NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to:

- clarify the rationale for recruiting patients with stage I and II disease into the PRIMA study
- explain why starting a new anti-lymphoma treatment was not counted as an event or a reason for censoring
- clarify the meaning of 'images were not collected after the start of a new treatment, patients who started a new anti-lymphoma treatment without IRC-assessed disease progression were censored for the IRC analysis'
- justify the differences in censoring methods between the investigator and independent review committee assessments
- provide all the results for the primary and secondary clinical end points from the last cut-off date (June 2010)
- provide data for event-free survival in the same format as they have been provided for progression-free survival
- provide product-limit survival tables from analysing the most recent follow-up PRIMA trial data for progression-free survival and consider progression-free survival by treatment arm; three patient populations defined by age (youngest, mid-age, oldest) and treatment arm; and three patient populations defined by induction response (complete, partial, unconfirmed) and by treatment arm
- provide product-limit survival tables showing for each event time: time of event from baseline, product-limit estimate of survival proportion, standard error of survival proportion, number of patients for whom treatment failed; and number of patients remaining at risk
- produce a complete quality assessment for the PRIMA study
- justify methods used to validate and quality assure the model.

Anticipated licensed indication

Rituximab (MabThera, Roche Products) does not currently have a UK marketing authorisation for maintenance therapy after first-line chemotherapy for follicular lymphoma. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on 23 September 2010 to extend the use of rituximab to include 'the treatment of follicular lymphoma patients responding to induction therapy'. Rituximab is administered by intravenous infusion (375 mg/m^2 every 8 weeks for 2 years, or until disease progression).

Related NICE guidance

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (review of NICE technology appraisal 37). NICE technology appraisal guidance 137 (2008). Available from www.nice.org.uk/guidance/TA137 Review date December 2010.

Rituximab for the treatment of follicular lymphoma NICE technology appraisal guidance110 (2006). Available from www.nice.org.uk/guidance/TA110 Review date June 2009.

Key issues for consideration

Clinical effectiveness

- Are there sufficient clinical data of rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma to inform conclusions on progression-free survival, event-free survival and overall survival?
- Does the Committee believe that the early closure of the PRIMA study had any impact on the estimation of the effect of rituximab as a first-line maintenance treatment of follicular non-Hodgkin's lymphoma?
- The primary end point of the PRIMA study was changed after 6 months from event-free survival to progression-free survival. What is the

Committee's view on this approach, and any impact it may have on the appraisal of rituximab?

- Given that people with follicular non-Hodgkin's lymphoma experience recurring and remitting disease over many years, are there optimal time points for the use of rituximab maintenance treatment?

Cost effectiveness

- The model assumes that people in the progression-free survival–second-line maintenance phase (PF2) health state have successfully completed second-line induction treatment before receiving second-line maintenance treatment or placebo. Does the Committee think that this assumption and the treatment pathway used in the manufacturer's economic model reflect the natural disease progression and UK clinical practice?
- The model assumes that almost the entire time gained in progression-free survival (96%) from treatment with rituximab translates into time gained in overall survival. Does the Committee think that this is a realistic assumption?
- The extrapolation function was used to model progression-free survival after the empirical phase led to different survival curves. What is the Committee's view on the manufacturer's decision to use the Gomperzt function to extrapolate long-term evidence?
- The maximum time over which any patients were observed within the PRIMA trial was 4 years, yet, the model assumes rituximab will have a sustained clinical benefit for the first 6 years. Does the Committee consider this assumption to be reasonable?
- Does the Committee think that the utility values used in the economic model reflect disease progression and the experience of people receiving treatment?

1 Decision problem

Decision problem approach in the manufacturer's submission

Population	**NICE scope** Adults with advanced follicular lymphoma that has responded to first-line chemotherapy. **Manufacturer's submission** Adults with advanced follicular lymphoma that has responded to first-line rituximab plus chemotherapy. **Rationale for change from scope** Rituximab plus chemotherapy induction treatment is the current gold standard in the UK for people with previously untreated follicular lymphoma. About 93% of those who are eligible receive this treatment option. The majority of people who are not offered rituximab plus chemotherapy receive chlorambucil monotherapy (about 5% of all eligible people with first-line follicular lymphoma). These people tend to be older, frailer, and have comorbidities that make them ineligible for treatment with either rituximab plus chemotherapy or rituximab maintenance therapy.
Intervention	Rituximab maintenance therapy.
Comparators	**NICE scope** Standard management without rituximab maintenance therapy. Ibritumomab tiuxetan (Zevalin). **Manufacturer's submission** Standard management without rituximab maintenance therapy (that is, observation). **Rationale for change from scope** No evidence to support clinical benefit of Ibritumomab tiuxetan in people with previously untreated advanced follicular lymphoma induced with rituximab plus chemotherapy. Also, minimal Ibritumomab tiuxetan usage in UK, therefore not included as a comparator.
Outcomes	The outcome measures considered included: progression-free survival, overall survival, response rates, adverse effects of treatment and health-related quality of life.
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Given the revised population in the decision problem (that is, adults with advanced follicular lymphoma that has responded to first-line chemotherapy plus rituximab), it is no longer relevant to consider subgroups where rituximab was received in combination with first-line chemotherapy, as suggested in the scope. In the PRIMA trial, all people with previously untreated follicular lymphoma received standard first-line therapy – which is rituximab plus chemotherapy. The following subgroups (non-randomised) will be addressed in the submission: age (≥ 60 years, < 60 years), gender (male, female), pre-induction FLIPI score (≤ 1, 2, ≥ 3), induction treatment (R-CHOP, R-CVP, R-FCM), and response to induction treatment (CR/CRu, PR).

R-CHOP: rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone
R-CVP: rituximab with cyclophosphamide, vincristine and prednisolone
R-FCM: rituximab with cyclophosphamide, fludarabine, mitoxantrone
CR/CRu: complete response/complete response unconfirmed
FLIPI: Follicular Lymphoma International Prognostic Index
PR: partial response

Evidence Review Group comments

1.1.1 Population

The scope defines the population as ‘adults with advanced follicular lymphoma that has responded to first-line chemotherapy’. The population considered by the manufacturer was ‘adults with advanced follicular lymphoma that has responded to first-line treatment with rituximab plus chemotherapy’.

The population addressed in the manufacturer’s submission matches the anticipated licensed indication. The manufacturer indicated that the population was restricted to people who had received first-line treatment with rituximab plus chemotherapy because this is considered to be the standard first-line

treatment used in UK clinical practice (93% of people with advanced follicular lymphoma are estimated to be eligible for this treatment regimen).

