NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Roche
   - Lymphoma Association, Leukaemia CARE and Leukaemia & Lymphoma Research
   - National Cancer Research Institute, Royal College of Physicians, Royal College of Radiologists, Association of Clinical Pathologists and Joint Collegiate Council for Oncology
   - Royal College of Nursing
   - Royal College of Pathologists and the British Society for Haematology
   - Department of Health

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **ERG critique of extra information submitted by Roche**

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

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

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD2)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.	Comment noted.
Lymphoma Association, Leukaemia CARE and Leukaemia & Lymphoma Research	On behalf of the patients likely to be adversely affected by any decision not to approve first line maintenance treatment, we wish to express our strong concern at the committee's change of position. We understand the need to seek additional information from the manufacturer and are grateful to have the opportunity to comment on the ACD. However, we are surprised that this has resulted in a reversal of a previously held position, particularly as the input from three commissioning bodies seems to have tipped the balance and outweighed the views of clinical experts and patients. **Government policy to improve cancer outcomes in England** At a time when the government has a clear policy to save 5,000 lives from cancer and acknowledges that this country's survival rates are worse than other European countries, with less spending on cancer drugs, it is important that NICE makes decisions that support the overall commitment to improving outcomes. This treatment has been approved and is funded in the US, Canada, Germany, Spain, Israel and Scotland. If it is not funded, patients in England and Wales will be disadvantaged and England will be out of step with common practice in other countries. **Choice** By refusing to fund the treatment, NICE would be depriving clinicians and their patients of choice based on clinical judgement, personal circumstances and preferences. Not all patients will want to have maintenance therapy after first line	Comment noted. During the second meeting, the Committee considered that the evidence submitted by the manufacturer did not fully address the uncertainties surrounding the clinical and cost-effectiveness of rituximab maintenance treatment. The Committee also took into consideration comments received during consultation from stakeholders who strongly disagreed with the preliminary advice to recommend rituximab maintenance treatment, because they considered that there was a lot of uncertainty around the effect of treatment on survival and improved quality of life. In view of this, the Committee was minded not to recommend rituximab maintenance treatment unless further data was submitted to address uncertainties surrounding the evidence base. During the third committee meeting, the Committee were satisfied that the manufacturer had provided sufficient evidence to address the uncertainties that the Committee originally had surrounding the data. The recommendation in the Final Appraisal Determination (FAD) has been updated to state that rituximab maintenance therapy is

Consultee	Comment	Response
	treatment but many will as it is very hard for people to live with a life-threatening disease that they know will return, possibly within 18 months to two years. The significant extension of time to next treatment is a huge plus for patients. As has been acknowledged, maintenance rituximab is much easier to tolerate than chemotherapy and delivers much longer periods free from debilitating and toxic treatment regimens. There may be family circumstances that make it imperative for a patient to know they will remain disease free for as long as possible – for example, a woman with follicular lymphoma in her late sixties who is the main carer for her husband. Or a parent who has children taking important exams and who needs to remain well.	recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy (see FAD, section 1.1).
Lymphoma Association, Leukaemia CARE and Leukaemia & Lymphoma Research	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We do not believe that the provisional recommendations are a suitable basis for guidance to the NHS. For more mature data to be available, patients would have to wait years. When there is so much positive evidence of the benefit to patients, it is unethical to delay implementation. The equitable solution would be to authorise the use of the drug immediately with a condition that data on long-term survival is accrued. NICE should set a date for review of the drug at the earliest point at which there is sufficient data. There are several references, notably in the PCT comments, to the PRIMA trial having closed early and suggesting that there is a shortage of long-term data proving an ongoing benefit. We understand from the manufacturer's submission that "the study was stopped because the independent DSMC (in Sept 2009) declared that the study had reached its primary endpoint at the pre-specified interim analysis." It would have been unethical, and a violation of patients' consent, to have continued the trial beyond this endpoint. This issue has highlighted a disparity between two regulatory bodies which in effect amounts to the moving of goalposts. It is not acceptable that patients should suffer as a result of an inconsistent approach between two regulators. We also question the focus on overall survival. In our view this is not as	Comment noted. The Committee noted that despite following patients beyond the end of the PRIMA trial, the manufacturer could not estimate the overall survival associated with rituximab maintenance treatment because of the small number of deaths during this period. The Committee was aware that the trial stopped earlier than originally planned on advice from the trial's statisticians, and heard from the ERG that there is evidence suggesting that studies that have stopped earlier than planned often overestimate the clinical benefit. However, the Committee was satisfied, after advice from the clinical specialists, that progression-free survival for people treated with rituximab maintenance therapy in the PRIMA trial reflected the clinicians' observations from clinical practice. The Committee therefore concluded that the available evidence shows that first-line maintenance treatment with rituximab significantly improves progression-free survival compared with observation (see FAD, section

Consultee	Comment	Response
	important as progression free survival in this condition and is difficult to assess because of the relapsing and remitting course of the disease. The key factor for patients with follicular lymphoma is to delay the time before they will need to have more chemotherapy because the chemotherapy is a more toxic treatment and also becomes less effective with each successive treatment. For older patients in particular, the ability to tolerate successive regimes of chemotherapy reduces and therefore time gained through longer remissions is extremely important. This is particularly the case for patients not eligible for high dose therapy and transplant which may be a treatment option for younger patients.	4.5). The provisional recommendation in the FAD has been revised to 'Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first line induction therapy with rituximab in combination with chemotherapy' (see FAD, section 1.1). The Committee heard from the patient experts that using rituximab maintenance treatment instead of watchful waiting may delay the need for eventual chemotherapy on relapse of the disease (see FAD section 4.4).
Lymphoma Association, Leukaemia CARE and Leukaemia & Lymphoma Research	**Conclusion** We recognise that NICE has a difficult role and that the issues are complex. In an ideal world, there would be longer-term data but it would be highly unethical to deny patients access to first line maintenance rituximab when the evidence for its positive benefit in giving patients longer progression free survival is so clear. Pending longer-term data, we urge NICE to approve funding and to review this decision in a few years time.	Comment noted. The recommendation in the FAD has been revised to 'Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first line induction therapy with rituximab in combination with chemotherapy' (see FAD, section 1.1). The guidance on this technology will be considered for review in May 2014, at which time the Guidance Executive will decide whether rituximab maintenance treatment should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators (see FAD, section 7.1).

Consultee	Comment	Response
Roche Products	**Background** In the second ACD for the appraisal of rituximab for first-line maintenance treatment of NHL, the Committee requested a revised cost-effectiveness analysis that incorporates all the following assumptions: • Age at first-line induction: mean age of 62.5 years at the start of treatment. • Treatment effect: duration of clinical benefit from first-line rituximab maintenance treatment is 28 months, 36 months or 48 months. • Survival modelling: the extent that the benefit of mean progression-free survival from first-line rituximab maintenance treatment translates to mean overall survival gain is 70%, 80% or 90% (undiscounted and not adjusted for health-related quality of life). Following the Committee's request for further sensitivity analysis, Roche have reviewed and updated the original base case economic model and conducted the requested sensitivity analysis. In addition, following feedback from the ERG, further minor structural changes to the model have been provided to consider an alternative approach to more credibly model the 28 month limited treatment benefit analysis. **Results** When considering those scenarios which provide a plausible fit to the observed Phase III (PRIMA study) data, the requested sensitivity analyses (based on changes to age, duration of treatment benefit and extrapolation of PFS to OS) generated ICERs below £20,000 per QALY gained. Existing Economic Model The base case model was updated by increasing the starting age to 62.5 as requested by the NICE Committee. In addition, an error identified in the model costings for 1st line induction treatment was corrected. These two	Comment noted. The Committee was satisfied that the manufacturer's sensitivity analyses addressed the uncertainty that the Committee initially had when it considered the original analysis and presented the most plausible range of estimates for the duration of treatment effect and the translation from progression-free survival to overall survival gain.

Consultee	Comment	Response
	changes combined resulted in a revised base case ICER of £15,404 per QALY gained which was used as the basis of all subsequent sensitivity analyses. The requested sensitivity analysis was conducted utilising the base case model and considers a variety of limited treatment effect durations (28, 36 and 48 months) as well as a variety of undiscounted PFS to OS gain conversation rates (70%, 80% and 90%). This resulted in ICERs ranging from £21,507 to £32,260 per QALY gained. The only two scenarios that generated an ICER above £30,000 per QALY gained were where the duration of treatment benefit is limited to 28 months and the PFS to OS undiscounted conversion rate was 70% (£32,260) and 80% (£30,655). <u>Updated Economic Model</u> Upon further inspection of the visual fit of these models compared to the observed PFS data, it is clear that these two extreme scenarios provide a very poor fit to the existing data and therefore an alternative scenario to model the 28 month limited treatment effect sensitivity analysis was conducted in order to provide a more credible fit to the PRIMA data. The reasons for the request of the 28 month limited treatment effect sensitivity analysis was not brought about due to clinical expert opinion but rather the conjecture of the ERG during the 2nd Committee meeting. The ERG presented a new hypothesis that the duration of treatment effect offered by rituximab maintenance was limited to 28 months based upon the cumulative hazard plots from the PRIMA study, originally presented in the manufacturer's submission. Roche have considered carefully these comments made during Part I of the Committee meeting and have attempted to provide an alternate scenario based upon these considerations. This alternative approach provides a much better visual fit to the existing data and results in an ICER of £17,681 per QALY gained at an undiscounted	Comment noted: The Committee noted the ERG's concerns that patient-level data from the PRIMA trial indicated that the duration of effect from rituximab maintenance treatment appears to be 28 months, after which time patients treated with rituximab maintenance therapy experience a rate of progression no better or worse than that of patients not treated with rituximab maintenance therapy. The Committee heard from the clinical specialists that data from the PRIMA trial demonstrated that rituximab maintenance treatment is clinically effective to 36 months at least and there is no evidence that the effect diminishes over time; therefore, assuming a duration of benefit of only 28 months, as suggested by the ERG, may underestimate the actual effect of treatment. The Committee also heard from the

Consultee	Comment	Response
	PFS to OS gain conversion rate of 84.1%. Whilst Roche believe that our base case (Gompertz) is a credible means of modelling the PRIMA data *when our base case modelling assumptions are utilised*, for the purposes of the modelling the Committee's requested sensitivity analysis, we believe that this new approach presented in Section 1.3 of the ACD reflects a more legitimate methodology than that which was presented in Section 1.2 using the base case model structure. The further sensitivity analysis by altering the PFS to OS gain conversation rates to 70%, 80% and 90% are presented below. *Table provided, but not reproduced here.* **Experience from previous assessment of rituximab in follicular lymphoma** Whilst nearly all requested sensitivity analyses provided results in ICERs below £30,000 per QALY gained, Roche would still caution against the consideration of these sensitivity analyses as anything other than extreme scenario analyses, particularly with regards to the limited treatment effect duration, given the wealth of evidence available on rituximab in NHL which would suggest that these limited treatment durations are implausible in practice, as suggested below by the EORTC 20981 study. In the EORTC 20981 study on the role of rituximab in remission induction and maintenance of relapsed/resistant follicular Non-Hodgkin's Lymphoma, NICE provided positive guidance on a limited median length of follow-up of 39.4 months (very similar to the current PRIMA median follow-up of 38 months). Since the publication of TA137, a further analysis based on 6 years of follow-up has been published. Over this median follow-up period of 6 years, the treatment benefit remains statistically significant and clinically meaningful with a hazard ratio of 0.69 in patients receiving rituximab maintenance following induction treatment with R-CHOP and 0.55 in overall maintenance population. Clinical expert opinion strongly suggests that the patients with relapsed/resistant follicular lymphoma (EORTC 20981 population) will have	clinical specialists that the period over which rituximab is likely to have a benefit is probably 3 to 4 years (that is, 1 to 2 years beyond treatment). However, it further heard from the clinical specialists that it was not possible to predict a definite time period, and a duration of effect of up to 6 years, as seen in the EORTC 20981 study for second-line rituximab maintenance treatment, could be plausible. The Committee considered sensitivity analyses conducted by the manufacturer that assumed a duration of treatment effect of 28 months, 36 months and 48 months and noted that the ICERs ranged from £17,300 to £27,400 per QALY gained. The Committee was satisfied that the manufacturer's sensitivity analyses presented the most plausible range of estimates for the treatment effect in line with clinical opinion and the available data (see FAD section 4.9).

Consultee	Comment	Response
	a shorter duration of remission compared to those with previously untreated follicular lymphoma (PRIMA population). Therefore, it is reasonable to assume that the duration of benefit in patients with previously untreated follicular lymphoma receiving maintenance treatment with rituximab following a response to induction treatment with rituximab plus chemotherapy would be no worse than that observed in EORTC 20981. Therefore any analysis assuming a treatment benefit enduring less than 6 years should be treated with caution.	
Roche Products	**Has all of the relevant evidence been taken into account?** Following the Committee's request for further sensitivity analysis, Roche have reviewed and updated the original base case economic model, conducted the requested sensitivity analysis, and attempted further minor structural changes to the model necessary to consider the 28 month limited treatment benefit analysis proposed by the ERG. The following section 1.1 to 1.3 outline the sensitivity analyses results based on the clinical assumptions requested by NICE/ERG. The validity of these assumptions will be discussed briefly in section 1.4. 1.1. Updated Base Case analyses Two changes were made to the base case model in order to prepare for the range of sensitivity analyses requested. 1.Upon review of the Roche base case model, it was noted that the cost of first-line rituximab induction therapy was contained in the model, and furthermore, both the inclusion and the calculation of this cost was incorrect and not identical for both arms. This should not have been included, given that this cost was incurred prior to the start of the model (which begins with the commencement of first-line maintenance therapy or observation). Therefore this incorrect cost was removed from each arm, resulting in a decrease to the ICER from £15,978 to £15,088 per QALY gained. 2.The new (NICE/ERG requested) base case starting age was changed from 56 to 62.5 years. The average mortality rate for an individual aged 62 and 63	Comment noted. Comment noted. The Committee considered the revised base-case ICER from the manufacturer of £15,400 per QALY gained, which assumed that the mean age at induction was 62.5 years. The Committee was satisfied that the manufacturer's base-case analysis had appropriately adjusted for age and reflected the average patient population seen in UK clinical practice (see FAD, section 4.8).

