
Incremental	£6,886	0.8919	£7,721
Induction and maintenance			
R-CHOP>R	£28,585	4.0906	
CHOP>R	£22,389	3.7207	
Incremental	£6,196	0.3699	£16,749
Extracted from Tables 5-5 and 5-6, page 58 of ERG report and amended by authors			

The sensitivity analysis of the two-arm model showed that the use of an alternative parametric model (log-logistic) does not impact the estimated ICER. However, by reducing the duration of treatment benefit to two years, doubling the frequency of relapse in both arms or doubling the cost of

treatment in both arms on relapse, the ICERs are raised to about £18,000 per QALY. Decreasing the duration of follow up to four years also increases the ICER to about £16,000 per QALY. The probabilistic sensitivity analysis (PSA) showed that at a willingness to pay threshold of £10,000, there was a 90% probability that rituximab was cost effective. The table below highlights important results from the sensitivity analysis for the two-arm model and a full version can be found on page 59 of the ERG report.

Sensitivity analysis: 2-arm model

Variables	Assumptions (Low and high)	Result (Cost per QALY gained)
Extrapolation	Weibull (Base case)	£7,721
	Log logistic	£6,040
Duration of treatment benefit	2 years	£18,124
	30 years	£6,270
Unit cost per line of treatment upon relapse	Double costs in observation arm	Rituximab dominant
	Double costs in both arms	£18,016
Frequency of treatment upon relapse	Double frequency in observation arm	Rituximab dominant
	Double frequency in both arms	£18,016
Utility values for PFS	Utility value equal to PD	£11,141
	Utility value equal to PFS	£8,553
Duration of follow-up	4 years	£15,933
	50 years	£7,721

Extracted from Table 5-8, page 59 of ERG report and amended by authors

In the four-arm model reducing the duration of treatment benefit to two years raised the ICER of R-CHOP>R against CHOP>R to £36,500 per QALY. Similarly doubling the frequency of relapse or the costs at relapse increased the ICER to above £30,000 per QALY when comparing the same strategies. Reducing the duration of follow-up to four years raised the ICER between these strategies to £48,100 per QALY. The model estimates were robust to the other sensitivity analyses with ICERs within the range normally accepted as cost effective. The PSA showed at a willingness to pay (WTP) of £18,000 or greater the R-CHOP>R strategy had the greatest probability of being cost effective. The same strategy had an 82% probability of being cost effective at a WTP threshold of £30,000. The table below highlights important results from

the sensitivity analysis for the four-arm model and a full version can be found on page 60 of the ERG report.

Sensitivity analysis: 4-arm model				
Variables	**Assumptions (low and High)**	**Result (Cost per QALY) R-CHOP>R vs CHOP>R**	**Result (Cost per QALY) R-CHOP>R vs R-CHOP>O**	**Result (Cost per QALY) R-CHOP>R vs CHOP>O**
R-CHOP and CHOP response rates (CHOP response rate kept constant)	Lower 95% CI of difference between the groups	£21,004	£11,654	£12,491
	Upper 95% CI of difference between the groups	£14,541	£12,108	£11,452
Extrapolation	Log logistic	£9,835	£8,606	£8,528
Duration of treatment benefit	2 years	£36,497	£91,373	£28,400
	30 years	£8,907	£6,765	£8,052
Unit cost per line of treatment upon relapse	Double costs in R-CHOP>R arm only	£37,868	£28,719	£19,712
	Double costs in all arms	£8,022	£8,614	£9,105
Frequency of treatment upon relapse	Double frequency in R-CHOP>R arm	£37,868	£28,719	£19,712
	Double frequency in all arms	£8,022	£8,614	£9,105
Administration costs	£0 (CHOP only arm)	£18,015	£11,904	£12,378
Utility values for PFS	Utility value equal to PD	£22,009	£16,037	£16,707
	Utility value equal to PFS	£16,896	£12,312	£12,826
Duration of follow-up	4 years	£48,116	£41,171	£25,278
	50 years	£16,749	£11,904	£11,910
Extracted from Table 5-9, page 60 of ERG report and amended by authors				

In addition, a scenario analysis for the four-arm model in which the incremental response rate from rituximab compared with chemotherapy at induction was varied, showed that at an incremental response rate of 4% for rituximab the ICER is below £30,000 per QALY gained. (further details on page 59 of ERG report)

3.2 Evidence Review Group comments

In general the ERG's impression of the manufacturer's models was that they were implemented to a high standard, clearly presented and generally logical with large amount of source information and straightforward formulae.