The ERG noted that 90% of people in the PRIMA study were classified as having disease at stages III or IV (advanced stages) and 10% had disease at stages I or II. The ERG asked the manufacturer to clarify why people at stages I or II, who are usually not considered to have advanced disease and are usually treated with radiotherapy, were included in the PRIMA study. The manufacturer acknowledged that people with stage I or II disease are generally treated with radiotherapy rather than chemotherapy; however, if these people have high tumour burden, they receive the same treatment options as for advanced disease (stages III and IV). Clinical advisors to the manufacturer and the ERG confirmed that this is clinical practice.

1.1.2 Intervention

The intervention (rituximab) in the manufacturer's submission was in accordance with the anticipated marketing authorisation for rituximab and the scope for this guidance. After a positive CHMP opinion in September 2010, the anticipated marketing authorisation for rituximab is for 'the treatment of follicular lymphoma patients responding to induction therapy'.

1.1.3 Comparators

The comparators in the scope were standard management without rituximab maintenance treatment and ibritumomab tiuxetan (Zevalin).

The only comparator included in the manufacturer's submission was observation because the manufacturer considered that this was current standard management of people whose advanced follicular lymphoma has responded to first-line induction treatment in the UK.

Ibritumomab tiuxetan was not included as a comparator because the manufacturer considered that there is no clinical evidence supporting its benefits in the population under consideration in this appraisal, and that it is

not often used in the UK. Hospital usage data for ibritumomab tiuxetan provided by the manufacturer suggested that up to five patients received ibritumomab tiuxetan (across all indications) in 2009 in the UK. The ERG noted that 86% of people in the FIT (first-line indolent trial) trial (which supports the use of ibritumomab tiuxetan as a consolidation therapy in people with advanced follicular non-Hodgkin's lymphoma that has responded to induction chemotherapy) received induction therapy that did not include rituximab. Of the 14% of people who did receive rituximab plus chemotherapy, a statistically significant difference between the intervention and control groups on the outcome of partial response–complete response conversion rate was demonstrated, but not on the outcome of progression-free survival. The ERG further noted that the summary of product characteristics states that the benefit of ibritumomab tiuxetan after rituximab chemotherapy has not been established.

The ERG considered that the manufacturer's justification for omitting ibritumomab tiuxetan as a comparator was convincing.

1.1.4 Outcomes

The outcomes included in the manufacturer's submission were progression-free survival, overall survival, response rates, adverse effects of treatment and health-related quality of life, which were in accordance with the NICE scope.

The ERG was concerned that the results from the PRIMA study that inform this appraisal are immature and may affect reliable conclusions being drawn about the efficacy of rituximab as a first-line maintenance treatment compared with observation for the population under consideration.

1.1.5 Economic evaluation

The manufacturer submitted a Markov model comparing rituximab maintenance treatment with observation (after first-line induction with R-CHOP, R-CVP or R-FCM). The model had four distinct health states:

progression-free survival–first-line maintenance phase (PF1), progression-free survival–second-line maintenance phase (PF2), progressive disease (PD) and death. The model had a time horizon of 25 years. A cycle of 1 month and a half cycle correction were applied to the model.

The manufacturer used clinical data from the PRIMA study ('snapshot' June 2010) and the EORTC 20981 study (from Van Oers et al. 2010) to populate the economic model.

1.1.6 Subgroups

If evidence permits, the following subgroups were suggested for consideration in the scope: whether rituximab was received in combination with first-line chemotherapy, type of first-line chemo-immunotherapy regimen received and type of response (that is, complete versus partial response) achieved after first-line treatment.

The manufacturer stated that because people in the PRIMA study received only rituximab plus chemotherapy as an induction treatment, the first subgroup suggested by NICE is no longer relevant. The manufacturer provided subgroup analyses for the other subgroups included in the scope. The ERG suggest that the results of these analyses should be treated with caution because of the immaturity of the results of the PRIMA trial and because the study was not powered to show significant differences between subgroups.

Statements from professional/patient groups and nominated experts

Clinical specialists stated that follicular lymphoma accounts for 20−30% of all cases of non-Hodgkin's lymphoma, equating to 2500 new cases being diagnosed each year in the UK. Life expectancy for people with advanced NHL on average is 8−10 years and depends on prognostic factors such as age and burden of disease. The clinical specialists highlighted the significance

of advanced age and the need for therapeutic options for people who are not fit for toxic treatments. They stated that chemotherapy regimens such as R-CHOP, R-CVP and R-FCM are currently used in the UK. Most people receiving these regimens experience symptoms of fatigue, which have a significant impact on their quality of life. Patient experts also highlighted that fatigue can exacerbate the complications of ageing, frailty and social isolation, which is of importance given the advanced age of many people with follicular NHL. Other symptoms which people may experience include anaemia, weight loss, fever and night sweats. People with lymphoma live with uncertainty and anxiety, and many experience depression.

Clinical specialists and patient experts stated that it is vital for a remission to be maintained as long as possible to reduce the need for treatment of relapsed disease. The patient experts considered that longer periods of time without disease and longer periods of time before treatments offers substantial benefits including longer periods without symptoms, greater capacity to care for oneself and return to work, and greater chance to fulfil other personal responsibilities such as caring for children.

Both the clinical specialists and patient experts believed that rituximab maintenance offers longer remissions, which can be translated into better quality of life. Rituximab treatment given for 2 years can improve the chance of remissions being converted from partial to complete. Clinical specialists noted that in the PRIMA study rituximab maintenance demonstrated superior responses for the second and subsequent relapse. Rituximab has relatively low toxicity and the side effects associated with the infusion can be well managed with paracetamol and antihistamine.

Patient experts cautioned that the administration of a maintenance dose of rituximab (for 2 years) leaves patients depleted of healthy B lymphocytes, which may place them at greater risk of bacterial infection. They considered

that this possible risk would be worth taking if remission from lymphoma may be significantly prolonged.

Clinical specialists believed that additional resources will be needed for the reconstitution of rituximab and some healthcare centres might use the pharmacy aseptic suite for this purpose.

Clinical specialists highlighted that people expect advanced lymphoma treatment to equal the treatment offered anywhere in the world and are aware that rituximab maintenance treatment is rapidly becoming standard practice.

2 Clinical effectiveness evidence

Clinical effectiveness in the manufacturer's submission

The manufacturer undertook a systematic literature review but only identified one study that met the inclusion criteria of the review; this was the PRIMA study. The results of this study were presented at two conferences (American Society of Clinical Oncology (ASCO) and European Haematology Association (EHA)) in 2010. The full publication of the results from the study is not expected until 2011. As only one study was identified, no meta-analyses or indirect or mixed treatment comparisons were conducted by the manufacturer.