Consultee	Comment	Response
	was utilised to obtain the appropriate starting background mortality figure. The result is an increase to the ICER from £15,088 to £15,404 per QALY gained. It should also be noted by increasing the age of the patients in the economic analysis, the effective undiscounted PFS to OS conversion rate decreases from 97.4% to 89.2%. *Table provided, but not reproduced here.* This updated base case ICER of £15,404 per QALY gained is used as the basis of the subsequent sensitivity analysis which tests various undiscounted PFS to OS conversation rates and durations of treatment effect.	
Roche Products	**Has all of the relevant evidence been taken into account?** **1.2 Sensitivity Analysis for limited treatment effect using the base case model** Based on the updated base case analysis described in Section 1.1, the results of limiting the treatment effect to 28, 36 and 48 months are presented in Table 3 below along with the base case scenario of 72 months. Three sets of results are presented for each treatment duration scenario, representing a 70%, 80%, or 90% undiscounted conversion of PFS to OS gains. This was generated by (1) calculating and applying the hazard ratio from PRIMA based on each requested truncation point (see Table 2), then (2) limiting the treatment duration to the specified number of months, and finally (3) adjusting the progression to death transition rate in the model for the intervention arm to calibrate the results to reflect a 70%, 80% or 90% undiscounted PFS to OS gain conversion rate. The adjustment factors required for this calibration are presented in the Appendix. *Table provided, but not reproduced here.* Roche would strongly suggest that if the assumed treatment duration is limited to a pre-specified time horizon, the assumed treatment effect should be calculated based on and consistent with the corresponding time horizon observed in PRIMA (as illustrated in Table 2 above).	Comment noted. The Committee considered sensitivity analyses conducted by the manufacturer that assumed a duration of treatment effect of 28 months, 36 months and 48 months and a conversion rate of PFS to OS of 70%, 80% and 90%, and noted that the ICERs ranged from £17,300 to £27,400 per QALY gained. The Committee was satisfied that the manufacturer's sensitivity analyses presented the most plausible range of estimates for the treatment effect and the conversion rates, in line with clinical opinion and the available data. The Committee heard from the manufacturer that the conversion rate was not an actual input in the model and could only be adjusted by artificially modifying other parameters. As such, the manufacturer was concerned that its

Consultee	Comment	Response
	Table provided, but not reproduced here. From Table 3, it is clear that all sensitivity analyses presented resulted in ICERs below the NICE defined threshold of £30,000 per QALY gained with the exception of only two extreme scenarios where the duration of treatment benefit is limited to 28 months and the PFS to OS undiscounted conversion rate is less than 80%. As described in the previous ACD, this sensitivity analyses should be considered with caution given that the underlying assumptions necessary to simulate this assumed conversion rate may not be based on clinically plausible assumptions. It should also be noted that these extreme analyses provide a poor fit to the observed PFS data from PRIMA, as demonstrated by the comparison of fits from the base case (72 months treatment effect) versus the most extreme sensitivity analysis assuming 28 months treatment effect and a 70% PFS to OS conversion ratio in Figures 1 and 2 respectively below). *Figures provided, but not reproduced here.*	revised analyses, which were requested by the Committee, were driven by implausible assumptions. The Committee noted the manufacturer's concerns but was satisfied that the sensitivity analyses addressed the uncertainty that the Committee initially had about the translation from progression-free survival to overall survival gain in the original analysis (see FAD sections 4.9 and 4.10).
Roche Products	**Has the relevant evidence has been taken into account?** **1.3 Alternative method for modelling cessation of treatment effect at 28 months** To provide a more credible reflection to the PRIMA data than that provided in the sensitivity analysis presented in Section 1.2, an alternative approach is provided below which presents an approach to the requested 28 month limited treatment benefit analysis that more accurately reflects the underlining phase III data. During the 2nd Committee meeting, the ERG representative proposed a new hypothesis that the duration of treatment effect offered by rituximab maintenance was limited to only 28 months based upon the cumulative hazard plots from the PRIMA study (see Figure 5 below). Roche have considered carefully the comments made during Part I of the Committee meeting and have provided an alternate scenario based upon our	Comment noted. The Committee was satisfied that the manufacturer's sensitivity analyses presented the most plausible range of estimates for the treatment effect in line with clinical opinion and the available data (see FAD section 4.9).

Consultee	Comment	Response
	understanding of the ERG's hypothesis in which the treatment effect associated with rituximab is limited to 28 months. The modelling concepts underlying this approach are described in Section 1.3.1 followed by the application of this approach to the PRIMA dataset in Section 1.3.2. 1.3.1 Interpreting Cumulative Hazard Plots A cumulative hazard plot allows one to present time to event data in a manner that enables relatively clear assessment of the way in which the hazard (instantaneous risk) of an event changes over time (the absolute hazard) and the way in which the relative hazard between two treatments changes over time (the hazard ratio). It can be generated by plotting the negative log of the Kaplan-Meier (KM) survival probability at each time point plotted against time. The slope of a cumulative hazard plot is the absolute hazard of the event occurring at that point in time. If the slope is higher then the risk of that event occurring at that time is higher. If presented with two cumulative hazard curves associated with an undesirable event (such as disease progression) then the curve with the flatter (i.e. lower gradient) slope is associated with a lower hazard and improved outcomes relative to the comparator (see Figure 3 below for a pictorial representation). The ratio of the slopes of any two cumulative hazard curves at any point in time is the ratio of the absolute hazards of an event at that time, or the hazard ratio. The greater the difference in slopes between two curves the greater the difference in the absolute hazards of the two curves and therefore the better the hazard ratio. *Figure provided, but not reproduced here.* From these two pieces of information from a cumulative hazard plot, we can determine both the extent (i.e. the value of the hazard ratio - how big the divergence in slopes between two curves) and duration the treatment effect (i.e. how long the curves continue to separate) provided by some intervention. For example in Figure 4 below, the two cumulative hazards appear to separate up to time t (the duration of treatment benefit) with a ratio of the two hazards of 0.5 (the treatment effect) with the hazard ratio then	

Consultee	Comment	Response
	equal to 1 beyond that (no further gain from treatment). Furthermore, a method for extrapolating curves can be based upon the trends observed in the cumulative hazard plots. A completely straight cumulative hazard plot would indicate that the absolute hazard of an event occurring is constant over time and that therefore an exponential function would be an appropriate fit for extrapolation (in which the straight line is extrapolated). If two defined constant hazard periods are observed (i.e. the curve appears to be a joining of two straight lines with different slopes) then it may be more appropriate to utilise two exponential functions with the latter 'stabilised' hazard utilised for extrapolation (i.e. if there is a 'kink' in the curve one extrapolates with the straight line observed after the kink). *Figure provided, but not reproduced here.*	
Roche Products	**Has the relevant evidence has been taken into account?** <u>1.3.2 Alternative PRIMA modelling approach for 28 month limited treatment duration</u> Considering the cumulative hazard plot for PRIMA in Figure 5 below, the data indicates that a single exponential function would be an appropriate way of extrapolating the rituximab arm (given that the rituximab cumulative hazard plot is a straight line throughout the observed period). As such, it may be expected that this constant slope (i.e. hazard) would continue beyond the observed period. Whilst the rituximab hazard is constant throughout the duration of follow-up, the observation arm may appear to be made of two defined linear phases (steadily separating from the rituximab hazard up to 28 months and then drawing parallel to the rituximab hazard after 28 months). *Figure provided, but not reproduced here.* Therefore following consideration of the observation made by the ERG during the 2nd NICE committee meeting, we have presented an alternative revised scenario based on ERG feedback in which a simple exponential function has been utilised for extrapolating the two curves rather than the	Comment noted. The Committee was satisfied that the manufacturer's sensitivity analyses presented the most plausible range of estimates for the treatment effect in line with clinical opinion and the available data (see FAD section 4.9). In response to the ERG's concern during the second Appraisal Committee meeting that the duration of clinical benefit may last only 28 months (based on the cumulative hazard plots from the PRIMA trial), the manufacturer provided an alternative method to model the rituximab treatment effect stopping at 28 months. This entailed using an exponential function (instead of the Gompertz function from

Consultee	Comment	Response
	Gompertz function utilised in the original submission. We have fitted a new exponential curve to the first 28 months of the observation arm and applied it within an economic model. Beyond this period we have utilised the hazard observed for the rituximab arm to extrapolate the observation arm, resulting in the same transition probabilities applied to the PFS state from month 28 onwards across both arms of the model. For the first 28 months, the PRIMA hazard ratio for this duration has been calculated from the latest cut of the data resulting in a HR of 0.48 95% CI (0.377; 0.613) compared to the 0.55 95%CI [0.44 ; 0.68] estimated using all available data at a median of 38 months of follow-up (June 2010 snapshot, post hoc analysis). This method results in an improved visual fit to the existing Kaplan-Meier curves as presented in Figure 7 compared to the base case analysis using a Gompertz function and hazard ratio representative of all the available data presented in Figure 6. All differences between this new modelling approach and the base case are provided in Table 4 below. *Figures provided, but not reproduced here.* A summary of the differences between this new modelling approach and the base case are provided in Table 4 below. It should be noted that the modelling approach in the base case is the same as that used for the sensitivity analysis presented in Section 1.2 with the exception of differences in the duration of treatment benefit and the PFS hazard ratio. Roche believe that our base case (Gompertz) is a credible means of modelling the PRIMA data *when our base case modelling assumptions are utilised*. However, we believe that this new approach presented in this section (1.3) reflects a more accurate methodology for the purposes of modelling the Committee's requested sensitivity analysis than that which was presented in Section 1.2. *Table provided, but not reproduced here.* The result of this alternative modelling approach is presented in Table 5 below alongside the updated base case analysis. The ICER increases from £15,404 to £17,681. The undiscounted PFS to OS conversion rate also decreases from 89.2% to 84.1%.	the original submission) to extrapolate the hazard ratio observed in the rituximab arm for 28 months to the observation arm (HR 0.48; 95% CI 0.377 to 0.613). The same transition probabilities were then applied to both arms from 28 months onwards in the model (HR 1.00). The manufacturer considered that this alternative modelling approach was a more accurate method for this particular sensitivity analysis, but emphasised that it represented the worst-case clinical scenario and was not in line with available clinical evidence or expert opinion and therefore should be treated with caution (see FAD section 3.26).

Consultee	Comment	Response
	Table provided, but not reproduced here. The further requested sensitivity analysis associated with varying the undiscounted PFS to OS conversion rate is provided in Table 5 below (along with the updated base case). This alternative modelling approach results in ICERs below the NICE accepted threshold of £30,000 per QALY gained, even in the worst case scenario of an undiscounted PFS to OS conversion rate of 70%. *Table provided, but not reproduced here.*	
Roche Products	**Has the relevant evidence has been taken into account?** **1.4 Interpretation of sensitivity analysis** Using the updated base case model, we have presented above the requested sensitivity analyses assuming limited treatment benefit and various PFS to OS gain undiscounted conversation rates. Given the poor fit to the observed PRIMA data resulting from these sensitivity analyses, for the 28 month limited treatment benefit analysis (which was brought about due to a hypothesis presented by the ERG), we have addressed this by modifying the model structure which addresses the underlying concern regarding the cumulative hazard plot, whilst also limiting the treatment benefit duration to the requested 28 months. In all analyses which represented a reasonable fit to the observed data, the ICERs were well below £30,000 per QALY gained. In the cumulative hazard plots from PRIMA presented in Figure 5, it should be noted that there is no established clinical explanation for why the hazard in the observation arm would decrease after 28 weeks. A plausible clinical explanation is that there is a higher risk of early relapse in patients with more aggressive disease which leaves a population of lower risk patients remaining in the observation arm. It is therefore also possible that over time, the hazard associated with the rituximab arm would also decrease (improve the hazard ratio further) when these similar 'high risk' patients also progress in this arm. We therefore must be cognisant of the possibility that with	Comment noted. The Committee noted that the ICERs for rituximab maintenance compared with observation in the manufacturer's submission and sensitivity analyses were less than £30,000 per QALY gained for most scenarios (see FAD section 4.13).

Consultee	Comment	Response
	greater length of follow-up, this change in risk after 28 months may change and a longer treatment effect of rituximab will be confirmed.	
	Has the relevant evidence has been taken into account? **Learnings from previous Rituximab folliulcar lymphoma appraisals** Whilst Roche have agreed to provide all requested sensitivity analyses, we would still consider these analyses as worst case clinical scenarios, particularly with regards to the modelled limited treatment benefit. This is supported by evidence from the EORTC 20981 study. In the EORTC 20981 study on the role of rituximab in remission induction and maintenance of relapsed/resistant follicular Non-Hodgkin's Lymphoma, NICE provided positive guidance on a limited median length of follow-up of 39.4 months (very similar to the current PRIMA median follow-up of 38 months). Since the publication of TA137, a further analysis based on 6 years of follow-up has been published. Over this median follow-up period of 6 years, the treatment benefit remains statistically significant and clinically meaningful with a hazard ratio of 0.69 (from 0.54 at 33 months) in patients receiving rituximab maintenance following induction treatment with R-CHOP and 0.55 (from 0.40 at 33 months) in overall maintenance population. A comparison of treatment benefit across three cuts of the data is provided in Table 6 below. Clinical expert opinion strongly suggests that the patients with relapsed/resistant follicular lymphoma (EORTC 20981 population) will have a shorter duration of remission compared to those with previously untreated follicular lymphoma (PRIMA population). Therefore, it is reasonable to assume that the duration of benefit in patients with previously untreated follicular lymphoma receiving maintenance treatment with rituximab following a response to induction treatment with rituximab plus chemotherapy would be no worse than that observed in EORTC 20981. Therefore any analysis suggesting a treatment benefit enduring less than 6 years should be treated with caution. *Table provided, but not reproduced here.*	Comment noted. The Committee also heard from the clinical specialists that the period over which rituximab is likely to have a benefit is probably 3 to 4 years (that is, 1 to 2 years beyond treatment). However, it further heard from the clinical specialists that it was not possible to predict a definite time period, and a duration of effect of up to 6 years, as seen in the EORTC 20981 study for second-line rituximab maintenance treatment, could be plausible. The Committee considered sensitivity analyses conducted by the manufacturer that assumed a duration of treatment effect of 28 months, 36 months and 48 months and was satisfied that they presented the most plausible range of estimates for the treatment effect in line with clinical opinion and the available data (see FAD section 4.9).