Model structure

The ERG was concerned that the simple structure of the manufacturer's models, with only two health states, may not provide a suitable framework for evaluating the intervention. In addition the two-arm model would not satisfy the assumption of homogeneity for all patients within a state with respect to all relevant variables. Patients in this model vary with respect to their treatment at induction (with regard to the use of rituximab) and this is not captured within the model as it cannot be assumed that the effect of maintenance rituximab would be the same in the two groups. Hence the ERG felt that the four-arm model was more appropriate to this evaluation.

In addition the ERG noted that subsequent treatments are assumed not to modify the patients' health state in the manufacturer's models. It felt that this limitation could be overcome by limiting apparent gains to the observation period only.

Costs

In estimating the costs the ERG felt that it was inappropriate to estimate administration costs in the outpatient setting as such treatment is routinely given in a day–case setting. Using day case costs (calculation detailed on page 65 of ERG report) in the four-arm model increases the ICER (R-CHOP>R vs CHOP>R) to £18,200 per QALY gained. The ERG also felt it inappropriate to include costs at relapse without any corresponding health benefit, as stated to previously. In addition the ERG proposed an alternative method of estimating costs of treatment which involved aggregating treatments at progression into a small number of meaningful categories (as

detailed on page 67 of the ERG report). Using this method raised the ICER further to £22,700 per QALY gained. The ERG also noted that other costs were absent, including those for primary care and medications. In addition the ERG conducted the analysis with an estimate of terminal care costs included though this only had a marginal impact on the ICER.

Utilities

In reviewing the utilities attached to health states the ERG was concerned that despite treatment at relapse and the cost incurred patients did not experience health utility improvements. However in a sensitivity analysis conducted by the ERG the ICERs were found to be robust to even substantial changes in post–progression utility.

Modelling of survival analysis

A major issue identified by the ERG was the modelling approach to the survival analysis. The ERG's concerns included:

- The assumption that the benefit assumed from trial data would persist without reduction over the long duration of 7–10 years of the model until death and that this would not be modified by subsequent treatments.

- The choice of a Weibull model is not justified when other functions may be preferable. The manufacturer responded in clarification (see p.12 of this document and questions B3 and B11 of clarification letter from the manufacturer).

- The assumption of a non-zero hazard immediately after randomisation (that is, no event-free period). This should be at least the duration of the induction chemotherapy for patients randomised to maintenance treatment. This alters the shape of the hazard function and 'goodness of fit' of the statistical models.

- For any comparison in the model only three parameters are estimated instead of the four required to fit the two functions independently. This assumption of proportional hazards is not substantiated with trial evidence.

The ERG conducted a reanalysis limiting the Kaplan Meier (K-M) estimates to 1500 days post randomisation and making appropriate adjustments to the care costs (routine maintenance and post-progression treatment). This had the effect of increasing all the ICERs between the various treatment groups, though the effect on the pairwise comparisons is to different degrees, illustrating the influence of joint parameter estimation on projection-based outcome gain results.