The PRIMA study was a phase III, open-label, multicentre, randomised trial with two treatment phases. In the induction phase (first phase), 1193 people had to respond to one of the three different rituximab induction regimens (R-CVP [n = 268], R-CHOP [n = 881], R-FCM [n = 44]) before they could be randomised to the second phase of the trial where they received either rituximab maintenance treatment or observation. Of the 1193 people who received induction treatment, [redacted] responded. A total of 1019 were subsequently randomised to maintenance therapy (n = 506) or observation (n = 513). People who received maintenance therapy had 375 mg/m^2 rituximab administered by intravenous infusion: one dose every 8 weeks for 2 years, for a total of 12 doses. People were treated or observed for 2 years

or until disease progression. Those who completed their maintenance or observation treatments were followed up for a period of 5 years. The primary end point was initially event-free survival but after an amendment to the protocol (August 2006) it was changed to progression-free survival. Secondary clinical end points included overall survival, event-free survival, time to next anti-lymphoma treatment, overall response rate at the end of maintenance observation phase, transformation rate at first progression, quality of life and safety. In 2009, after a median follow-up of 25 months the required number of events was reached. A Data and Safety Monitoring Committee (DSMC) judged that the trial met its primary objective and recommended premature closure of the study.

In the PRIMA study, only people with an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 were selected. The median age at randomisation was 57 years. The manufacturer stated that in the induction phase of the trial, patient characteristics across the three induction treatments were well balanced, and that they had similar baseline disease characteristics and follicular lymphoma international prognostic index scores. The manufacturer further stated that in the maintenance or observation phase of the trial the demographic characteristics of the participants and the disease characteristics assessed before induction were well balanced between treatment arms.

Quality of life data were collected in the PRIMA study using the FACT-G and EORTC QLQ-C30 questionnaires.

The manufacturer used data from the EORTC 20981 study to predict the long-term outcomes of the people in the PRIMA trial. The EORTC 20981 study was a phase III, open-label randomised trial. The trial included people with relapsed or resistant follicular non-Hodgkin's lymphoma (n = 465) who had not previously been treated with rituximab, who received induction treatment with R-CHOP or CHOP alone after enrolment. People whose disease responded

to induction therapy (n = 334) were then randomised to either maintenance treatment with 375 mg/m^2 rituximab (one dose every eight weeks for 2 years or until disease progression) or observation for 2 years until relapse.

The primary and secondary clinical end points presented in the manufacturer's submission were derived from data up to January 2009. In response to clarification questions from NICE, the manufacturer also provided additional results using data up to January 2010 and a 'snapshot' of progression-free survival up to June 2010.

A summary of the results for progression-free survival are provided in table 1.

Table 1 Primary end point – progression-free survival

PRIMA clinical data cut-off date	**Median follow-up**	**Rituximab + chemotherapy N = 505**	**Observation N = 513**	**HR (95% CI)**	**p value**
14 January 2009 − **investigator assessed** PFS	25 months				
Median time to event		NE	NE	0.50 (0.39 to 0.64)	p < 0.0001
25th percentile		1096 days (36.0 months)	507 days (16.7 months)	0.50 (0.39 to 0.64)	p < 0.0001
1-year PFS rate (95% CI)		0.89 (0.87 to 0.92)	0.82 (0.79 to 0.85)		
2-year PFS rate (95% CI)		0.82 (0.79 to 0.86)	0.66 (0.62 to 0.71)		
14 January 2009 − **IRC assessed** PFS	25 months				
Median time to event		[redacted]	[redacted]	HR = 0.54 (0.42 to 0.70)	p < 0.0001
25th percentile		[redacted]	[redacted]		
1-year PFS rate (95% CI)		[redacted]	[redacted]		

15 January 2010	36 months				
Median time to event		[redacted]	[redacted]	[redacted]	[redacted]
25th percentile		[redacted]	[redacted]		
3-year PFS rate (95% CI)		[redacted]	[redacted]		
14 June 2010	38 months				
Median time to event		[redacted]	[redacted]	[redacted]	[redacted]
CI, confidence interval; HR, hazard ratio; IRC, independent review committee; NE, not estimable; NS, not specified, PFS, progression-free survival.					

The comparison between investigators' and IRC's assessments demonstrated a high concordance rate [redacted] for an event (progression or death) in both the rituximab and observation arms. However, among people with disease progression in either arm, the concordance rate in terms of the timing of disease progression was lower [redacted]. The manufacturer states that for both arms, discordance in the timing of disease progression was mostly due to progression events that occurred earlier based on IRC assessments compared with the investigators' assessments.

Secondary outcomes

A summary of the results of the secondary outcomes, that is, event-free survival, overall survival, time to next anti-lymphoma treatment, time to next chemotherapy treatment, overall response rate at the end of maintenance observation and transformation rate at first progression, is presented for the January 2009 and 2010 data cut-off periods in tables 2 and 3.

Table 2 Secondary outcomes – January 2009

End point	Rituximab maintenance (N = 515)	Observation (N = 505)	HR/OR (95% CI)	p value
Secondary end points				
Event-free survival				
Median time to event	[redacted]	[redacted]		

End point	Rituximab maintenance (N = 515)	Observation (N = 505)	HR/OR (95% CI)	p value
25th percentile	[redacted]	[redacted]	[redacted]	[redacted]
1-year event-free rate (95% CI)	[redacted]	[redacted]		
Overall survival				
Median time to event	[redacted]	[redacted]		
25th percentile	[redacted]	[redacted]	[redacted]	[redacted]
1-year event-free rate (95% CI)	[redacted]	[redacted]		
Time to next anti-lymphoma treatment				
Median time to event	NE	NE		
25th percentile	1135 days (37.3 months)	746 days (24.5 months)	HR = 0.61 (0.46 to 0.80)	p = 0.0003
1-year event-free rate (95% CI)	0.92 (0.89 to 0.94)	0.89 (0.87 to 0.92)		
Time to next CTX treatment				
Median time to event	NE	NE		
25th percentile	1135 days (37.3 months)	884 days (29.0 months)	HR = 0.60 (0.44 to 0.82)	p = 0.0011
1-year event-free rate (95% CI)	0.92 (0.90 to 0.95)	0.91 (0.89 to 0.94)		
Overall response rate at the end of maintenance/observation				
N (excluding patients still ongoing maintenance)	N = 389	N = 398		
Responders (CR, CRu, PR)	288 (74%)	219 (55%)	Diff: 19.01 (12.3 to 25.7)	p < 0.0001
Non-responders	101 (26%)	179 (45%)	OR = 2.33 (1.73 to 3.15)	
Patients with complete response (CR/CRu)	260 (66.8%)	190 (47.7%)		
partial response	28 (7.2%)	29 (7.3%)		
stable disease	0 (0%)	1 (0.3%)		
progressive disease	79 (20.3%)	162 (40.7%)		
Transformation rate at first progression				
Patients with progression	[redacted]	[redacted]		
Transformation	[redacted]	[redacted]	[redacted]	[redacted]
No transformation (no progression/missing)	[redacted]	[redacted]	[redacted]	

CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; CTX, chemotherapy; HR, hazard ratio; NE, not estimable; OR, odds ratio; PR, partial response.