Consultee	Comment	Response
Roche Products	**II) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** In Section 3.4 of the ACD, it is stated that people whose disease responded to second-line therapy could be randomised to maintenance treatment with rituximab with one dose every 8 weeks. This is incorrect and should say one dose every 3 months.	Comment noted. FAD section 3.4 has been amended accordingly.
Roche Products	**III) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Following the Committee's comments and request for additional analysis, Roche has provided a wide range of sensitivity analyses in order to address all the remaining uncertainties in rituximab's cost effectiveness. All analyses resulted in an ICER of below £30,000 per QALY, with the exception of only two which lacked face validity when considering their fit to the observed PRIMA progression-free survival curves, demonstrating that rituximab is a cost effective use of NHS resources in this setting.	Comment noted. The Committee noted that the ICERs for rituximab maintenance compared with observation in the manufacturer's submission and sensitivity analyses were less than £30,000 per QALY gained for most scenarios. The Committee was aware that the model did not include the utility associated with delaying chemotherapy, and that if it were included, it would decrease the ICER (that is, improve the cost effectiveness) to an estimate which would be considered as a cost-effective use of NHS resources. Therefore, the Committee considered that rituximab maintenance therapy should be recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy (see FAD section 4.13).
Roche Products	**IV) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**	

Consultee	Comment	Response
	None	Comment noted.
Royal College of Nursing	**Has the relevant evidence has been taken into account?** The evidence considered seems comprehensive.	Comment noted.
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with follicular non-hodgkin's lymphoma. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted.
Royal College of Nursing	**Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted.
Royal College of Nursing	**Are there any equality related issues that need special consideration that are not covered in the ACD?** We are not aware of any specific issue at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	Comment noted. No equalities issues were raised during the scoping exercise or during the course of the appraisal.
Royal College of Pathologists and British Society for	We are surprised and disappointed to see this document, which reverses the opinion in the initial appraisal consultation document (ACD) issued after the meeting of 4th November 2010. This reversal appears to have been carried	Comment noted. During the second meeting, the Committee considered that the evidence submitted by the manufacturer did not fully

Consultee	Comment	Response
Haematology Identical response also received from Royal College of Physicians/ National Cancer Research Institute/Royal College of Radiologists/ Association of Clinical Pathologists/Joint Collegiate Council for Oncology	out without the benefit of any new evidence, but following the submission of a single objection from an NHS commissioning body, which has been copied verbatim by two others. This contains significant errors of information and interpretation as detailed below. Following the Appraisal meeting an ACD was produced that reflected expert opinion in the UK and worldwide, that Rituximab maintenance in first remission is both clinically and cost effective. The recommendations in the second ACD are simply not consistent with the first and have been arrived at without the benefit of any expert clinical input. The reasons for the acceptance of Rituximab maintenance were extensively discussed at the Appraisal panel. We make the following comments upon the revised ACD and the objection from the NHS commissioners: 1)The improvement in progression free survival (PFS) in the Rituximab maintenance arm of the PRIMA study at two and now at three years is both statistically significant and clinically meaningful in this population. There is nothing to suggest that the difference between the two arms diminishes with time. The concerns voiced by the ERG and the suggestion by the NHS commissioners that the initial data would not be sustained with further follow up are not borne out by the evidence that continues to emerge at international scientific meetings and which has now been published in the Lancet 2)A sustained advantage has been observed in all other published studies of Rituximab as first and second line therapy in follicular lymphoma with long term follow up, and there is nothing to suggest the data from the PRIMA study will diverge from this pattern. 3)No single trial in this condition has demonstrated a major survival benefit, since patients are able to receive further treatment at recurrence. However, the continued separation of the PFS curves indicates that Rituximab is contributing to an overall increase in the freedom from symptomatic disease, in what is an incurable cancer	address the uncertainties surrounding the clinical and cost-effectiveness of rituximab maintenance treatment. The Committee also took into consideration comments received during consultation from stakeholders who strongly disagreed with the preliminary advice to recommend rituximab maintenance treatment, because they considered that there was a lot of uncertainty around the effect of treatment on survival and improved quality of life. In view of this, the Committee was minded not to recommend rituximab maintenance treatment unless further data was submitted to address uncertainties surrounding the evidence base. During the third committee meeting, the Committee was satisfied that the manufacturer had provided sufficient evidence to address the uncertainties surrounding the data that the Committee originally had. The Committee noted that despite following patients beyond the end of the PRIMA trial, the manufacturer could not estimate the overall survival associated with rituximab maintenance treatment because of the small number of deaths during this period. The Committee was aware that the trial stopped earlier than originally planned on advice from the trial's statisticians, and heard from the ERG that there is evidence suggesting that studies that have stopped earlier than planned often overestimate the clinical benefit. However, the Committee was satisfied, after advice from the

Consultee	Comment	Response
	4)Registry studies have clearly demonstrated an improvement in overall survival for patients with follicular lymphoma since 2000. In the absence of any major shifts in the demographics or other major changes in management, this is widely accepted to be due to the impact of Rituximab during this time. 5)NICE have previously accepted PFS as a legitimate endpoint in the other studies of follicular lymphoma and other indolent lymphoid malignancies. It is not correct for the NHS commissioners to suggest that the original ACD recommendation was questionable in the absence of overall survival benefit, given the natural history of this illness and its responsiveness to salvage therapy. 6)The published results of the PRIMA study clearly demonstrate that all subgroups of patients have increased freedom from disease if they receive maintenance Rituximab. This specifically includes those above or below the age of 60. It is not legitimate to require an unplanned retrospective analysis of a subset of patients with median age comparable to that in registry studies for re-analysis of the data. It is sufficient to demonstrate, as the trial clearly does, that both older and younger patients derive benefit from the addition of 2 years maintenance therapy. 7)It must be re-emphasised that the trial was not stopped prematurely, but when the pre-planned endpoints were met. The decision to analyse the data was not taken by the sponsoring company or by the investigators but by the properly constituted independent data monitoring and safety committee. 8)The NHS commissioners suggest in their submission that the recommendations "could increase the use and therefore the overall cost of this drug for a PCT population" as if this undermines the evidence in favour of its use. Treatments should be approved subject to the existing standards of value for money to the NHS, which this treatment has passed. Furthermore, it is unlikely that the implementation of first line maintenance therapy will very substantially increase the use of Rituximab, since the great	clinical specialists, that progression-free survival for people treated with rituximab maintenance therapy in the PRIMA trial reflected the clinicians' observations from clinical practice. The Committee therefore concluded that the available evidence shows that first-line maintenance treatment with rituximab significantly improves progression-free survival compared with observation (see FAD, section 4.5). The potential budget impact of the adoption of a technology is not considered by the Committee. See Guide to the Methods of Technology Appraisal section 6.2.14 (available from http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf). The Committee does not consider the affordability, that is, costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources ('Guide to the Methods of Technology Appraisal', paragraphs 6.2.6.1–6.2.6.3; see URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf). The Committee noted that the ICERs for rituximab maintenance compared with observation in the manufacturer's submission and sensitivity analyses were less than £30,000 per QALY gained for most scenarios. The Committee was also aware that the model did not include the utility associated with

Consultee	Comment	Response
	majority of patients will receive it in any case in second remission or at subsequent relapses. 9) The NHS commissioners suggest that "there is no convincing evidence of improved…quality of life and this calls into question the assumptions of the cost-effectiveness model". This is not the case. The PRIMA study demonstrated clearly that there is no reduction in quality of life during maintenance treatment, as the NHS commissioners point out. The patients who gave evidence at the appraisal hearing were categorical in their view that Rituximab treatment is greatly preferable to the known side-effects of chemotherapy, which is instituted sooner for patients who do not receive maintenance Rituximab. It is thus evident that the application of maintenance Rituximab carries a substantial premium for quality of life, as has been applied in the model. It is not tenable to assert, as the NHS commissioners have, that "the assumption that patients' quality of life is improved by the more manageable side effects of Rituximab maintenance…was not clearly demonstrated..." On the contrary, this is precisely the experience of patients and clinicians alike. 10) The statement by the NHS commissioners that "The ERG agreed to the manufacturer's small changes to the decision problem" is of no relevance. The assessment of benefit only in patients who had received Rituximab as part of induction treatment would if anything have diluted the effect of maintenance treatment and reduced the benefit. Similarly, the omission of an expensive comparator treatment, Ibritumomab tiuxetan, also works against Rituximab rather than in its favour. This revised ACD runs directly counter to current national and international guidelines and standard practice for the treatment of follicular lymphoma. Maintenance therapy with Rituximab in first remission has now become a universal standard of care, based upon a large well-conducted prospective clinical trial. This treatment has been approved and funded in Scotland (Scottish Medicines Consortium guidance 7th Feb 2011) so to maintain equity of care within the UK, this should also be available for patients in England and Wales.	delaying chemotherapy, and that if it were included, it would decrease the ICER (that is, improve the cost effectiveness) to an estimate which would be considered as a cost-effective use of NHS resources. Therefore, the Committee considered that rituximab maintenance therapy should be recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy (see FAD section 4.13).

Consultee	Comment	Response
	There are no other studies planned in this indication, since the results of this study are widely recognised as definitive. Further studies comparing rituximab maintenance to observation would now be unlikely to gain ethical approval as rituximab maintenance is considered a standard of care. There is little purpose to trial groups in this country designing and participating in such studies if their globally accepted results cannot be incorporated into clinical practice, and the UK's capacity to participate in future trials designed with the leading independent international groups will be compromised if patients in this country cannot receive the internationally agreed standard of care. For these reasons we would ask the committee to reverse its opinion in the second ACD and recommend, as it did originally, the use of Rituximab as first-line maintenance therapy for responding patients with advanced stage follicular lymphoma.	

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional 1	1	Maintenance rituximab is used second line and there is first line data. I havent given it personally but understand it is being given via the ICDF. To stop would be a retrograde step.	Comment noted.
NHS Professional 2	1	The committee should recommend first-line maintenance treatment for patients with Follicular Lymphoma. The recommendation fails to take accont of patient choice - there are many situations where it may be extremely valuable for a patient to delay the time to relapse. It will be hard for patients who have completed their first course of chemotherapy (R-CVP) then to be told that they will have not have access to maintenance therapy knowning that there is strong trial data to support this intervention. I am concerned that improved PFS has been used to approve	Comment noted. During the third committee meeting, the Committee was satisfied that the manufacturer had provided sufficient evidence to address the uncertainties they originally had surrounding the data. The recommendation in the FAD states that rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		other technologies by NICE. I am also concerned that this intervention is widely available in Europe, the US and other parts of the UK.	first-line induction therapy with rituximab in combination with chemotherapy (see FAD, section 1.1).
NHS Professional 3	1	At NICE's request, the manufacturer has already conducted health economic analyses based on a number of assumptions. These demonstrated ICER values between £15,000 and £30,000 implying cost-effective use of NHS resources. However there are fundamental issues about how much weight can be attributed to the manufacturer's projections of benefits up to 6 years, which is considerably beyond the period of observation (the median follow up was 38 months). These factors were highlighted in the previous PCT and CSAS submission to NICE. It is expected that the manufacturer will produce further analyses for consideration at the next Appraisal Committee. The assumptions put forward in the manufacturers model do not seem plausible. Any model must be considered in the context of failure to demonstrate improvements in overall survival, and uncertainties about the use of salvage chemotherapy following disease progression. The manufacturer's model was based over a 6 year time period, despite only 4 years' follow up in the PRIMA study.	Comment noted: The Committee heard from the clinical specialists that data from the PRIMA trial indicated that rituximab maintenance treatment is clinically effective to 36 months at least and there is no evidence that the effect diminishes over time. The Committee also heard from the clinical specialists that the period over which rituximab is likely to have a benefit is probably 3 to 4 years (that is, 1 to 2 years beyond treatment). However, it was not possible to predict a definite time period, and a duration of effect of up to 6 years, as seen in the EORTC 20981 study for second-line rituximab maintenance treatment, could be plausible. The Committee considered sensitivity analyses conducted by the manufacturer that assumed a duration of treatment effect of 28 months, 36 months and 48 months and noted that the ICERs ranged from £17,300 to £27,400 per QALY gained. The Committee considered that the duration of clinical benefit of rituximab maintenance was a key driver of cost effectiveness, but was satisfied that the manufacturer's sensitivity analyses presented the most plausible range of estimates for the treatment effect in line with clinical opinion and the available data (see FAD, section 4.9).

Role*	Section	Comment	Response
NHS Professional 3	2	Were NICE to reverse this minded no, a positive recommendations could increase the use and therefore the overall cost of this drug for a PCT population. According to the manufacturer's estimates, the cost of treating a person with an average body surface area of $1.8m^2$ with rituximab maintenance treatment for 2 years is £14,669. Implementing this guidance could carry additional annual drug costs of approximately £380,000 for the average PCT of 300,000 people with an estimated 52 people receiving maintenance treated with rituximab for this indication per year. PCTs would need to give consideration to which haematology services would not receive investment to make way for a requirement to fund this indication.	Comment noted. The potential budget impact of the adoption of a technology is not considered by the Committee. See Guide to the Methods of Technology Appraisal section 6.2.14 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf). The Committee does not consider the affordability, that is, costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources ('Guide to the Methods of Technology Appraisal', paragraphs 6.2.6.1–6.2.6.3; see URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf).
NHS professional 3	3	l amounts of data were redacted in the original ERG report. The most relevant study was the PRIMA trial and this forms the basis of the manufacturer's submission. Data from the post-study observational follow-up period, which had a median follow-up of 38 months, were submitted to the ERG as 'academic in confidence' and will become more generally available when and if they are published. We note that the ERG cautioned that the data were immature and that the early closure of the trial might have led to an overestimation of the clinical benefits of rituximab maintenance treatment with the level of redaction (presumably on grounds of commercial sensitivity) it makes it hard to form a balanced view.	Comment noted. The PRIMA trial has now been published and therefore none of the data in the ERG report or the manufacturer's submission is considered 'academic in confidence'. The ERG was concerned that follow-up data were not available beyond 4 years and that the manufacturer could not estimate the median time to progression or to death by treatment group. The ERG cautioned that the data were immature (few events), which might have led the results to overestimate the clinical benefits of rituximab maintenance treatment (see FAD, section 3.17). The Committee considered the concerns of the ERG that the early closure of the PRIMA trial may have overestimated the benefit from rituximab, and the revised sensitivity analyses from the ERG, which included an adjustment for early reporting bias. The Committee

Role*	Section	Comment	Response
			considered that adjusting for early reporting bias is not routinely included in technology appraisals and is not a current requirement in the NICE Methods Guide. The Committee therefore concluded that the ERG's revised analyses using the higher hazard ratio would not be considered (see FAD, section 4.11).
NHS professional 3	4	In the manufacturer's base case analysis, rituximab maintenance was cost effective compared with observation when the benefits of rituximab are assumed to last for 6 years (ICER £15,978/QALY). In sensitivity analyses undertaken by the ERG, ICERs ranged from £21,000 to £26,000 per QALY when the benefit was assumed to be sustained for the first 3 to 4 years. given our view that the manufacturers assumptions are somewhat optimistic" we do not view the manufacturers model as a reliable estimate, and would place more emphasis on the (worst case) assumptions in the sensitivity analysis to be more reflective of a true base case.	Comment noted. The Committee heard from the clinical specialists that data from the PRIMA trial indicated that rituximab maintenance treatment is clinically effective to 36 months at least and there is no evidence that the effect diminishes over time. The Committee also heard from the clinical specialists that the period over which rituximab is likely to have a benefit is probably 3 to 4 years (that is, 1 to 2 years beyond treatment). However, it was not possible to predict a definite time period, and a duration of effect of up to 6 years, as seen in the EORTC 20981 study for second-line rituximab maintenance treatment, could be plausible. The Committee considered sensitivity analyses conducted by the manufacturer that assumed a duration of treatment effect of 28 months, 36 months and 48 months and noted that the ICERs ranged from £17,300 to £27,400 per QALY gained. The Committee considered that the duration of clinical benefit of rituximab maintenance was a key driver of cost effectiveness, but was satisfied that the manufacturer's sensitivity analyses presented the most plausible range of estimates for the treatment effect in line with clinical opinion and the available data (see FAD, section 4.9).

Role*	Section	Comment	Response
NHS professional 4	1	After reviewing the available information, and consulting with our regional East Midlands cancer commissioners, I can confirm that NHS Nottingham City is supportive of the provisional recommendation outlined within NICE's second Appraisal Consultation Document for the Technology Appraisal of Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy. This is to not recommend Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first line chemotherapy.	Comment noted. During the third committee meeting, the Committee was satisfied that the manufacturer had provided sufficient evidence to address the uncertainties that it originally had surrounding the data. The recommendation in the FAD has been updated to state that rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy (see FAD, section 1.1).

[redacted]

21st March 2011

Jeremy Powell
MidCity Place
71 High Holborn
London
WC1V 6NA

BY E-MAIL

Re: Second Appraisal Consultation Document - Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy

Dear Jeremy,

Thank you for providing us with the second Appraisal Consultation Document. Please find below Roche's response to the second ACD. The results of the additional analyses requested by the Committee demonstrate that rituximab for the treatment of 1st line maintenance is a cost effective use of NHS resources under all plausible scenarios requested. It is important to note that the 2 scenarios which resulted in ICERs of £30,655 and £32,260 are based on a model structure, which as outlined in our response below, is not appropriate for conducting the specific sensitivity analysis requested.