Using K–M outcome estimates restricted to 1500 days

Reanalysis with horizon limited to 1500 days

	Model projections	K-M estimates
Comparison	**ICER**	**ICER**
R-CHOP>R vs CHOP>R	£16,749	£36,718
R-CHOP>R vs R-CHOP>O	£11,904	£30,665
R-CHOP>R vs CHOP>O	£11,910	£23,721
CHOP>R vs R-CHOP>O	Dominant	£73,140
CHOP>R vs CHOP>O	£9,076	£13,895
R-CHOP>O vs CHOP>O	£11,916	£19,657
Extracted from Table 5-17, page 73 of ERG report and amended by authors		

The ERG then conducted the analysis with all the suggested amendments and corrections (see table below). The ERG concludes that treatment strategies involving only single use of rituximab (only at induction or as maintenance) are the most cost effective options, resulting in ICERs of £16,500 per QALY for single use as induction and £13,100 per QALY for single use as maintenance. Comparing dual use rituximab to no use at all results in an ICER of £26,000. However when considering sequential decision making the ICER for dual use rituximab compared to single use is approximately £42,000. The improved cost effectiveness from using rituximab for maintenance only compared with induction followed by maintenance

results mainly from the avoidance of cost of rituximab at induction for non-responders.

Reanalysis with alternative costs, correction and with different time horizons

	Model projections	ERG modifications but using original outcome projections	ERG modifications including K-M outcome estimates
Comparison	**ICER**	**ICER**	**ICER**
R-CHOP>R vs CHOP>R	£16,749	£23,882	£42,982
R-CHOP>R vs R-CHOP>O	£11,904	£16,509	£42,192
R-CHOP>R vs CHOP>O	£11,910	£12,108	£25,978
CHOP>R vs R-CHOP>O	Dominant	- £12,232	£47,734
CHOP>R vs CHOP>O	£9,076	£5,214	£13,122
R-CHOP>O vs CHOP>O	£11,916	£8,298	£16,488

Extracted from Table 5-18, page 75 of ERG report and amended by authors

4 Authors

Elangovan Gajraj and Helen Chung, with input from the Lead Team (Dr Christine Davey and Dr David W Black)

References

British Committee for Standards in Haematology: Guidelines on diagnosis and therapy. Nodal non-Hodgkin's lymphoma. August 2002

EMEA Mabthera Scientific Discussion.

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group:

- Dickson R et al, Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma. ERG report (August 2007).

The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope and assessment report. Organisations listed in I were invited to make written submissions. Organisations listed in II gave their expert views on rituximab by providing a written statement to the Committee.

I Manufacturer/sponsor:

- Roche Products Ltd

II Professional/specialist, patient/carer and other groups:

- Anglesey Local Health Board
- Association of Cancer Physicians
- British National Lymphoma Investigation
- British Oncological Association
- British Psychosocial Oncology Society
- British Society for Haematology
- Cancer Networks Pharmacists Forum
- Cancer Research UK
- Cancer Voices
- Cancerbackup
- Community Practitioners & Health Visitors Association
- Department of Health
- East Riding of Yorkshire PCT
- Leukaemia Care Society
- Lymphoma Association
- Macmillan Cancer Relief
- Marie Curie Cancer Care
- National Cancer Alliance
- National Council for Palliative Care
- Royal College of General Practitioners

- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians Medical Oncology Joint Special Committee
- Specialised Healthcare Alliance
- Tenovus Cancer Information Centre
- UK Oncology Nursing Society
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- Board of Community Health Councils in Wales
- British National Formulary
- Cancer Care Cymru
- Cephalon (Doxorubicin)
- Department of Health, Social Services and Public Safety for Northern Ireland
- GlaxoSmithKline (Chlorambucil)
- Institute of Cancer Research
- Leukaemia Research Fund
- Liverpool Reviews and Implementation Group, University of Liverpool
- Mayne Pharma plc (Vincristine, Doxorubicin, Mitoxantrone)
- Medac (Doxorubicin)
- Medicines and Healthcare products Regulatory Agency (MHRA)
- MRC Clinical Trials Unit, Cancer Division
- National Cancer Research Institute
- National Cancer Research Network
- National Collaborating Centre for Cancer
- National Coordinating Centre for Health Technology Assessment
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supply Agency
- NHS Quality Improvement Scotland
- Pfizer Ltd (Cyclophosphamide, Doxorubicin)
- Schering Healthcare (Fludarabine)
- Schering Plough (Doxorubicin)
- Scottish Medicines Consortium
- Vincristine, Doxorubicin)
- Wockhardt (Doxorubicin, Mitoxantrone)