Table 3 Secondary outcomes – January 2010

End point	Rituximab maintenance (N = 515)	Observation (N = 505)	HR/OR (95% CI)	p value
Secondary end points				
Event-free survival				
Median time to event				
25th percentile				
1-year event-free rate (95% CI)				
Overall survival				
Median time to event				
25th percentile				
1-year event-free rate (95% CI)				
Time to next anti-lymphoma treatment				
Median time to event				
25th percentile				
1-year event-free rate (95% CI)				
Time to next CTX treatment				
Median time to event				
25th percentile				
1-year event-free rate (95% CI)				
Overall response rate at the end of maintenance/observation				
N (excluding patients still ongoing maintenance)				
Responders (CR, CRu, PR)				
Non-responders				
Patients with complete response (CR/CRu)				
partial response				
stable disease				
progressive disease				
Patients with progression				
Death without progression				

CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; CTX, chemotherapy; HR, hazard ratio; NE, not estimable; OR, odds ratio; PR, partial response.

EORTC 20981 results

In the EORTC 20981 study (people with relapsed or resistant follicular non-Hodgkin's lymphoma), maintenance treatment with rituximab significantly improved progression-free survival compared with observation (median 3.7 years versus 1.3 years). Five-year overall survival was not significantly different between the arms (74% in the rituximab maintenance arm and 64% in the observation arm). The authors suggest that this lack of difference may be partly because of the 'unbalanced use of rituximab in post-protocol salvage treatment'. Maintenance with rituximab was associated with statistically significant increases in grade 3 and 4 infections.

Adverse events

A summary of the results of the toxicities and adverse events from the PRIMA study for the maintenance rituximab and observation arms is presented for the January 2009 and 2010 data cut-off periods in tables 4 and 5.

Table 4 January 2009 – adverse events

Safety parameter	Rituximab maintenance N = 501 n (%)	Observation N = 508 n (%)
Toxicities	485 (97)	459 (90)
Adverse events	263 (52)	179 (35)
Grade 3/4 adverse events	114 (23)	81 (16)
Serious adverse events	95 (19)	63 (12)
Withdrawal from treatment because of toxicity	10 (2)	1 (<1)
Adverse events leading to treatment discontinuation	19 (4)	8 (2)
Adverse events leading to dose modification	30 (6)	–
Adverse events leading to death	3 (<1)	2 (<1)
Infection adverse events (Grade ≥ 2)	184 (37)	114 (22)
Grade 3/4 infections	22 (4)	5 (<1)
Adverse events occurring within 1 day of treatment or observation visit	61 (12)	46 (9)
Total deaths	13 (3)	18 (4)
Death due to cause other than lymphoma	3 (<1)	6 (1)

The incidence of adverse events was higher in the rituximab maintenance arm compared with the observation arm. This difference was mainly driven by the infections and infestations observed in the rituximab maintenance arm (37% of people in the rituximab arm compared to 22% in the observation arm). The manufacturer stated that rituximab maintenance therapy was well tolerated and no unexpected safety findings were observed.

Table 5 January 2010 – adverse events

Safety parameter	Rituximab N = 501 n (%)	Observation N = 508 n (%)
Adverse events	[redacted]	[redacted]
Grade 3/4 adverse events	[redacted]	[redacted]
Serious adverse events	[redacted]	[redacted]
Adverse events leading to treatment discontinuation	[redacted]	[redacted]
Toxic death	[redacted]	[redacted]

Grade 1 infections and Grade 1 and 2 adverse events other than infections were not reported during the maintenance or observation phase in the PRIMA study except as toxicities. The study protocol also did not clearly specify the mandatory collection of serious adverse events in the observation arm. However, the manufacturer assessed the proportion of adverse events that were reported as serious adverse events in both arms of the PRIMA trial and was confident that systematic under-reporting of serious adverse effects in the observation arm did not occur.

Health-related quality of life

In general, no difference in quality of life was observed between the rituximab maintenance and observation arms (for more information see pages 46−47 of the ERG report).

Evidence Review Group comments

In general, the ERG considered that all major electronic databases were searched by the manufacturer and that a clear definition of the searches carried out by the manufacturer was provided. The ERG noted that although more than 30 publications were identified that included maintenance therapy with various regimens these were not included in the final review stage. The manufacturer did not justify why these trials were not included and therefore the ERG has been unable to verify whether these trials have been correctly excluded.

The ERG was confident that the PRIMA study was relevant in regard to the inclusion criteria set by the manufacturer. The ERG noted that in the inclusion criteria set by the manufacturer for their search, studies where chemotherapy alone was used an induction treatment, were not considered. The ERG thought that this could have led to the exclusion of studies in which chemotherapy is given as an induction treatment, followed by rituximab maintenance treatment. The ERG gave the ECOG 1496 study as an example of such a study that had not been identified by the manufacturer and which

might have been relevant for this appraisal. In the ECOG 1496 study, people with previously untreated follicular non-Hodgkin's lymphoma were randomised to CVP (cyclophosphamide, vincristine and prednisolone) induction therapy and those whose disease responded were further randomised to rituximab maintenance therapy or observation.

PRIMA study

The ERG considered that the PRIMA study was of good design with centralised, random allocation that was stratified in terms of induction regimen, centre and response to induction therapy. The ERG considered the method of stratification appropriate.

The ERG noted that the PRIMA study was open-label and that blinding is important in trials in which the primary outcome is progression-free survival. It noted that the results of the PRIMA study were also assessed by an independent review committee (IRC) of radiological and clinical data. This IRC was blinded to treatment allocation and investigator assessment of response and/or progression so that possible bias would be avoided. The ERG noted that the robustness of the results of progression-free survival was verified by the results from the IRC, and therefore they considered that the unblinding of investigators was not an issue.

The ERG considered that the baseline characteristics and gender distribution of people in the PRIMA study at the induction phase and maintenance or observation phase were similar. It noted that people in the PRIMA study were slightly younger than those usually seen in the clinical setting. However, the ERG acknowledged that this is often reported in randomised controlled studies.

The ERG considered that the rituximab chemotherapy regimens used in the PRIMA trial (that is, R-CHOP, R-CVP and R-FCM) are appropriate and in line with the rituximab chemotherapy regimens used in UK clinical practice. In

general, the ERG believed that the results of the PRIMA study are generalisable to the UK setting.

The main areas of concern and uncertainty highlighted by the ERG on the clinical-effectiveness section in the manufacturer's submission included:

- The ERG noted that in January 2009 (after a follow-up period of 25 months) the DSMC suggested a premature closure of the study on the grounds that the primary objective had been met. At the time of e study closure, only 18.4% (93 out of 505) of the participants in the rituximab arm and 33.9% (174 out of 513) of those in the observation arm had experienced an event (disease progression, relapse or death). The follow-up was no longer than 4 years (despite the protocol amendment that specified a follow-up of 7 years) and in most of the cases the manufacturer could not estimate the median time to event. The ERG was concerned that the data were immature and that an early closure of a trial might lead to an overestimation of the clinical benefits of an intervention that might not necessarily be verified by later data.