In addition to the results of the analysis provided in response to the minded not recommendation, Roche would like to highlight to the institute some concerns regarding the process by which specific elements of the further analysis was generated within the second appraisal committee.

During Part 1 of the second appraisal committee meeting, the ERG presented a new hypothesis that the duration of treatment effect offered by rituximab maintenance was possibly limited to 28 months, based upon a visual inspection of the cumulative hazard plots of the PRIMA study originally presented in the manufacturer's submission. The ERG subsequently indicated they would only elaborate further on this hypothesis during the closed Part II session of the Committee meeting and therefore Roche did not obtain full clarity on the rationale behind the request for the 28 month treatment effect sensitivity analysis, as we were not invited to stay for Part 2 of the meeting. To address this issue and to obtain the necessary clarity, Roche requested a teleconference between the NICE technical team and the ERG, however the ERG was not available to attend.

Despite these issues, Roche have considered carefully the comments made during Part I of the Committee meeting and have provided an alternate scenario based upon this hypothesis and provided a more appropriate analysis to evaluate an assumed 28 month limited treatment effect. The modelling concepts underlying this approach are described in Section 1.3.1 followed by the application of this approach to the PRIMA dataset in Section 1.3.2.

If you require any further information or clarification then please do not hesitate to contact us.

Yours Sincerely,

[redacted]

[redacted]

Executive Summary

Background

In the second ACD for the appraisal of rituximab for first-line maintenance treatment of NHL, the Committee requested a revised cost-effectiveness analysis that incorporates all the following assumptions:

- Age at first-line induction: mean age of 62.5 years at the start of treatment.
- Treatment effect: duration of clinical benefit from first-line rituximab maintenance treatment is 28 months, 36 months or 48 months.
- Survival modelling: the extent that the benefit of mean progression-free survival from first-line rituximab maintenance treatment translates to mean overall survival gain is 70%, 80% or 90% (undiscounted and not adjusted for health-related quality of life).

Following the Committee's request for further sensitivity analysis, Roche have reviewed and updated the original base case economic model and conducted the requested sensitivity analysis.

In addition, following feedback from the ERG, further minor structural changes to the model have been provided to consider an alternative approach to more credibly model the 28 month limited treatment benefit analysis.

Results

When considering those scenarios which provide a plausible fit to the observed Phase III (PRIMA study) data, the requested sensitivity analyses (based on changes to age, duration of treatment benefit and extrapolation of PFS to OS) generated ICERs below £20,000 per QALY gained.

Existing Economic Model

The base case model was updated by increasing the starting age to 62.5 as requested by the NICE Committee. In addition, an error identified in the model costings for 1st line induction treatment was corrected. These two changes combined resulted in a revised base case ICER of £15,404 per QALY gained which was used as the basis of all subsequent sensitivity analyses.

The requested sensitivity analysis was conducted utilising the base case model and considers a variety of limited treatment effect durations (28, 36 and 48 months) as well as a variety of undiscounted PFS to OS gain conversation rates (70%, 80% and 90%). This resulted in ICERs ranging from £21,507 to £32,260 per QALY gained.

The only two scenarios that generated an ICER above £30,000 per QALY gained were where the duration of treatment benefit is limited to 28 months and the PFS to OS undiscounted conversion rate was 70% (£32,260) and 80% (£30,655).

Updated Economic Model

Upon further inspection of the visual fit of these models compared to the observed PFS data, it is clear that these two extreme scenarios provide a very poor fit to the existing data and therefore an alternative scenario to model the 28 month limited treatment effect sensitivity analysis was conducted in order to provide a more credible fit to the PRIMA data.

The reasons for the request of the 28 month limited treatment effect sensitivity analysis was not brought about due to clinical expert opinion but rather the conjecture of the ERG during the 2nd Committee meeting. The ERG presented a new hypothesis that the duration of treatment effect offered by rituximab maintenance was limited to 28 months based upon the cumulative hazard plots from the PRIMA study, originally presented in the manufacturer's submission. Roche have considered carefully these comments made during Part I of the Committee meeting and have attempted to provide an alternate scenario based upon these considerations.

This alternative approach provides a much better visual fit to the existing data and results in an ICER of £17,681 per QALY gained at an undiscounted PFS to OS gain conversion rate of 84.1%. Whilst Roche believe that our base case (Gompertz) is a credible means of modelling the PRIMA data *when our base case modelling assumptions are utilised*, for the purposes of the modelling the Committee's requested sensitivity analysis, we believe that this new approach presented in Section 1.3 of the ACD reflects a more legitimate methodology than that which was presented in Section 1.2 using the base case model structure. The further sensitivity analysis by altering the PFS to OS gain conversation rates to 70%, 80% and 90% are presented below.

Cost per QALYS for the new approach to the 28 month treatment effect sensitivity analysis (exponential) compare to the original model (Gompertz)

ICER	**Duration of treatment effect** (based on new corrected base case using starting age 62.5)	
PFS to OS	**28 months sensitivity analysis**	**Base case (72 months)**
70%	£18,615	£16,284
80%	£17,930	£15,792
Base case	£17,681	£15,404
90%	£17,349	£15,372

Experience from previous assessment of rituximab in follicular lymphoma

Whilst nearly all requested sensitivity analyses provided results in ICERs below £30,000 per QALY gained, Roche would still caution against the consideration of these sensitivity analyses as anything other than extreme scenario analyses, particularly with regards to the limited treatment effect duration, given the wealth of evidence available on rituximab in NHL which would suggest that these limited treatment durations are implausible in practice, as suggested below by the EORTC 20981 study.

In the EORTC 20981 study on the role of rituximab in remission induction and maintenance of relapsed/resistant follicular Non-Hodgkin's Lymphoma, NICE provided positive guidance on a limited median length of follow-up of 39.4 months (very similar to the current PRIMA median follow-up of 38 months). Since the publication of TA137, a further analysis based on 6 years of follow-up has been published. Over this median follow-up period of 6 years, the treatment benefit remains statistically significant and clinically meaningful with a hazard ratio of 0.69 in patients receiving rituximab maintenance following induction treatment with R-CHOP and 0.55 in overall maintenance population.

Clinical expert opinion strongly suggests that the patients with relapsed/resistant follicular lymphoma (EORTC 20981 population) will have a shorter duration of remission compared to those with previously untreated follicular lymphoma (PRIMA population). Therefore, it is reasonable to assume that the duration of benefit in patients with previously untreated follicular lymphoma receiving maintenance treatment with rituximab following a response to induction treatment with rituximab plus chemotherapy would be no worse than that observed in EORTC 20981. Therefore any analysis assuming a treatment benefit enduring less than 6 years should be treated with caution.

I. Has all of the relevant evidence been taken into account?

Following the Committee's request for further sensitivity analysis, Roche have reviewed and updated the original base case economic model, conducted the requested sensitivity analysis, and attempted further minor structural changes to the model necessary to consider the 28 month limited treatment benefit analysis proposed by the ERG. The following section 1.1 to 1.3 outline the sensitivity analyses results based on the clinical assumptions requested by NICE/ERG. The validity of these assumptions will be discussed briefly in section 1.4.

1.1. Updated Base Case analyses

Two changes were made to the base case model in order to prepare for the range of sensitivity analyses requested.

1. Upon review of the Roche base case model, it was noted that the cost of first-line rituximab induction therapy was contained in the model, and furthermore, both the inclusion and the calculation of this cost was incorrect and not identical for both arms. This should not have been included, given that this cost was incurred prior to the start of the model (which begins with the commencement of first-line maintenance therapy or observation). Therefore this incorrect cost was removed from each arm, resulting in a decrease to the ICER from £15,978 to £15,088 per QALY gained.
2. The new (NICE/ERG requested) base case starting age was changed from 56 to 62.5 years. The average mortality rate for an individual aged 62 and 63 was utilised to obtain the appropriate starting background mortality figure. The result is an increase to the ICER from £15,088 to £15,404 per QALY gained. It should also be noted by increasing the age of the patients in the economic analysis, the effective undiscounted PFS to OS conversion rate decreases from **97.4%** to **89.2%.**

Table 1. Updated base case analyses

	Roche Base case (age 56)	Roche Base case corrected (age 56)	New NICE/ERG Base Case (age 62.5)
Age	56	56	62.5
Duration of treatment effect	72	72	72
Undiscounted PFS to OS conversion rate	97.4%	97.4%	89.2%
Inc Cost	*£18,681*	*£17,641*	*£16,918*
Inc QALY	1.17	1.17	1.10
ICER	£15,978	£15,088	**£15,404**

This updated base case ICER of £15,404 per QALY gained is used as the basis of the subsequent sensitivity analysis which tests various undiscounted PFS to OS conversation rates and durations of treatment effect.

1.2 Sensitivity Analysis for limited treatment effect using the base case model

Based on the updated base case analysis described in Section 1.1, the results of limiting the treatment effect to 28, 36 and 48 months are presented in Table 3 below along with the base case scenario of 72 months. Three sets of results are presented for each treatment duration scenario, representing a 70%, 80%, or 90% undiscounted conversion of PFS to OS gains. This was generated by (1) calculating and applying the hazard ratio from PRIMA based on each requested truncation point (see Table 2), then (2) limiting the treatment duration to the specified number of months, and finally (3) adjusting the progression to death transition rate in the model for the intervention arm to calibrate the results to reflect a 70%, 80% or 90% undiscounted PFS to OS gain conversion rate. The adjustment factors required for this calibration are presented in the Appendix.

Table 2. PRIMA hazard ratios for each limited duration of treatment benefit

Data set considered	Hazard Ratio [T]	95% confidence interval
Full dataset*	0.55	0.44 - 0.68
First 48 months only	0.552	0.446 - 0.684
First 36 months only	0.513	0.409 - 0.643
First 28 months only	0.480	0.377 - 0.613

* Based on a median of 38 months and a maximum of 57.8 months of follow-up (June 2010 snapshot)
[T] These hazard ratios are derived from an post hoc analysis of PRIMA and should be considered exploratory

Roche would strongly suggest that if the assumed treatment duration is limited to a pre-specified time horizon, the assumed treatment effect should be calculated based on and consistent with the corresponding time horizon observed in PRIMA (as illustrated in Table 2 above).

Table 3. Sensitivity analysis for each limited duration of treatment benefit

Inc Cost Inc QALY **ICER**	**Duration of treatment effect** (based on new corrected base case using starting age 62.5)			
PFS to OS	**28 months**	**36 months**	**48 months**	**72 months**
70%	*£17,296*	*£16,887*	*£16,430*	*£15,498*
	0.54	0.62	0.70	0.95
	£32,260	**£27,397**	**£23,355**	**£16,284**
80%	*£17,691*	*£17,348*	*£16,965*	*£16,241*
	0.58	0.66	0.76	1.03
	£30,665	**£26,128**	**£22,360**	**£15,792**
90%	*£18,084*	*£17,805*	*£17,496*	*£16,977*
	0.62	0.71	0.81	1.10
	£29,287	**£25,038**	**£21,507**	**£15,372**

From Table 3, it is clear that all sensitivity analyses presented resulted in ICERs below the NICE defined threshold of £30,000 per QALY gained with the exception of only two extreme scenarios where the duration of treatment benefit is limited to 28 months and the PFS to OS undiscounted conversion rate is less than 80%. As described in the previous ACD, this sensitivity analyses should be considered with caution given that the underlying assumptions necessary to simulate this assumed conversion rate may not be based on clinically plausible assumptions. It should also be noted that these extreme

analyses provide a poor fit to the observed PFS data from PRIMA, as demonstrated by the comparison of fits from the base case (72 months treatment effect) versus the most extreme sensitivity analysis assuming 28 months treatment effect and a 70% PFS to OS conversion ratio in Figures 1 and 2 respectively below).

Figure 1: Base case with treatment duration 72 months (Gompertz)

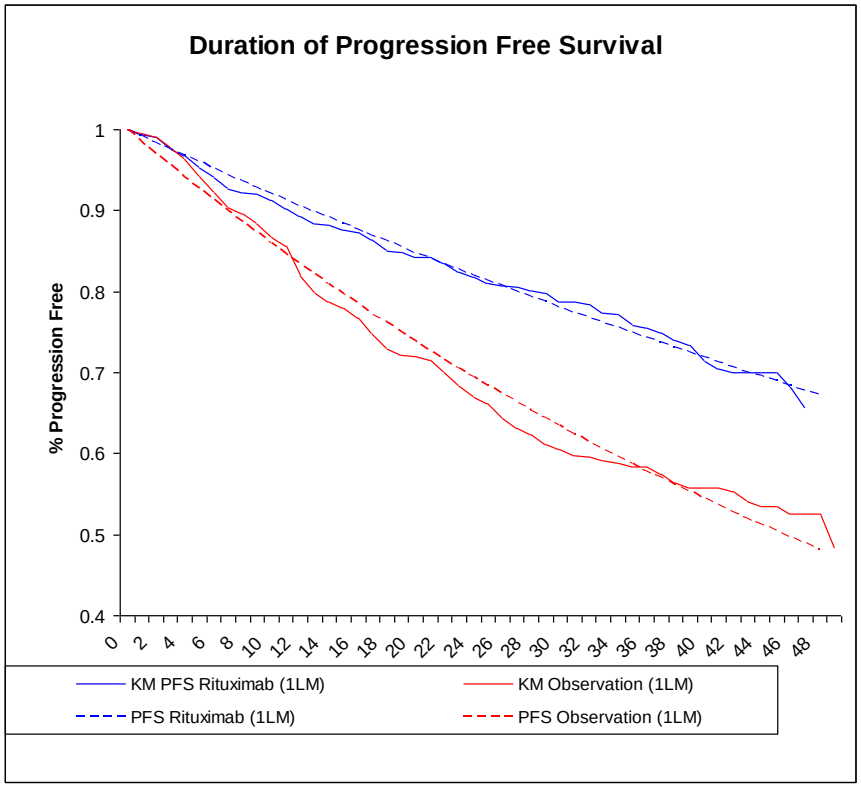
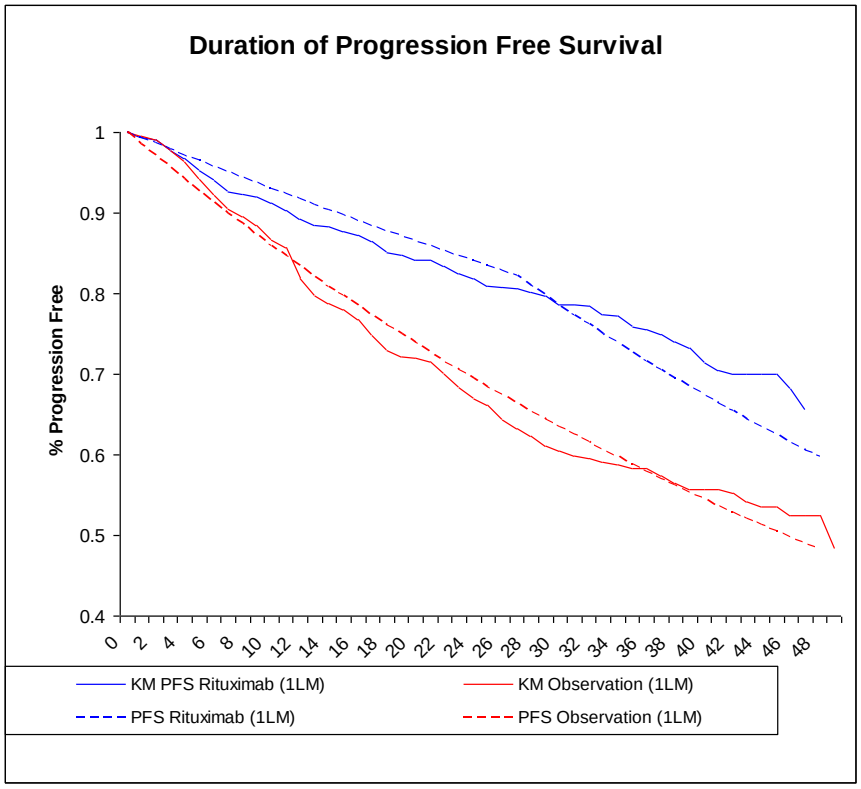


Figure 2: Sensitivity analysis with treatment duration 28 months and 70% PFS to OS Conversion rate (Gompertz)



1.3 Alternative method for modelling cessation of treatment effect at 28 months

To provide a more credible reflection to the PRIMA data than that provided in the sensitivity analysis presented in Section 1.2, an alternative approach is provided below which presents an approach to the requested 28 month limited treatment benefit analysis that more accurately reflects the underlining phase III data..