- The ERG noted that 6 months after the start of the study the primary end point of event-free survival was changed to progression-free survival. The ERG thought that this change was implemented in line with the outcomes of interest of the FDA, EMA and NICE. The ERG considered that event-free survival is a more informative primary end point than progression-free survival because it better reflects clinical practice. However, the ERG acknowledged that because of the open-label design of the study, the use of event-free survival as a primary end point might include a higher risk of bias. The ERG further noted that a number of other amendments were made to the study protocol.

- Post-progression treatments are likely to affect the overall survival outcome. The ERG noted that the post-progression treatments

considered in the manufacturer's submission are in line with those used in UK clinical practice. However, it was unclear from the data whether the time that these treatments were offered in the trial truly reflects the time that they would be used in routine practice.

- The ERG noted the information fraction approach adopted in the trial (that is, after 75% of events had occurred) and acknowledged that this is an approach commonly used and is considered appropriate from a statistical point of view. However, it noted that its use might be controversial in the case where reported events are rare. The ERG suggested the use of the calendar time approach may have been a better alternative as, in cases where few events are observed, it can provide a reasonable approximation of information fraction (that is, yearly, after the first 2 years of recruitment) because it can lead to a longer follow-up period.

- The ERG noted that the percentage of people experiencing an event was based on the total number of participants in each arm rather than the total number of people assessed by the IRC. This approach led to a slight difference in the progression-free results reported; that is, [redacted]% in the maintenance rituximab arm (instead of [redacted]%) and [redacted]% in the observation arm (instead of [redacted]%).

- The clinical advisors to the ERG confirmed that people generally tolerate rituximab well.

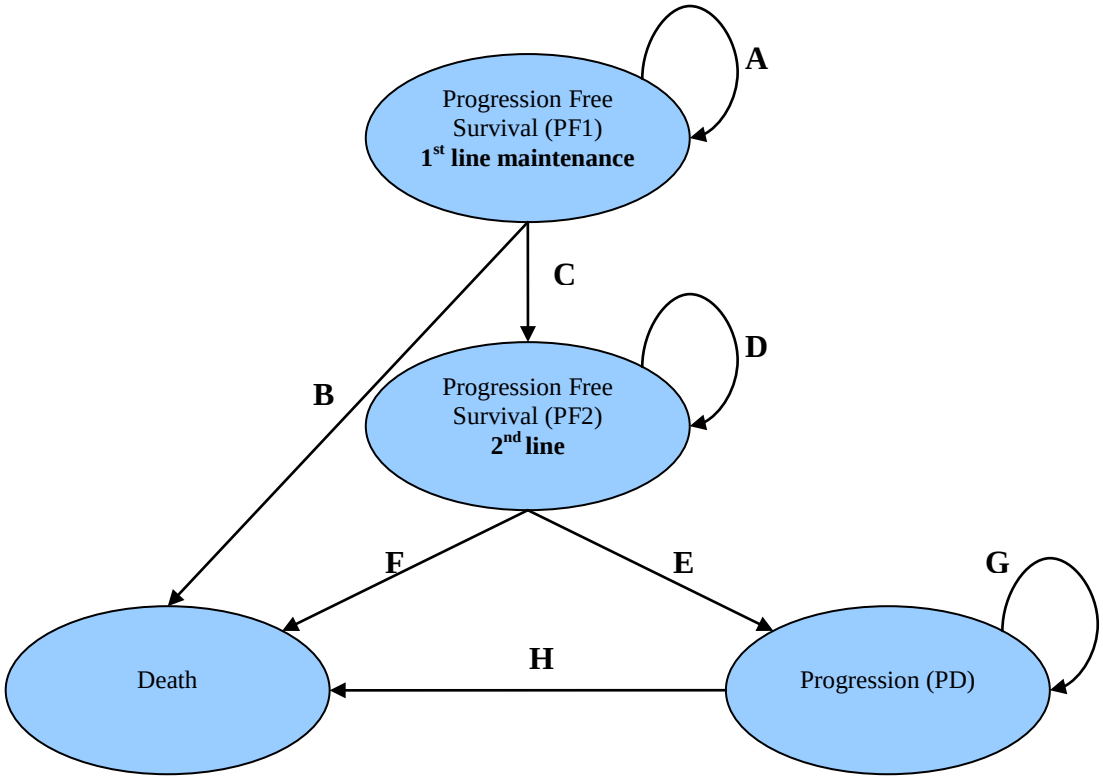
3 Cost effectiveness

Cost effectiveness in the manufacturer's submission

The manufacturer undertook a systematic literature review to identify cost-effectiveness studies of rituximab as a first-line maintenance treatment of

follicular lymphoma. None of the identified studies (n = 397, 14 potential cost-effectiveness studies) met the inclusion criteria set by the manufacturer.

The manufacturer produced a Markov economic model to estimate all-life time costs and benefits resulting from the treatment of follicular lymphoma after first-line induction with different regimens of rituximab chemotherapy (R-CHOP, R-CVP, R-FCM). The population included in the economic analysis was people who had been treated in the first-line setting with rituximab plus chemotherapy (in line with the indicative licensed indication). The model had four distinct health states: progression-free survival–first-line maintenance phase (PF1), progression free survival–second-line maintenance phase (PF2), progressive disease (PD) and death, as shown in the figure below. The manufacturer stated that based on clinical expert opinion the structure of the model reflects current clinical practice and the treatment pathway, and how these might change after the introduction of first-line maintenance treatment. It was assumed that all people enter the economic model in the PF1 health state ('A' in the figure below) after successful completion of the induction treatment with rituximab chemotherapy (that is, the start of the model reflects the start of the PRIMA study). At the end of each cycle, patients either remain in the PF1 state or move to PF2 ('C' in the figure below) or die ('B' in the figure below). Once a patient is in the PF2 health state, then can remain in that state ('D' in the figure below) and continue to receive either rituximab chemotherapy or chemotherapy, or they can die at the end of each cycle ('F' in the figure below) or they can transition to the progressive disease (PD) state ('E' in the figure below). Patients in the progressive disease state either remain in that state ('G' in the figure below) or die at the end of each cycle ('H' in the figure below). The manufacturer stated that although all patients incur the cost of the induction treatment (a one-off cost), they do not receive an additional benefit. The model had a cycle of 1 month and a follow-up period of 25 years. A half cycle correction was applied to the model.



The manufacturer used the latest data from the PRIMA study ('snapshot' June 2010) and EORTC 20981 study (from Van Oers et al. 2010) to estimate the transition probabilities for all health states in the economic model. The data from the PRIMA study were used to inform the transition probabilities and the monthly probability of dying in the PF1 health state. In this health state, the progression-free survival data for both arms were extrapolated using the Gompertz function because it was found to have the best fit. It was assumed that people in the PF1 health state retain the clinical benefit from rituximab maintenance treatment in the first 72 months (based on the results from the Van Oers study) and then PF1 is assumed to be equal in both arms. The manufacturer stated that this assumption was also supported by clinical expert opinion on the long-term effect of rituximab maintenance treatment. The percentage of people who relapsed − in both arms of the PRIMA study − within 1 year of stopping rituximab was used to determine the second-line assumption for each patient group.

The latest data from the EORTC 20981 study were used to estimate the transition probabilities for the PD health state for people receiving rituximab induction followed by rituximab maintenance and for those receiving chemotherapy. Data from the EORTC 20981 study were also used to determine the monthly probability in the PF2 and PD health states. The progression-free and overall survival data from the EORTC 20981 study were combined to estimate post-progression survival because of the high censoring in overall survival in the PRIMA study ([redacted]% for rituximab and [redacted]% in the observation arm, June 2010). Data from the 2006 cut-off period of the EORTC 20981 study were used to calculate post-progression treatments, adverse events and their associated costs.

Health-related quality of life data were collected and assessed in the PRIMA study using the FACT-G and EPRTC QLQ-C30 questionnaires. The manufacturer stated that in general no differences in this data were observed between the rituximab maintenance and observation arms. The manufacturer also conducted a systematic literature review to identify quality of life studies. In total, 143 studies were identified but only one of them (Pettengel et al, 2008) met the inclusion criteria. In this study, 222 people aged 18 or older with histologically-confirmed follicular lymphoma and an ECOG of 0−2 were included. EQ-5D questionnaires were collected from 215 people (for more information on utility values, please see page 281 of the manufacturer's submission). A summary of the utility values used in the economic model and their respective sources are summarised in table 6.

Table 6 Utility values used in the economic model

State	Utility value	Confidence interval	Reference in submission	Justification
PF1	0.88	(0.81, 0.95)	Section 6.4.6 of the manufacturer's submission	Published utility value (Pettengell et al. 2008)
PF2	0.79	(0.72, 0.86)	Section 6.4.6 of the manufacturer's	Published utility value (Pettengell

			submission	et al. 2008)
Progressive disease	0.62	(0.48, 0.76)	Section 6.4.6 of the manufacturer submission	Published utility value (Pettengell et al. 2008)
PF1, progression-free survival–first-line maintenance phase; PF2, progression-free survival–second-line maintenance phase.				

The following resources were included in the economic model: drug acquisition and administration costs, supportive care costs, management of adverse events and health state, and associated costs (for more information, please see tables 107−109, pages 293−296 of the manufacturer's submission). The main sources of these costs were the British National Formulary (edition 56 used by the manufacturer, edition 59 used by the ERG), the NHS Reference Cost Schedule 08−09 and PSSRU 2009 (unit costs of health and social care). It was assumed that grade 3 and 4 adverse events incur the same costs. The average cost of managing adverse events was estimated from the PRIMA and EORTC 20981 studies. Costs and benefits were discounted at 3.5% per annum. For more information, please see pages 59−60 of the ERG report and pages 287−297 of the manufacturer's submission.

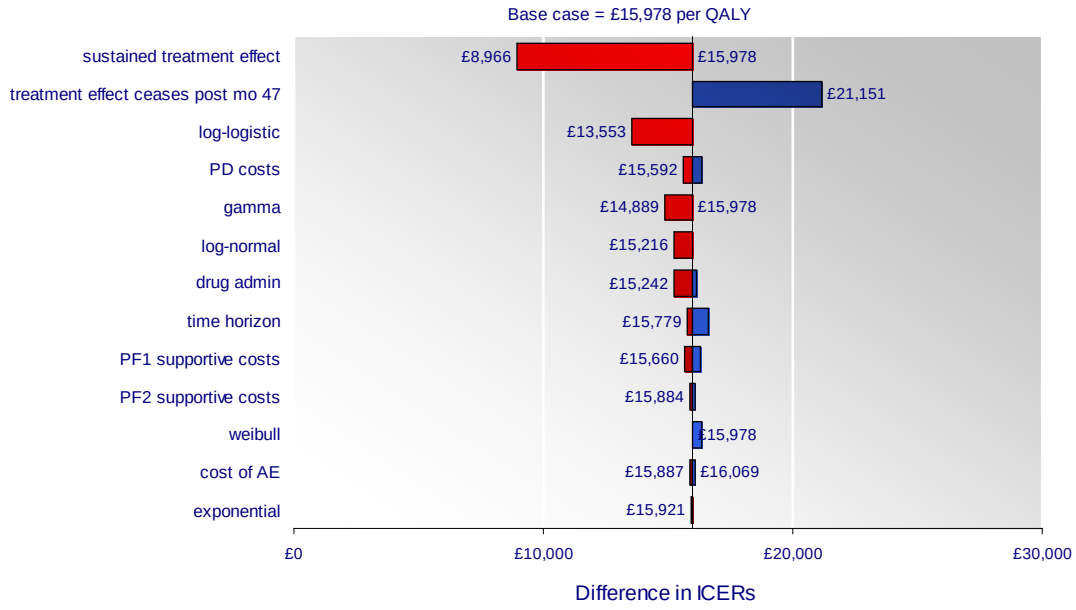
Results

A summary of the results of the base case is provided in table 7.

Table 7 Summary results of the base case

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Observation in first-line maintenance treatment	£66,721	9.017	7.207	£18,681	1.271	1.169	£15,978
Rituximab in first-line maintenance treatment	£85,403	10.288	8.376				
ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.							

In sensitivity analyses, the impact of varying adverse event costs (± 50%), monthly supportive care costs (± 50%), rituximab administration costs (upper = £267, lower = £167), time horizon (20 years, 30 years), extreme scenario (people who progress in PF1 transition to death) were explored. The incremental cost-effectiveness ratios (ICERs) were sensitive when sustained treatment effect was assumed (£8966 per quality-adjusted life year [QALY] gained) and when treatment effect was assumed to cease after 47 months of treatment (£21,151 per QALY gained). Changes to the other parameters did not greatly influence the ICERs, as shown in the diagram below.



In the extreme scenario, where it is assumed that people from PF1 transition to death, the results were presented separately by the manufacturer. These are shown in table 8.

Table 8 Extreme scenario

	Intervention arm (rituximab first-line maintenance)	Comparator arm (observation)	Incremental
Mean life years	6.151	4.579	1.572
Mean total QALYS	5.41	4.04	1.37
Mean total cost	£35,779	£16,734	£19,045
ICER			£13,901 per QALY
ICER, incremental cost-effectiveness ratio; LYG, life year gained; QALY, quality-adjusted life year.			