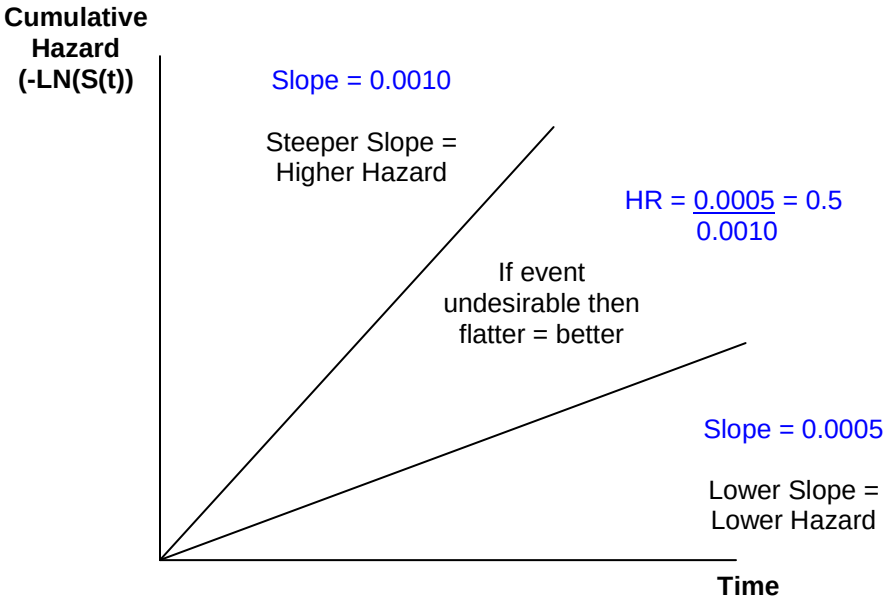
During the 2nd Committee meeting, the ERG representative proposed a new hypothesis that the duration of treatment effect offered by rituximab maintenance was limited to only 28 months based upon the cumulative hazard plots from the PRIMA study (see Figure 5 below). Roche have considered carefully the comments made during Part I of the Committee meeting and have provided an alternate scenario based upon our understanding of the ERG's hypothesis in which the treatment effect associated with rituximab is limited to 28 months. The modelling concepts underlying this approach are described in Section 1.3.1 followed by the application of this approach to the PRIMA dataset in Section 1.3.2.

1.3.1 Interpreting Cumulative Hazard Plots

A cumulative hazard plot allows one to present time to event data in a manner that enables relatively clear assessment of the way in which the hazard (instantaneous risk) of an event changes over time (the absolute hazard) and the way in which the relative hazard between two treatments changes over time (the hazard ratio). It can be generated by plotting the negative log of the Kaplan-Meier (KM) survival probability at each time point plotted against time.

The slope of a cumulative hazard plot is the absolute hazard of the event occurring at that point in time. If the slope is higher then the risk of that event occurring at that time is higher. If presented with two cumulative hazard curves associated with an undesirable event (such as disease progression) then the curve with the flatter (i.e. lower gradient) slope is associated with a lower hazard and improved outcomes relative to the comparator (see Figure 3 below for a pictorial representation). The ratio of the slopes of any two cumulative hazard curves at any point in time is the ratio of the absolute hazards of an event at that time, or the hazard ratio. The greater the difference in slopes between two curves the greater the difference in the absolute hazards of the two curves and therefore the better the hazard ratio.

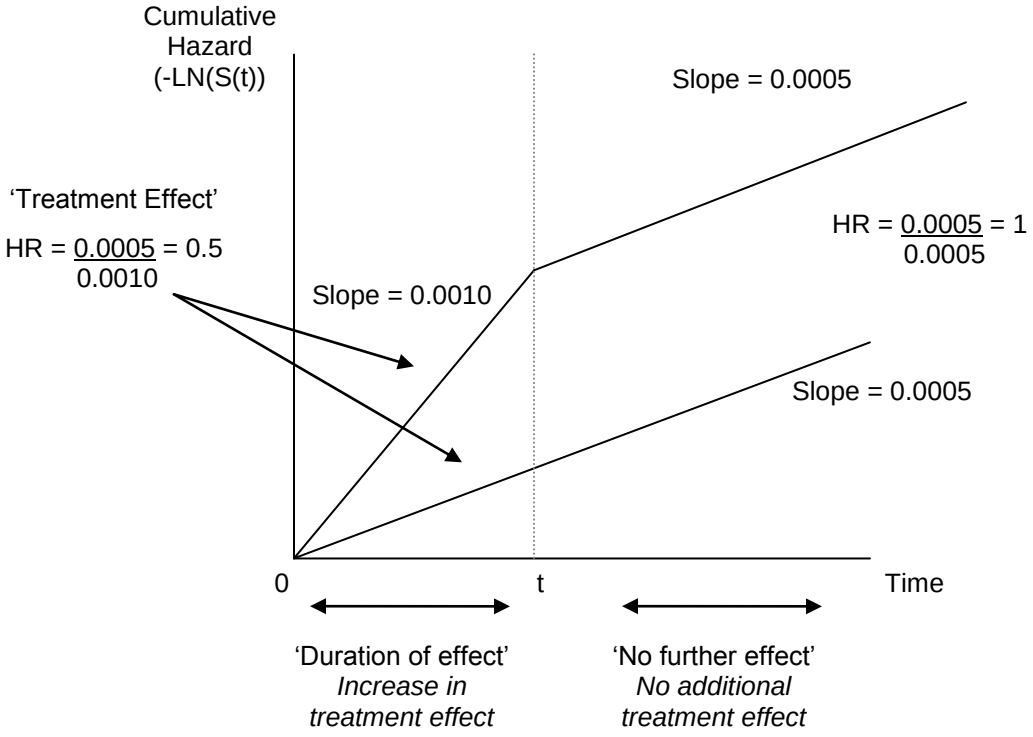
Figure 3: Example of cumulative hazard plots (1)



From these two pieces of information from a cumulative hazard plot, we can determine both the extent (i.e. the value of the hazard ratio - how big the divergence in slopes between two curves) and duration the treatment effect (i.e. how long the curves continue to separate) provided by some intervention. For example in Figure 4 below, the two cumulative hazards appear to separate up to time t (the duration of treatment benefit) with a ratio of the two hazards of 0.5 (the treatment effect) with the hazard ratio then equal to 1 beyond that (no further gain from treatment).

Furthermore, a method for extrapolating curves can be based upon the trends observed in the cumulative hazard plots. A completely straight cumulative hazard plot would indicate that the absolute hazard of an event occurring is constant over time and that therefore an exponential function would be an appropriate fit for extrapolation (in which the straight line is extrapolated). If two defined constant hazard periods are observed (i.e. the curve appears to be a joining of two straight lines with different slopes) then it may be more appropriate to utilise two exponential functions with the latter 'stabilised' hazard utilised for extrapolation (i.e. if there is a 'kink' in the curve one extrapolates with the straight line observed after the kink).

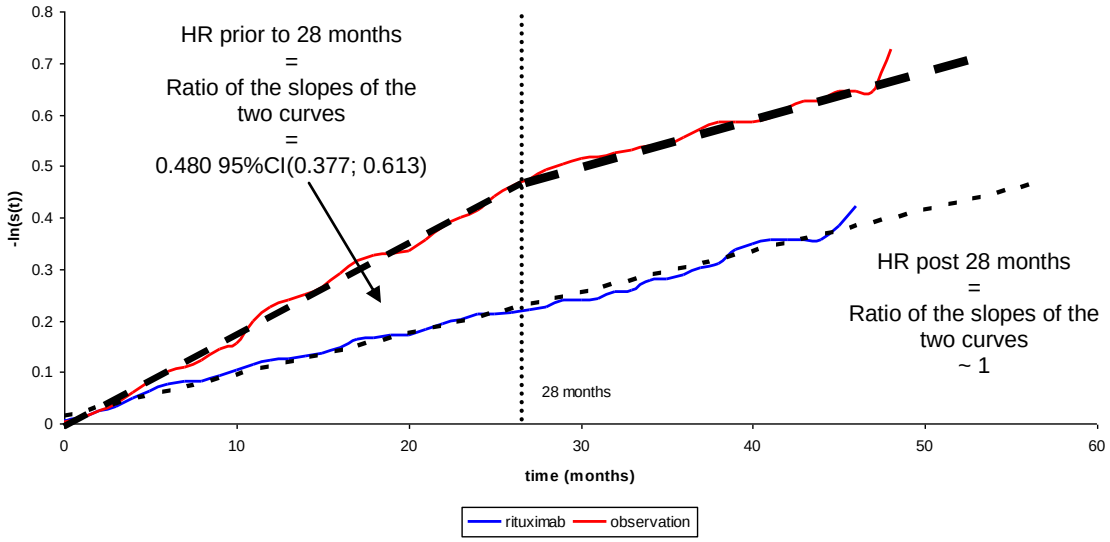
Figure 4: Example of cumulative hazard plots (2)



1.3.2 Alternative PRIMA modelling approach for 28 month limited treatment duration

Considering the cumulative hazard plot for PRIMA in Figure 5 below, the data indicates that a single exponential function would be an appropriate way of extrapolating the rituximab arm (given that the rituximab cumulative hazard plot is a straight line throughout the observed period). As such, it may be expected that this constant slope (i.e. hazard) would continue beyond the observed period. Whilst the rituximab hazard is constant throughout the duration of follow-up, the observation arm may appear to be made of two defined linear phases (steadily separating from the rituximab hazard up to 28 months and then drawing parallel to the rituximab hazard after 28 months).

Figure 5: The PRIMA Study Cumulative Hazard Curves



Therefore following consideration of the observation made by the ERG during the 2nd NICE committee meeting, we have presented an alternative revised scenario based on ERG feedback in which a simple exponential function has been utilised for extrapolating the two curves rather than the Gompertz function utilised in the original submission. We have fitted a new exponential curve to the first 28 months of the observation arm and applied it within an economic model. Beyond this period we have utilised the hazard observed for the rituximab arm to extrapolate the observation arm, resulting in the same transition probabilities applied to the PFS state from month 28 onwards across both arms of the model. For the first 28 months, the PRIMA hazard ratio for this duration has been calculated from the latest cut of the data resulting in a HR of 0.48 95% CI (0.377; 0.613) compared to the 0.55 95%CI [0.44 ; 0.68] estimated using all available data at a median of 38 months of follow-up (June 2010 snapshot, post hoc analysis).

This method results in an improved visual fit to the existing Kaplan-Meier curves as presented in Figure 7 compared to the base case analysis using a Gompertz function and hazard ratio representative of all the available data presented in Figure 6. All differences between this new modelling approach and the base case are provided in Table 4 below.

Figure 6: Base case with treatment duration 72 months (Gompertz)

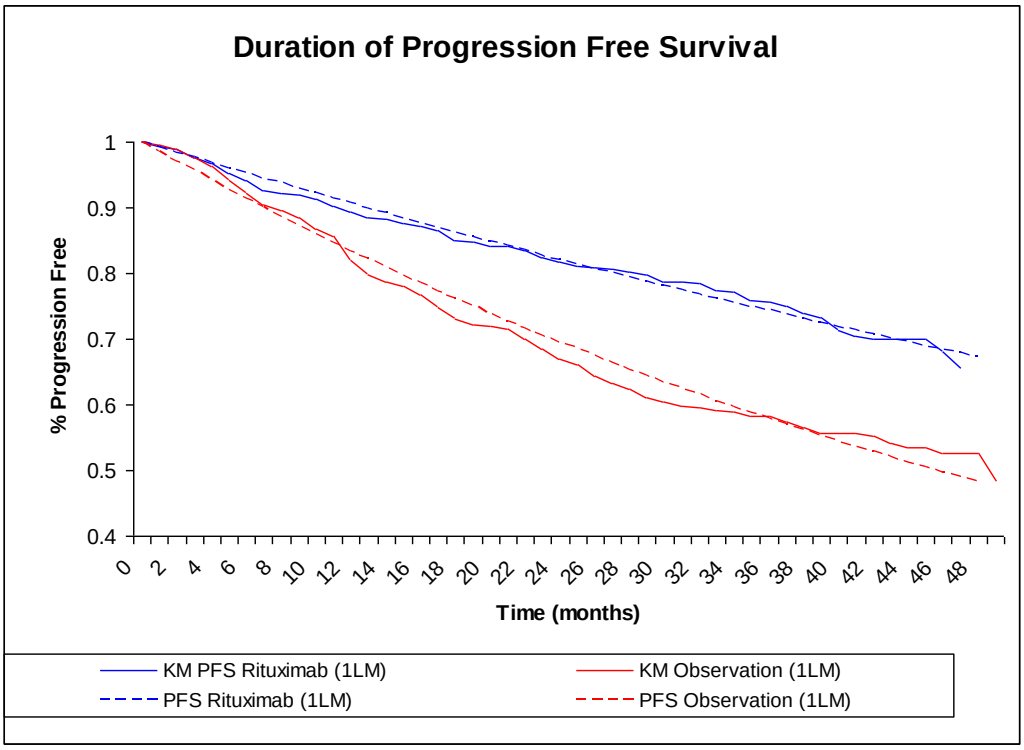
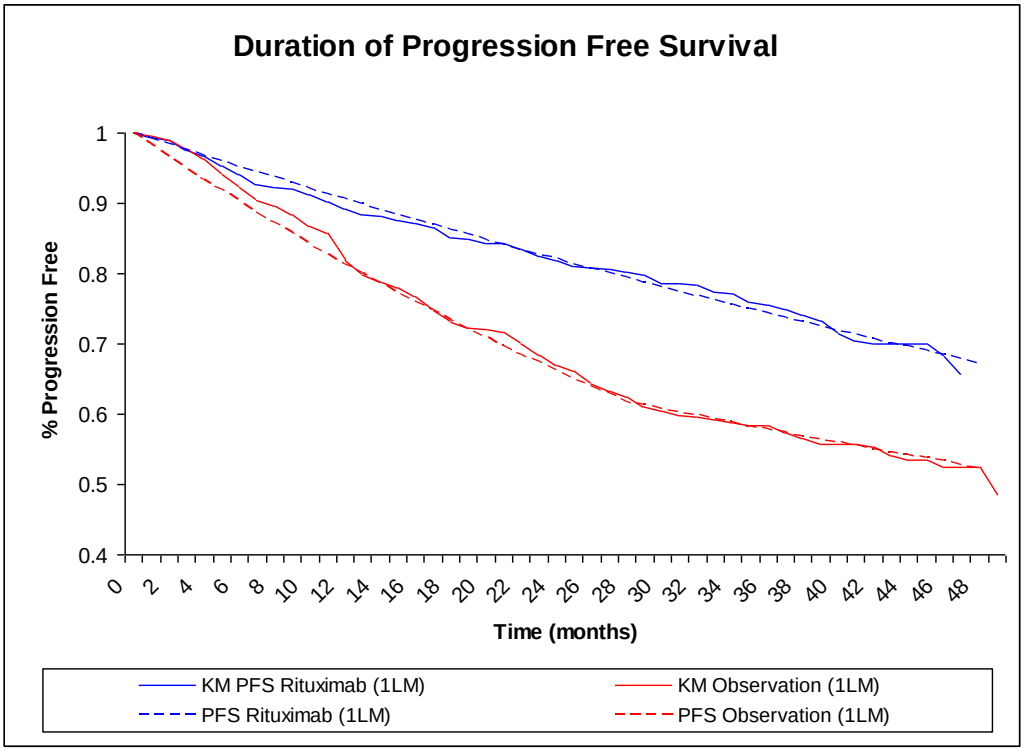