Probabilistic sensitivity analyses were conducted by the manufacturer where all the parameters, except for age, weight and height, were included. The mean ICER was £15,770 per QALY gained. The probability of rituximab being cost effective at a threshold of £20,000 or less was 84.2%, at a threshold of £30,000 or less was 99.7% and at a threshold of more than £30,000 was 0.3%.

Evidence Review Group comments

The ERG noted the systematic literature review undertaken by the manufacturer and was confident that no relevant cost-effectiveness studies were available.

The ERG thought that the manufacturer's approach not to include Zevalin as a comparator in the economic analysis was well justified. The ERG thought that the economic model included a number of implementation problems however they were considered not to have a major impact on the cost-effectiveness results. These included the estimation of deaths, and of event rates from the EORTC 20981 study, calculation of the proportion of patients failing the first PFS period (observation or RTX maintenance) but who did not progress to second-line induction therapy, discounting, mid-cycle correction, adverse events and health state costs, utility values used in PF1 and PF2 health states, cost of rituximab and the timing of rituximab maintenance doses.

It further noted a number of structural problems in the economic model. The ERG stated that it could not correct some of these problems but that it was unlikely that they will have an impact on any decision based on the assessment of cost effectiveness.

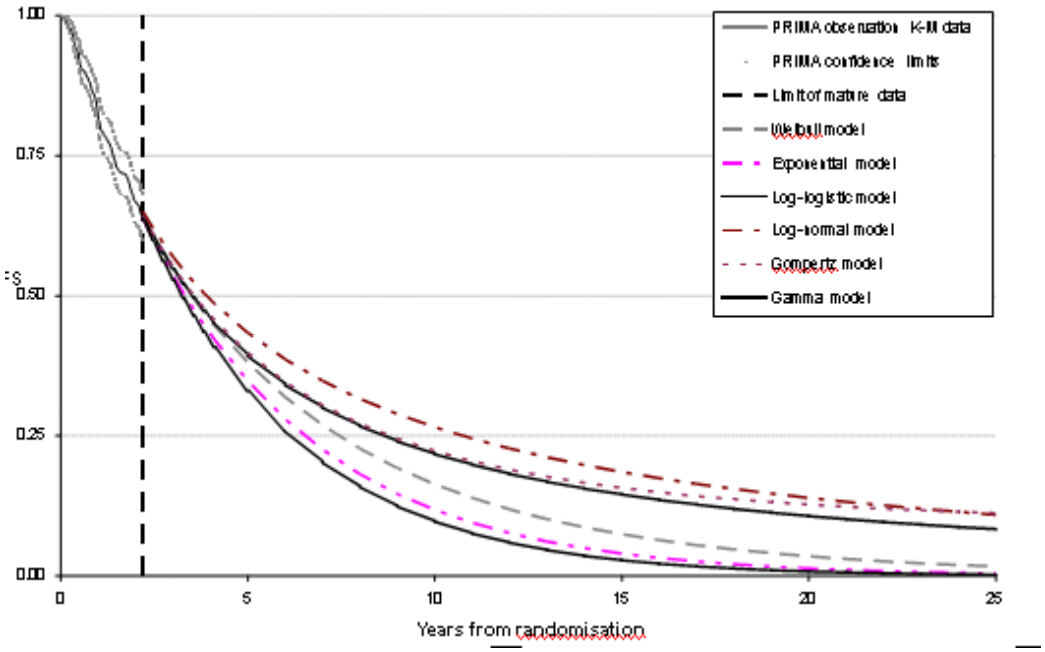
The main areas of concern and uncertainty about the cost-effectiveness evidence highlighted by the ERG included the following points:

Extrapolation of trial data

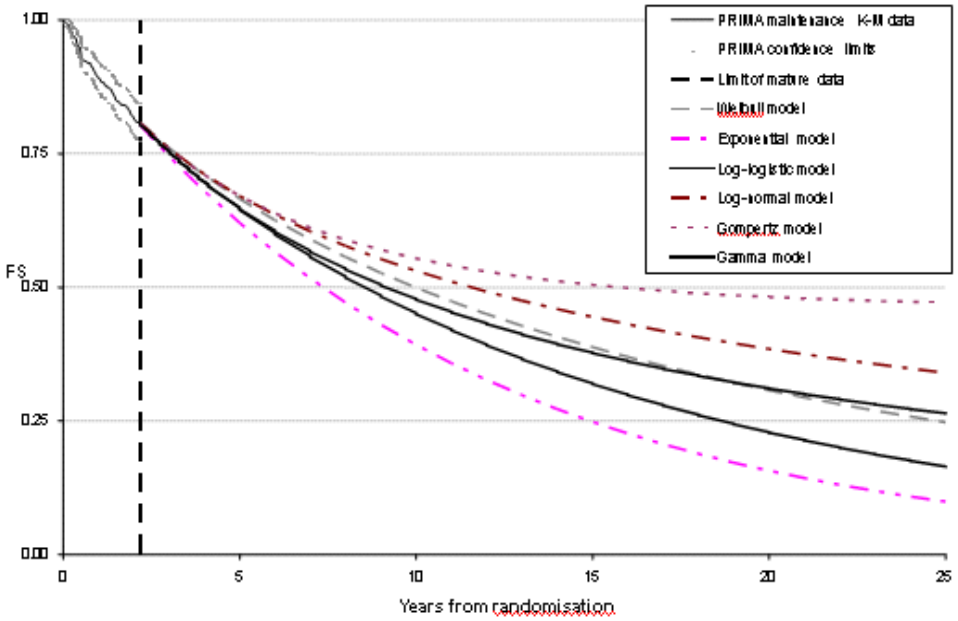
- The ERG noted that the proportion of censored patients is low (less than 3%) during the first 800 days but greatly increases by 1600 days (70% for rituximab maintenance and 50% for observation). The ERG believes that although the Kaplan–Meier survival estimate up to 800 days is reliable, it becomes uncertain after that time point and therefore raises concerns about the use of long-term modelling to inform the duration of the economic model. The ERG noted that the manufacturer used the parametric function that generated the highest overall survival estimate (that is, the Gompertz

parametric function) to model progression-free survival for the model. The diagrams below depict the difficulty of choosing a parametric function to model progression-free survival, suggesting that the decision on modelling progression-free survival should be based on criteria other than statistical grounds.

Observation Arm



Maintenance Arm



- The clinical advisors to the ERG confirmed that only few people are expected to be alive with either progression-free or relapse-free disease after 25 years.

- The ERG noted that in the base case the manufacturer assumed a 6-year duration of rituximab clinical benefit and alternative durations were explored in sensitivity analyses (4 years and 40 years). The ERG noted that when the duration of clinical benefit of rituximab maintenance treatment is assumed to be continued up to 800 days, this result in an ICER of £32,230 per QALY gained. The ERG noted the approach used by the manufacturer is such that even after the end of the assumed rituximab benefit period, the rituximab arm will continue to achieve survival gains and the observation and rituximab curves will never converge. The ERG noted that in the base case more than 72% of the progression-free survival gain is observed after 4 years. Therefore, if progression-free survival gain is progressively lost, it will result in a reduction in the incremental outcomes and the ICER could

increase by three times depending on the time period over which the difference in progression-free survival curves stops.

- The ERG noted that the manufacturer assumed a 96.6% conversion rate of progression-free survival gain to overall survival gain (that is, all the overall survival gain comes from the extra progression-free survival gain and not the post-progression survival). The ERG explored the impact of different rates of conversion of progression-free survival gain into overall survival gain on the estimated ICER. In this analysis at least 50% of progression-free survival gain would need to be converted into overall survival gain to achieve an ICER below £30,000 per QALY gained. The ERG further noted that if an extrapolation function other than the Gompertz parametric function was used, then the required conversion rate from progression-free survival into overall survival would probably need to be higher to achieve similar ICERs.

- The ERG noted from the manufacturer's analyses that there is evidence to show that as the age of the person receiving treatment increases, the clinical benefit of rituximab decreases. The clinical advisors to the ERG confirmed that the age of a person diagnosed with follicular non-Hodgkin's lymphoma can possibly determine the clinical benefit that the person can receive from a novel regimen. The ERG adjusted the hazard ratio of progression-free survival in the manufacturer's base case to reflect specific age groups. The results showed that an increase in mortality and a decrease in effectiveness can have a major impact on the ICERs.

- The ERG was concerned about the manufacturer's approach of using data from the EORTC 20981 study to inform the economic model. The ERG noted that the participants in this study are at different stages of the disease and are rituximab-naive. Therefore, the ERG questioned whether

the outcomes from the EORTC 20981 study can be reliably used to predict future outcomes for participants in the PRIMA study.

- The ERG noted that the manufacturer used a simple exponential model. Ordinary least squares regression was used and the monthly risk parameter was calculated as the average rate over the first 12 months. The ERG identified the following two problems with the manufacturer's approach:

  - The ordinary least squares regression models allow variable starting values for survival to be computed, although it is noted that Kaplan–Meier data start with 100% of people event free at baseline.
  - The cumulative hazard plots for some of the data (especially for progression-free survival) show that there is strong evidence of non-linearity, with a period of early high risk, followed by a lower long-term risk.

Therefore, the ERG was concerned that these two points may cause some of the fitted models to be inaccurate or inappropriate for calibrating the manufacturer's model for the second-line maintenance phase.

Structural and implementation problems of the economic model

- The ERG considered that the time to next anti-lymphoma treatment may be a more informative endpoint than progression-free survival to drive the timing of transitioning to different health states. After a request by the ERG, the manufacturer provided a sensitivity analysis in which the impact of using the hazard ratio for event-free survival on the ICERs was explored. The ERG commented that this had a marginal impact on the ICER, which increased to £18,853 per QALY gained.

- The ERG noted that people who transition from PF1 to PF2 health states in the manufacturer's model were assumed to have disease that successfully responded to a second induction treatment. The ERG considered that the

non-inclusion of the second induction treatment in the model may result in a number of structural problems including the following:

- Time spent in second-line therapy is not included in the overall survival calculations and therefore costs and benefits might not have been properly discounted.
- Cost of the second-line therapy is incurred at the first cycle of PF2 health state and cannot be located in time.
- Disutilities of the progressive disease health state and for undergoing chemotherapy are not included.
- There has not been a pathway included that allows for failure to achieve remission at second induction therapy.

The ERG further noted that people could transition from PF2 to the progressive disease health state (in which a third-line treatment is embedded) although there are studies showing that it is common to have four lines of active treatment.

- The ERG considered that the approach used by the manufacturer to estimate death in the PF1 health state is problematic. It noted that the manufacturer used the estimated monthly death rate from the PRIMA study and the published mortality rates by age and sex for England and Wales. The ERG believed that the most appropriate approach to estimate death is to use the sum of the lymphoma rate and the age-specific population rate. It further suggested that the mortality rate should be applied to the number of people who survived at the start of the relevant period and not to a mid-cycle average as in the manufacturer's model.

- The ERG noted that disutilities for grade 3 and 4 adverse events have not been included in the model. This omission is more likely to favour the rituximab maintenance arm because people experience higher adverse events with rituximab. The ERG further believed that the second-line

adverse event costs are underestimated because most of the people had not progressed from the first-line maintenance or observation phase.

- The ERG noted that the manufacturer uses a utility of 0.88 for PF1 and 0.79 for PF2 health states. The ERG considered that the same utilities should be used in these two health states because people are in remission or full response in both PF1 and PF2.

- The ERG noted that when calculating the cost of rituximab (which is administered at a dose of 375 mg/m^2 body surface area) the manufacturer did not adjust for the wide range of body surface area (BSA) values in the population and gender-specific BSA differences (mean BSA: females 1.71 m^2, males 1.95 m^2). The ERG ran exploratory analyses in which these factors were considered and noted that the mean cost per dose of rituximab increased by 4.8% and the ICER by £882 per QALY gained.

- The ERG noted that discounting was not implemented correctly in the manufacturer's model (it was applied monthly instead of annually). The ERG ran exploratory analyses using annual discounting which increased the overall discounted cost per patient by 3.9% (£736), the incremental undiscounted QALY per patient by 1.9% (0.019) and the ICER by £370 per QALY gained.

- The ERG noted that in at least one variable (that is, death in progression-free survival) the mid-cycle correction was not applied correctly. It noted that death in progression-free survival was calculated by averaging a second variable in which a mid-cycle correction had already been implemented. The ERG stated that it is difficult to estimate the impact of this incorrect approach without reconstructing the economic model.

4 Equalities issues

No equalities issues were raised during the scoping exercise or in the manufacturer's submission for this appraisal.

5 Authors

Panagiota Vrouchou and Fiona Rinaldi, with input from the Lead Team (Neil Iosson, Rosa Legood and Eleanor Grey).

Appendix A: Sources of evidence considered in the preparation of the pre-meeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group:

- Bagust A, Boland A, Blundell M, et al. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma, October, 2010

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Roche Products

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

- Cancer Network Pharmacists Forum
- Leukaemia CARE
- Lymphoma Association
- Royal College of Physicians (on behalf of NCRI/RCP/RCR/ACP/JCCO)

The following individuals gave their expert personal view on rituximab maintenance treatment:

- Dr Robert Marcus – clinical specialist
- Professor Peter Johnson – clinical specialist

C Additional references used:

- Van Oers MHJ, van Glabbeke M, Giurgea L et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 Phase III randomized intergroup study. Journal of Clinical Oncology; 2010;28(17):2853-8.

- Pettengell R, Donatti C, Hoskin P et al. The impact of follicular lymphoma on health-related quality of life. Ann Oncol; 2008;19:570-76.