Figure 7: Sensitivity analysis: Treatment duration 28 months (Exponential)



A summary of the differences between this new modelling approach and the base case are provided in Table 4 below. It should be noted that the modelling approach in the base case is the same as that used for the sensitivity analysis presented in Section 1.2 with the exception of differences in the duration of treatment benefit and the PFS hazard ratio. Roche believe that our base case (Gompertz) is a credible means of modelling the PRIMA data *when our base case modelling assumptions are utilised*. However, we believe that this new approach presented in this section (1.3) reflects a more accurate methodology for the purposes of modelling the Committee's requested sensitivity analysis than that which was presented in Section 1.2.

Table 4. Comparison of alternative modelling approach vs updated base case

Model characteristic:	**28 months sensitivity analysis - alternative approach**	**Updated NICE/ERG Base case**
Duration of treatment benefit	28 months	72 months
PFS Hazard ratio	0.48	0.55
Extrapolation method	Exponential: based on the linear nature of the cumulative hazard plots for PFS from PRIMA	Gompertz: based on the best statistical fit to the PRIMA KM PFS curves
Adjustment mechanism when treatment benefit ceases	Reduce probability of progression in the observation arm to match probability in the rituximab arm – as indicated by the cumulative hazard plot	Increase probability of progression in the rituximab arm to match probability in the observation arm

The result of this alternative modelling approach is presented in Table 5 below alongside the updated base case analysis. The ICER increases from £15,404 to £17,681. The undiscounted PFS to OS conversion rate also decreases from 89.2% to 84.1%.

Table 5. Comparison of alternative modelling approach vs updated base case

	28 months Sensitivity analysis (Exponential)	**Updated NICE/ERG Base case (Gompertz)**
Age	62.5	62.5
Duration of treatment effect	28	72
Undiscounted PFS to OS conversion rate	84.1%	89.2%
Inc Cost	*£16,800*	*£16,918*
Inc QALY	0.95	1.10
ICER	**£17,681**	**£15,404**

The further requested sensitivity analysis associated with varying the undiscounted PFS to OS conversion rate is provided in Table 5 below (along with the updated base case). This alternative modelling approach results in ICERs below the NICE accepted threshold of £30,000 per QALY gained, even in the worst case scenario of an undiscounted PFS to OS conversion rate of 70%.

Table 5. Sensitivity analysis for 28 and 72 month limited treatment duration

Inc Cost Inc QALY **ICER**	**Duration of treatment effect** (based on new corrected base case using starting age 62.5)	
PFS to OS	**28 months sensitivity analysis**	**Base case (72 months)**
70%	*£15,837*	*£15,498*
	0.85	0.95
	£18,615	**£16,284**
80%	*£16,522*	*£16,241*
	0.92	1.03
	£17,930	**£15,792**
Base case (84.1%; 89.2%)	*£16,800*	*£16,918*
	0.95	1.10
	£17,681	**£15,404**
90%	*£17,200*	*£16,977*
	0.99	1.10
	£17,349	**£15,372**

1.4 Interpretation of sensitivity analysis

Using the updated base case model, we have presented above the requested sensitivity analyses assuming limited treatment benefit and various PFS to OS gain undiscounted conversation rates. Given the poor fit to the observed PRIMA data resulting from these sensitivity analyses, for the 28 month limited treatment benefit analysis (which was brought about due to a hypothesis presented by the ERG), we have addressed this by modifying the model structure which addresses the underlying concern regarding the cumulative hazard plot, whilst also limiting the treatment benefit duration to the requested 28 months. In all analyses which represented a reasonable fit to the observed data, the ICERs were well below £30,000 per QALY gained.

In the cumulative hazard plots from PRIMA presented in Figure 5, it should be noted that there is no established clinical explanation for why the hazard in the observation arm would decrease after 28 weeks. A plausible clinical explanation is that there is a higher risk of early relapse in patients with more aggressive disease which leaves a population of lower risk patients remaining in the observation arm. It is therefore also possible that over time, the hazard associated with the rituximab arm would also decrease (improve the hazard ratio further) when these similar 'high risk' patients also progress in this arm. We therefore must be cognisant of the possibility that with greater length of follow-up, this change in risk after 28 months may change and a longer treatment effect of rituximab will be confirmed.

Learnings from previous Rituximab folliulcar lymphoma appraisals

Whilst Roche have agreed to provide all requested sensitivity analyses, we would still consider these analyses as worst case clinical scenarios, particularly with regards to the

modelled limited treatment benefit. This is supported by evidence from the EORTC 20981 study.

In the EORTC 20981 study on the role of rituximab in remission induction and maintenance of relapsed/resistant follicular Non-Hodgkin's Lymphoma, NICE provided positive guidance on a limited median length of follow-up of 39.4 months (very similar to the current PRIMA median follow-up of 38 months). Since the publication of TA137, a further analysis based on 6 years of follow-up has been published. Over this median follow-up period of 6 years, the treatment benefit remains statistically significant and clinically meaningful with a hazard ratio of 0.69 (from 0.54 at 33 months) in patients receiving rituximab maintenance following induction treatment with R-CHOP and 0.55 (from 0.40 at 33 months) in overall maintenance population. A comparison of treatment benefit across three cuts of the data is provided in Table 6 below.

Clinical expert opinion[1,2] strongly suggests that the patients with relapsed/resistant follicular lymphoma (EORTC 20981 population) will have a shorter duration of remission compared to those with previously untreated follicular lymphoma (PRIMA population). Therefore, it is reasonable to assume that the duration of benefit in patients with previously untreated follicular lymphoma receiving maintenance treatment with rituximab following a response to induction treatment with rituximab plus chemotherapy would be no worse than that observed in EORTC 20981. Therefore any analysis suggesting a treatment benefit enduring less than 6 years should be treated with caution.

Table 6. Results from EORTC/van Oers study – several points of follow-up

Follow up / Parameter	Information at Submission (NICE TA137)	1st Publication van Oers 2006	Follow up 1 van Oers2010 (6 year)
Median Length of follow up	39.4 months (Sept 2005 Data) from study entry. (longer than regulatory submission of 31 months from induction and 28.3 months from mtx randomization – Dec 2004 data)	Sept 2005 data, fully cleaned 33.3 months from 2nd Randomisation	72 months from 2nd Randomisation
Hazard Ratio for Progression	Maintenance phase: 0.39 (Dec 2004) (p=<0.0001) 0.40 (Sept 2005) (p=<0.0001)	Maintenance phase: 0.40 (p=<0.001)	Maintenance phase: 0.55 (p=<0.0001)
Median PFS	42.2 months (maint) vs. 14.3 months (obs)	51.5 months vs. 14.9 months	44.4 months vs. 15.6 months
Hazard Ratio for progression after R-CHOP induction	**Dec 2004** 0.54 (p=0.0071) **Sept 2005** 0.54 (p=<0.0043)	0.54 (p=0.004)	0.69 (p=0.043)
Median PFS after R-CHOP induction	**Dec 2004** 51.9 months (maint) vs. 22.1 months (obs) **Sept 2005** 51.8 months (maint) vs. 23.0 months (obs)	51.8 months (maint) vs. 23 months (obs)	52.8 months (maint) vs. 22.8 months (obs)

II. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

In Section 3.4 of the ACD, it is stated that people whose disease responded to second-line therapy could be randomised to maintenance treatment with rituximab with one dose every 8 weeks. This is incorrect and should say one dose every 3 months.[3]

III. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Following the Committee's comments and request for additional analysis, Roche has provided a wide range of sensitivity analyses in order to address all the remaining uncertainties in rituximab's cost effectiveness. All analyses resulted in an ICER of below £30,000 per QALY, with the exception of only two which lacked face validity when considering their fit to the observed PRIMA progression-free survival curves, demonstrating that rituximab is a cost effective use of NHS resources in this setting.

IV. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

None

Appendix

The base case assumes identical transition probabilities from the Progressed State to Death irrespective of whether an individual received 1st line maintenance rituximab or observation.

Multiplicative factors were applied to the probability of post-progression mortality for the rituximab arm only in order to create the sensitivity analyses to reflect a 70%, 80% or 90% undiscounted conversion rate from PFS to OS gains for each treatment effect duration scenario.

Undiscounted PFS to OS gain conversion rate	Base case	Sensitivity analysis presented in Sec 1.2			New Approach in Sec 1.3
	72 months	48 months	36 months	28 months	28 months
70%	1.1981	1.1861	1.1811	1.1741	1.1544
80%	1.0872	1.1095	1.1161	1.1193	1.0409
90%	0.9929	1.0412	1.0573	1.0689	0.9455

For example, in order to provide a sensitivity analysis which assumes the treatment benefit duration is limited to 48 months and the undiscounted PFS to OS gain conversion rate is 70% (shaded in grey above), the probability of post-progression mortality for the rituximab arm was increased by 18.61%, whilst the progression to death transition probabilities for the observation arm remained the same.

References

[1] Communication with Dr. Andrew Haynes

[2] Johnson PWM et al. Patterns of Survival in Patients With Recurrent Follicular Lymphoma: A 20-Year Study From a Single Center. *J Clin Oncol* 1995; 13: 140-147

[3] MabThera Summary of Product Characteristics. March 2011.

Rituximab for the maintenance treatment of follicular non-Hodgkin lymphoma following response to first-line chemotherapy

Response from the Lymphoma Association, Leukaemia CARE and Leukaemia & Lymphoma Research to the ACD

On behalf of the patients likely to be adversely affected by any decision not to approve first line maintenance treatment, we wish to express our strong concern at the committee's change of position. We understand the need to seek additional information from the manufacturer and are grateful to have the opportunity to comment on the ACD. However, we are surprised that this has resulted in a reversal of a previously held position, particularly as the input from three commissioning bodies seems to have tipped the balance and outweighed the views of clinical experts and patients.

Government policy to improve cancer outcomes in England
At a time when the government has a clear policy to save 5,000 lives from cancer and acknowledges that this country's survival rates are worse than other European countries, with less spending on cancer drugs, it is important that NICE makes decisions that support the overall commitment to improving outcomes.

This treatment has been approved and is funded in the US, Canada, Germany, Spain, Israel and Scotland. If it is not funded, patients in England and Wales will be disadvantaged and England will be out of step with common practice in other countries.

Choice
By refusing to fund the treatment, NICE would be depriving clinicians and their patients of choice based on clinical judgement, personal circumstances and preferences.

Not all patients will want to have maintenance therapy after first line treatment but many will as it is very hard for people to live with a life-threatening disease that they know will return, possibly within 18 months to two years. The significant extension of time to next treatment is a huge plus for patients. As has been acknowledged, maintenance rituximab is much easier to tolerate than chemotherapy and delivers much longer periods free from debilitating and toxic treatment regimens.

There may be family circumstances that make it imperative for a patient to know they will remain disease free for as long as possible – for example, a woman with follicular lymphoma in her late sixties who is the main carer for her husband. Or a parent who has children taking important exams and who needs to remain well.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
We do not believe that the provisional recommendations are a suitable basis for guidance to the NHS. For more mature data to be available, patients would have to wait

years. When there is so much positive evidence of the benefit to patients, it is unethical to delay implementation. The equitable solution would be to authorise the use of the drug immediately with a condition that data on long-term survival is accrued. NICE should set a date for review of the drug at the earliest point at which there is sufficient data.

There are several references, notably in the PCT comments, to the PRIMA trial having closed early and suggesting that there is a shortage of long-term data proving an ongoing benefit. We understand from the manufacturer's submission that "the study was stopped because the independent DSMC (in Sept 2009) declared that the study had reached its primary endpoint at the pre-specified interim analysis." It would have been unethical, and a violation of patients' consent, to have continued the trial beyond this endpoint. This issue has highlighted a disparity between two regulatory bodies which in effect amounts to the moving of goalposts. It is not acceptable that patients should suffer as a result of an inconsistent approach between two regulators.

We also question the focus on overall survival. In our view this is not as important as progression free survival in this condition and is difficult to assess because of the relapsing and remitting course of the disease. The key factor for patients with follicular lymphoma is to delay the time before they will need to have more chemotherapy because the chemotherapy is a more toxic treatment and also becomes less effective with each successive treatment. For older patients in particular, the ability to tolerate successive regimes of chemotherapy reduces and therefore time gained through longer remissions is extremely important. This is particularly the case for patients not eligible for high dose therapy and transplant which may be a treatment option for younger patients.

Conclusion

We recognise that NICE has a difficult role and that the issues are complex. In an ideal world, there would be longer-term data but it would be highly unethical to deny patients access to first line maintenance rituximab when the evidence for its positive benefit in giving patients longer progression free survival is so clear. Pending longer-term data, we urge NICE to approve funding and to review this decision in a few years time.

[redacted] [redacted] [redacted]

[redacted] [redacted] [redacted]

Lymphoma Association | Leukaemia CARE | Leukaemia & Lymphoma Research

Royal College of Physicians
Setting higher medical standards

11 St. Andrews Place
Regent's Park, London NW1 4LE

Telephone +44(0) 20 7935 1174
Textphone +44(0) 20 7486 5687
Facsimile +44(0) 20 7487 5218

www.rcplondon.ac.uk

From The Registrar
[redacted] FRCP

Telephone extension [redacted]
Direct facsimile [redacted]
[redacted]@rcplondon.ac.uk

Dr Carole Longson
Director, Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

22 March 2011

Dear Dr Longson

Re: 2nd ACD re Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with relation to this ACD consultation. We are grateful for the opportunity to respond and would like to make the following comments.

We are surprised and disappointed to see this document, which reverses the opinion in the initial appraisal consultation document (ACD) issued after the meeting of 4th November 2010. This reversal appears to have been carried out without the benefit of any new evidence, but following the submission of a single objection from an NHS commissioning body, which has been copied verbatim by two others. This contains significant errors of information and interpretation as detailed below.

Following the Appraisal meeting an ACD was produced that reflected expert opinion in the UK and worldwide, that Rituximab maintenance in first remission is both clinically and cost effective. The recommendations in the second ACD are simply not consistent with the first and have been arrived at without the benefit of any expert clinical input.

The reasons for the acceptance of Rituximab maintenance were extensively discussed at the Appraisal panel. We make the following comments upon the revised ACD and the objection from the NHS commissioners:

1) The improvement in progression free survival (PFS) in the Rituximab maintenance arm of the PRIMA study at two and now at three years is both statistically significant and clinically meaningful in this population. There is nothing to suggest that the difference between the two arms diminishes with time. The concerns voiced by the ERG and the suggestion by the NHS commissioners that the initial data would not be sustained with further follow up are not borne out by the evidence that continues to emerge at international scientific meetings and which has now been published in the Lancet
2) A sustained advantage has been observed in all other published studies of Rituximab as first and second line therapy in follicular lymphoma with long term follow up, and there is nothing to suggest the data from the PRIMA study will diverge from this pattern.
3) No single trial in this condition has demonstrated a major survival benefit, since patients are able to receive further treatment at recurrence. However, the continued separation of the PFS curves indicates that Rituximab is contributing to an overall increase in the freedom from symptomatic disease, in what is an incurable cancer

4) Registry studies have clearly demonstrated an improvement in overall survival for patients with follicular lymphoma since 2000. In the absence of any major shifts in the demographics or other major changes in management, this is widely accepted to be due to the impact of Rituximab during this time.
5) NICE have previously accepted PFS as a legitimate endpoint in the other studies of follicular lymphoma and other indolent lymphoid malignancies. It is not correct for the NHS commissioners to suggest that the original ACD recommendation was questionable in the absence of overall survival benefit, given the natural history of this illness and its responsiveness to salvage therapy.
6) The published results of the PRIMA study clearly demonstrate that all subgroups of patients have increased freedom from disease if they receive maintenance Rituximab. This specifically includes those above or below the age of 60. It is not legitimate to require an unplanned retrospective analysis of a subset of patients with median age comparable to that in registry studies for re-analysis of the data. It is sufficient to demonstrate, as the trial clearly does, that both older and younger patients derive benefit from the addition of 2 years maintenance therapy.
7) It must be re-emphasised that the trial was not stopped prematurely, but when the pre-planned endpoints were met. The decision to analyse the data was not taken by the sponsoring company or by the investigators but by the properly constituted independent data monitoring and safety committee.
8) The NHS commissioners suggest in their submission that the recommendations "could increase the use and therefore the overall cost of this drug for a PCT population" as if this undermines the evidence in favour of its use. Treatments should be approved subject to the existing standards of value for money to the NHS, which this treatment has passed. Furthermore, it is unlikely that the implementation of first line maintenance therapy will very substantially increase the use of Rituximab, since the great majority of patients will receive it in any case in second remission or at subsequent relapses.
9) The NHS commissioners suggest that "there is no convincing evidence of improved…quality of life and this calls into question the assumptions of the cost-effectiveness model". This is not the case. The PRIMA study demonstrated clearly that there is no reduction in quality of life during maintenance treatment, as the NHS commissioners point out. The patients who gave evidence at the appraisal hearing were categorical in their view that Rituximab treatment is greatly preferable to the known side-effects of chemotherapy, which is instituted sooner for patients who do not receive maintenance Rituximab. It is thus evident that the application of maintenance Rituximab carries a substantial premium for quality of life, as has been applied in the model. It is not tenable to assert, as the NHS commissioners have, that "the assumption that patients' quality of life is improved by the more manageable side effects of Rituximab maintenance…was not clearly demonstrated..." On the contrary, this is precisely the experience of patients and clinicians alike.
10) The statement by the NHS commissioners that "The ERG agreed to the manufacturer's small changes to the decision problem" is of no relevance. The assessment of benefit only in patients who had received Rituximab as part of induction treatment would if anything have diluted the effect of maintenance treatment and reduced the benefit. Similarly, the omission of an expensive comparator treatment, Ibritumomab tiuxetan, also works against Rituximab rather than in its favour.

This revised ACD runs directly counter to current national and international guidelines and standard practice for the treatment of follicular lymphoma. Maintenance therapy with Rituximab in first remission has now become a universal standard of care, based upon a large well-conducted prospective clinical trial. There are no other studies planned in this indication, since the results of this study are widely recognised as definitive. There is little purpose to trial groups in this country designing and participating in such studies if their globally accepted results cannot be incorporated into clinical practice, and the UK's capacity to participate in future trials designed with the leading independent international groups will be compromised if patients in this country cannot receive the internationally agreed standard of care.

For these reasons we would ask the committee to reverse its opinion in the second ACD and recommend, as it did originally, the use of Rituximab as first-line maintenance therapy for responding patients with advanced stage follicular lymphoma.

Yours sincerely

[redacted]

[redacted]
Registrar

National Institute for Health and Clinical Excellence

Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy.

Nurses caring for this group of patients reviewed the documents on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the four questions on which comments were requested is set out below:

i) **Has the relevant evidence has been taken into account?**

The evidence considered seems comprehensive.

ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?**

We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with follicular non-hodgkin's lymphoma. The preliminary views on resource impact and implications should be in line with established standard clinical practice.

iii) **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?**

Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add.

The RCN would welcome guidance to the NHS on the use of this health technology.

iv) **Are there any equality related issues that need special consideration that are not covered in the ACD?**

We are not aware of any specific issue at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.

Response to NICE on 2nd ACD re Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma

We are surprised and disappointed to see this document, which reverses the opinion in the initial appraisal consultation document (ACD) issued after the meeting of 4th November 2010. This reversal appears to have been carried out without the benefit of any new evidence, but following the submission of a single objection from an NHS commissioning body, which has been copied verbatim by two others. This contains significant errors of information and interpretation as detailed below.

Following the Appraisal meeting an ACD was produced that reflected expert opinion in the UK and worldwide, that Rituximab maintenance in first remission is both clinically and cost effective. The recommendations in the second ACD are simply not consistent with the first and have been arrived at without the benefit of any expert clinical input.

The reasons for the acceptance of Rituximab maintenance were extensively discussed at the Appraisal panel. We make the following comments upon the revised ACD and the objection from the NHS commissioners:

1) The improvement in progression free survival (PFS) in the Rituximab maintenance arm of the PRIMA study at two and now at three years is both statistically significant and clinically meaningful in this population. There is nothing to suggest that the difference between the two arms diminishes with time. The concerns voiced by the ERG and the suggestion by the NHS commissioners that the initial data would not be sustained with further follow up are not borne out by the evidence that continues to emerge at international scientific meetings and which has now been published in the Lancet
2) A sustained advantage has been observed in all other published studies of Rituximab as first and second line therapy in follicular lymphoma with long term follow up, and there is nothing to suggest the data from the PRIMA study will diverge from this pattern.
3) No single trial in this condition has demonstrated a major survival benefit, since patients are able to receive further treatment at recurrence. However, the continued separation of the PFS curves indicates that Rituximab is contributing to an overall increase in the freedom from symptomatic disease, in what is an incurable cancer
4) Registry studies have clearly demonstrated an improvement in overall survival for patients with follicular lymphoma since 2000. In the absence of any major shifts in the demographics or other major changes in management, this is widely accepted to be due to the impact of Rituximab during this time.
5) NICE have previously accepted PFS as a legitimate endpoint in the other studies of follicular lymphoma and other indolent lymphoid malignancies. It is not correct for the NHS commissioners to suggest that the original ACD recommendation was

questionable in the absence of overall survival benefit, given the natural history of this illness and its responsiveness to salvage therapy.

6) The published results of the PRIMA study clearly demonstrate that all subgroups of patients have increased freedom from disease if they receive maintenance Rituximab. This specifically includes those above or below the age of 60. It is not legitimate to require an unplanned retrospective analysis of a subset of patients with median age comparable to that in registry studies for re-analysis of the data. It is sufficient to demonstrate, as the trial clearly does, that both older and younger patients derive benefit from the addition of 2 years maintenance therapy.
7) It must be re-emphasised that the trial was not stopped prematurely, but when the pre-planned endpoints were met. The decision to analyse the data was not taken by the sponsoring company or by the investigators but by the properly constituted independent data monitoring and safety committee.
8) The NHS commissioners suggest in their submission that the recommendations "could increase the use and therefore the overall cost of this drug for a PCT population" as if this undermines the evidence in favour of its use. Treatments should be approved subject to the existing standards of value for money to the NHS, which this treatment has passed. Furthermore, it is unlikely that the implementation of first line maintenance therapy will very substantially increase the use of Rituximab, since the great majority of patients will receive it in any case in second remission or at subsequent relapses.
9) The NHS commissioners suggest that "there is no convincing evidence of improved…quality of life and this calls into question the assumptions of the cost-effectiveness model". This is not the case. The PRIMA study demonstrated clearly that there is no reduction in quality of life during maintenance treatment, as the NHS commissioners point out. The patients who gave evidence at the appraisal hearing were categorical in their view that Rituximab treatment is greatly preferable to the known side-effects of chemotherapy, which is instituted sooner for patients who do not receive maintenance Rituximab. It is thus evident that the application of maintenance Rituximab carries a substantial premium for quality of life, as has been applied in the model. It is not tenable to assert, as the NHS commissioners have, that "the assumption that patients' quality of life is improved by the more manageable side effects of Rituximab maintenance…was not clearly demonstrated..." On the contrary, this is precisely the experience of patients and clinicians alike.
10) The statement by the NHS commissioners that "The ERG agreed to the manufacturer's small changes to the decision problem" is of no relevance. The assessment of benefit only in patients who had received Rituximab as part of induction treatment would if anything have diluted the effect of maintenance treatment and reduced the benefit. Similarly, the omission of an expensive comparator treatment, Ibritumomab tiuxetan, also works against Rituximab rather than in its favour.

This revised ACD runs directly counter to current national and international guidelines and standard practice for the treatment of follicular lymphoma. Maintenance therapy with Rituximab in first remission has now become a universal standard of care, based upon a large well-conducted prospective clinical trial. This treatment has been approved and funded in Scotland (Scottish Medicines Consortium guidance 7th Feb 2011) so to maintain equity of care within the UK, this should also be available for patients in England and Wales.

There are no other studies planned in this indication, since the results of this study are widely recognised as definitive. Further studies comparing rituximab maintenance to observation would now be unlikely to gain ethical approval as rituximab maintenance is

considered a standard of care. There is little purpose to trial groups in this country designing and participating in such studies if their globally accepted results cannot be incorporated into clinical practice, and the UK's capacity to participate in future trials designed with the leading independent international groups will be compromised if patients in this country cannot receive the internationally agreed standard of care.

For these reasons we would ask the committee to reverse its opinion in the second ACD and recommend, as it did originally, the use of Rituximab as first-line maintenance therapy for responding patients with advanced stage follicular lymphoma.

Consultant Haematologists
(Representing the Royal College of Pathologists and the British Committee for Standards in Haematology).

From: [redacted]@dh.gsi.gov.uk [mailto:[redacted]@dh.gsi.gov.uk] On Behalf Of [redacted]@dh.gsi.gov.uk
Sent: 22 March 2011 07:43
To: TA Comm B
Cc: [redacted]@dh.gsi.gov.uk
Subject: NICE STA - Follicular non-Hodgkin's lymphoma - rituximab - February 2011 Appraisal Consultation Document and comments on November 2010 ACD:

Dear NICE

Thank you for the opportunity to comment on the appraisal consultation document for the above single technology appraisal.

I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.

Many thanks and best wishes

[redacted]
NICE Sponsor Team
Department of Health

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	Yes
Notes	Roche drugs are used in various clinical trials in which I am involoved
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Maintenance rituximab is used second line and there is first line data. I havent given it personally but understand it is being given via the ICDF. To stop would be a retrograde step.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	22/03/2011 16:39

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	yes
Notes	Honoraria medical advisor for Roche
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The committee should recommend first-line maintenance treatment for patients with Follicular Lymphoma. The recommendation fails to take accont of patient choice - there are many situations where it may be extremely valuable for a patient to delay the time to relapse. It will be hard for patiemts who have completed their first course of chemotherapy (R-CVP) then to be told that they will have not have access to maintenance therapy knowning that there is strong trial data to support this intervention. I am concerned that improved PFS has been used to approve other technologies by NICE. I am also concerned that this intervention is widely available in Europe, the US and other parts of the UK
Section 2 (The technology)	

Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	17/03/2011 14:03

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	At NICE's request, the manufacturer has already conducted health economic analyses based on a number of assumptions. These demonstrated ICER values between Â£15,000 and Â£30,000 implying cost-effective use of NHS resources. However there are fundamental issues about how much weight can be attributed to the manufacturer's projections of benefits up to 6 years, which is considerably beyond the period of observation (the median follow up was 38 months). These factors were highlighted in the previous PCT and CSAS submission to NICE. It is expected that the manufacturer will produce further analyses for consideration at the next Appraisal Committee. the assumptions put forward in the manufacturers model do not seem plausible. Any model must be considered in the context of failure to demonstrate improvements in overall survival, and uncertainties about the use of salvage chemotherapy following disease progression. The manufacturer's model was based over a 6 year time period, despite only 4 years' follow up in the PRIMA study.
Section 2 (The technology)	Were NICE to reverse this minded no, a positive recommendations could increase the use and therefore the overall cost of this drug for a PCT population. According to the manufacturer's estimates, the cost of treating a person with an average body surface area of 1.8m2 with rituximab maintenance treatment for 2 years is Â£14,669. Implementing this guidance could carry additional annual drug costs of approximately Â£380,000 for the average PCT of 300,000 people with an estimated 52 people receiving maintenance treated with rituximab for this indication per year. PCTs would need to give consideration to which haematology services would not receive investment to make way for a requirement to fund this indication.
Section 3 (The manufacturer's submission)	l amounts of data were redacted in the origional ERG report. The most relevant study was the the PRIMA trial and this forms the basis of the manufacturer's submission. Data from the post-study observational follow-up period, which had a median follow-up of 38

	months, were submitted to the ERG as ‘academic in confidence’ and will become more generally available when and if they are published. We note that the ERG cautioned that the data were immature and that the early closure of the trial might have led to an overestimation of the clinical benefits of rituximab maintenance treatment. with the level of redaction (presumably on grounds of commercial sensitivity) it makes it hard to form a balanced view.
Section 4 (Consideration of the evidence)	In the manufacturer’s base case analysis, rituximab maintenance was cost effective compared with observation when the benefits of rituximab are assumed to last for 6 years (ICER £15,978/QALY). In sensitivity analyses undertaken by the ERG, ICERs ranged from £21,000 to £26,000 per QALY when the benefit was assumed to be sustained for the first 3 to 4 years. given our view that the manufacturers assumptions are "somewhat optimistic" we do not view the manufacturers model as a reliable estimate, and would place more emphasis on the (worst case) assumptions in thesensitivity analysis to be more reflective of a true base case.
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	16/03/2011 22:03

Name	NHS Nottingham City
Role	PCT
Other role	
Location	
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	After reviewing the available information, and consulting with our regional East Midlands cancer commissioners, I can confirm that NHS Nottingham City is supportive of the provisional recommendation outlined within NICE’s second Appraisal Consultation Document for the Technology Appraisal of Rituximab for the maintenance treatment of follicular non-Hodgkin's lymphoma following response to first-line chemotherapy. This is to not recommend Rituximab for the maintenance treatment of follicular non-Hodgkin’s lymphoma following response to first line chemotherapy.
Section 2 (The technology)	
Section 3 (The manufacturer’s submission)	
Section 4 (Consideration of the evidence)	
Section 5	

(Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	

STA ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Rituximab for the first-line maintenance treatment of patients with follicular non-Hodgkin's lymphoma: Addendum

This report was commissioned by the NIHR HTA Programme as project number 08/218

Completed March 28th 2011

DOES NOT CONTAIN IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Table of Contents

1 INTRODUCTION

Following the second NICE Appraisal Committee meeting for the single technology appraisal of rituximab (RTX) as a first-line maintenance therapy for the treatment of patients with follicular non-Hodgkin's lymphoma on 25th February 2011, a request was made to the manufacturer of RTX to undertake additional economic analyses to inform specific issues of concern to the Appraisal Committee. At the same time the Evidence Review Group (ERG) decided to explore these issues while the matters discussed and familiarity with the economic model were still at the forefront of our minds. The first part of this Addendum (sections 2-4) details our findings in relation to the questions posed. The second part (sections 5-6) contains a brief description and critique of the new analyses submitted by the manufacturer to NICE in response to the second Appraisal Consultation Document (ACD).

2 ERG CORRECTIONS TO MANUFACTURER'S MODEL

Five model related problems were reported in the submitted ERG report which potentially impact on the results of the manufacturer's economic evaluations.

2.1 Revised cost of rituximab maintenance therapy

The manufacturer estimated RTX costs using an overall average body surface area (BSA) figure (mean BSA 1.84m^2) to estimate the cost per dose of RTX, without adjusting for the wide range of BSA values in the population, gender-specific BSA differences, and the relative proportions of male and female patients. Based on PRIMA[1] trial information supplied by the manufacturer, the mean cost of RTX has been estimated by the ERG as £1,281.52 (an increase of 4.84% on the model value).

2.2 Correction to discounting method

The manufacturer applied discounting on a monthly basis, which is not in accord with UK practice. The ERG incorporated a change from monthly to annual discounting.

2.3 Correction to timing of rituximab doses

Rituximab first-line maintenance treatment is administered 12 times at 8 week intervals. This means that the last dose occurs 88 weeks (20.2 months) after the first dose. In the submitted model the cost of the 12 doses is spread evenly over 24 months which is equivalent to assuming half a dose mid-way through each month. In fact the dosing schedule leads to an uneven dosing across the monthly model periods, with seven doses in the first year and five doses in the second year (when discounting applies). Correction of the model by the ERG affects both the discounted cost of RTX and the discounted cost of RTX administration.

2.4 Correction to proportion of patients receiving second-line chemotherapy

The submitted model uses data from the trial to estimate the proportion of patients failing the first progression-free survival (PFS) period (observation or RTX maintenance) but not progressing to second-line induction therapy. These proportions were calculated relative to the whole randomised population (at the start of the PFS period), but are applied in the model only to those patients who are still alive at the end of PFS. These proportions have been corrected by use of the appropriate ratios identified from the PRIMA[1] trial.

2.5 Correction of utility values in progression-free survival states

The submitted model features two PFS health states: PFS1 relates to patients achieving a complete or partial response following first-line chemotherapy (CTX) and PFS2 for patients achieving a response to second-line CTX. The health utilities are drawn from a study reported by Wild[2, 3] in which EQ-5D values were elicited for five health states. The manufacturer uses an estimated utility value (0.88) for the 'disease free' state in estimating QALYs in the PFS1 model state, and uses a different estimated utility value (0.79) for the 'remission/full response to therapy' state when patients are in the PFS2 model state. This choice is not appropriate, since the PRIMA[1] trial does not report what number, if any, of patients were disease free. The most appropriate approach to determining a PFS1 utility value is to weight the estimates corresponding to complete and partial responders (0.79 and 0.77) in the paper by Wild[2,3] by the corresponding proportions of first-line therapy responders in the PRIMA[1] trial. Similarly, a compatible utility value for the PFS2 model state can be derived from the relative proportions of complete and partial responders to second-line RTX-based CTX in the EORTC 20981 trial[4, 5] (the basis of the NICE appraisal[6] of RTX second-line maintenance therapy). On this basis the ERG calculates that the utility value for PFS1 should be 0.78417 and for PFS2 should be 0.77694.

3 APPRAISAL COMITTEE EXPLORATORY ISSUES

During the Appraisal Committee meetings of 4th November 2010 and 3rd February 2011, four issues were identified to be of particular concern which relate to the sensitivity of the results from the manufacturer's model to different assumptions or parameter values. This section describes the steps taken by the ERG to explore each of these concerns.

3.1 Age of population

It was noted that patients in the PRIMA[1] trial were significantly younger than follicular lymphoma patients receiving for first-line CTX in UK clinical practice, and the Appraisal Committee wished to know how model results would change if the mean age of patients were to be increased from 56 to 62.5 years. The submitted model allows the mean age to be varied, but this serves only to limit the death probabilities following first- and second-line treatments by reference to national UK mortality rates at the corresponding age. It does not reflect the prognostic importance of incident age, as is recognised in the FLIPI prognostic index[7] and confirmed by the ERG's clinical advisor.

To allow this concern to be explored, the ERG requested additional results from the PRIMA[1] trial, via the clarification process, to allow a comparison of clinical effectiveness between three age-based subgroups. The manufacturer provided these data in the form of numbers of PFS events and estimated odds ratios (ORs) for RTX vs observation for patients aged younger than 44 years, 44-64 years and 65+ years. Despite the immaturity of the PRIMA[1] data, and the unsophisticated nature of the analysis, there appears to be evidence of an emerging trend indicating a reduction of clinical effect as patient age increases – a curvilinear trend in OR, equivalent to a linear trend in relative risk. To illustrate the sensitivity of model results to this effect, the hazard ratio (HR) of PFS in the base case model was adjusted by the ERG to reflect specific patient ages and to show the combined effect of increasing mortality and reducing effectiveness on the estimated incremental cost-effectiveness ratio (ICER).

3.2 Correction for early reporting bias

A recent meta-analysis[8] compared the reported results of 91 randomised controlled trials (RCTs) that were halted early for benefit with 424 similar RCTs that ran to full term. The authors found large differences in treatment effect size between trials that were stopped early and similar trials that ran their full course. This was true regardless of the methodological quality of the trial or the presence of statistical stopping rules. One implication of this finding is that early closure of trials can lead to exaggerated treatment effects that would not be borne out in the longer term. Personal communication with the corresponding author of this study provided the ERG with details of the meta-regression equation, and allowed the adjusted magnitude of PFS benefit to be estimated as HR

0.719 (95% CI 0.575 to 0.889), an increase of 30.7% on the reported trial HR (0.55). This revised value has been used in the sensitivity analyses conducted by the ERG.

3.3 Duration of effect of rituximab maintenance therapy

As a consequence of the immaturity of the PRIMA[1] trial data, the manufacturer's model included a parameter governing the maximum period over which RTX maintenance therapy could be expected to provide direct benefit (i.e. reduced risk of disease progression). Rituximab was given in the maintenance arm for less than 2 years. In the submitted base case, the manufacturer set this parameter to 6 years and did not refer to any supporting evidence. Two alternatives were offered in the manufacturer's model results: 4 years (equivalent to the maximum time over which any patients had been observed within the PRIMA[1] trial), and 40 years (equivalent to a lifetime).

To consider likely values for this variable, the trajectory of the cumulative PFS function was compared for the PRIMA[1] trial arms. Although the maintenance arm data are suggestive of a steady period risk throughout the trial period, the same does not appear to be the case in the observation arm (Figure 1) which indicates an increased risk for 2-3 years after first-line CTX followed by a significantly reduced risk thereafter. The ERG shows that fitting a bi-phase exponential model to the observation arm results in a change in risk occurring at 27.3 months. Moreover the estimated risk parameter values in the two trial arms are quite similar beyond 27 months. The implications of this analysis are that most, if not all, the benefit of RTX maintenance therapy in the PRIMA[1] trial appears to have accrued within the first three years.

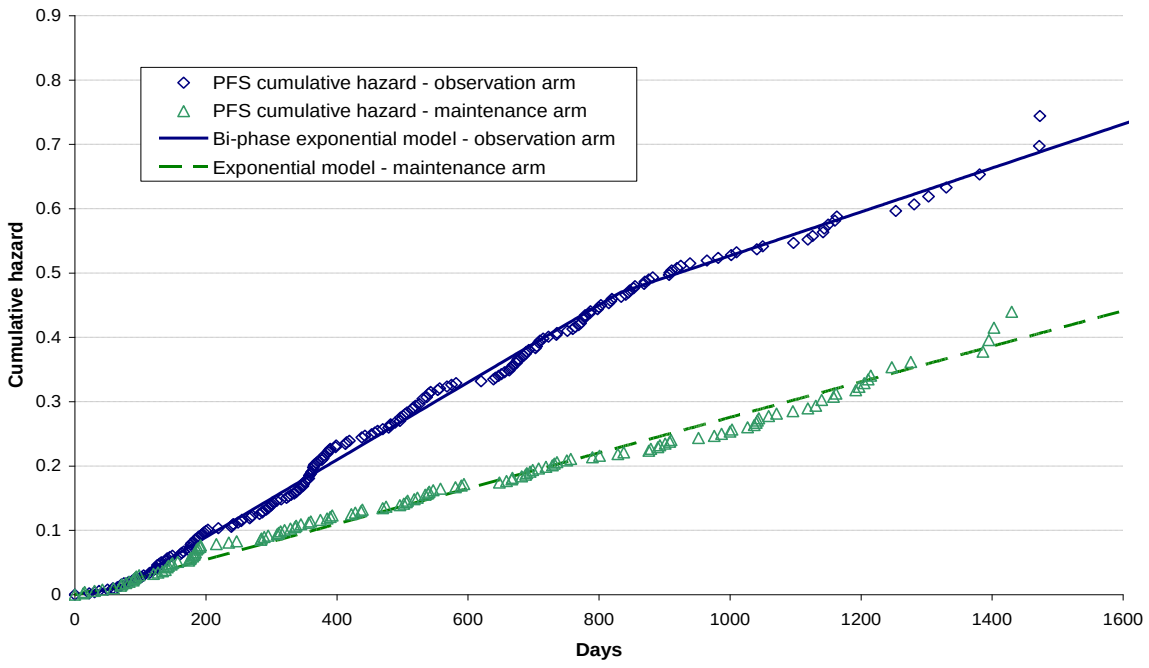


Figure 1 PRIMA PFS cumulative hazard data modelled to estimate risk parameter values

In order to test that these patterns of risk are not merely the result of statistical accident in the observation arm, the ERG examined data from the M39021[9] trial of first-line R-CVP (cyclophosphamide, vincristine, prednisolone) vs CVP in follicular lymphoma. The time to treatment failure results for the intervention arm (R-CVP) should be a close match to the observation arm of PRIMA,[1] being from a similar population, at the same stage of the disease natural history and using a similar trial outcome. After discounting the first-line CTX period (which was prior to randomisation in PRIMA[1]), the M39021[9] results show a very similar hazard trajectory to that found in the PRIMA[1] observation arm. This appears to indicate that the 2-phase risk dynamic may be a reflection of R-CTX in follicular non-Hodgkin's lymphoma. The mechanism by which this phenomenon is generated is necessarily speculative without detailed investigations of individual patient data, but may involve the persistence of RTX and its metabolites in the body or targeted suppression of progression applicable to a subgroup of patients.

Values of the effective duration of benefit from RTX at 28, 36 and 48 months have been used to test the sensitivity of model results.

3.4 Relationship of progression free survival gain to overall survival gain

The submitted model projects future benefits in terms of increased patient time in PFS, and this is the dominant driver of cost effectiveness. In the manufacturer's base case, the model estimates the gain in mean (undiscounted) survival as 1.94 years. The model also estimates the mean (undiscounted) PFS as 2.01 year implying that virtually all the PFS gains are translated into overall survival (OS) gains.

At present there is no unequivocal evidence from any clinical trial or meta-analysis of RTX maintenance treatment of patients with follicular non-Hodgkin's lymphoma for any significant OS gains, despite strong evidence of PFS gains. The immaturity of the PRIMA[1] trial data compounds this problem, since the extent of PFS gain cannot be estimated directly, but only by projective modelling. (NB the PFS advantage from first-line RTX maintenance measurable directly from the mature trial data up to 800 days from randomisation is no more than 60 days).

It was not possible to amend the submitted model logic or adjust model parameters to assess the likely impact of less generous assumptions about the proportion of PFS gains which might be expected to ultimately result in OS gains. Instead, the ERG has applied adjustments to the outcomes and costs generated by the model to reflect alternative long-term outcome scenarios. Starting from a pre-specified OS:PFS gain ratio (70%, 80% or 90%), the reduced undiscounted OS gain was computed and used to calculate a revised value for the undiscounted OS per patient receiving RTX maintenance therapy, and hence the implied PPS per patient. The revised estimates were then discounted using a

simple linear regression equation to ensure compatibility with the discounting multipliers generated in the manufacturer's model results. The revised discounted PPS estimate was then used to revise the estimated cost per patient in PPS in the RTX arm, and hence the overall discounted cost per patient.

4 SUMMARY OF ECONOMIC RESULTS FROM THE MANUFACTURER'S MODEL AS REVISED BY THE ERG

A full set of model results have been calculated and are shown in Tables 1-4.

4.1 Revised base case

Table 1 shows the sensitivity of model results to each of the ERG corrections discussed in Section 2, together with the combined effect of all these alterations in order to arrive at an ERG revised base case analysis. Individually these changes cause only minor variations in the results, so that the revised base case ICER is only £2,058 per quality adjusted life year (QALY) gained greater than the original result.

4.2 Sensitivity of cost-effectiveness ratios to four additional issues

Table 2 provides one-way sensitivity analyses for four additional issues identified as being of interest to the Appraisal Committee:

1) increasing the mean age of the population to 62.5 to more closely match the age of patients presenting in UK practice;

2) meta-regression adjustment of the primary outcome of the PRIMA[1] trial (PFS hazard ratio) to reflect potential bias caused by the trial reporting early;

3) assumptions concerning the duration of effect that 2 years RTX maintenance treatment may have in reducing the risk of disease progression or death (compared to the model base case assumption of 72 months);

4) different estimates of the proportion of estimated gain in PFS from RTX maintenance treatment which may result in additional survival time.

It is apparent from Table 2 that issues (1) and (4) have considerably less impact individually on the magnitude of the estimate ICER, than issues (2) and (3).

4.3 Combined effects of all changes

Table 3 and Table 4 provide a comprehensive account of all combinations of the values identified as being of interest to the Appraisal Committee in relation to these four issues. All results use the revised base case as the starting point, and adjust results to a mean age of 62.5 years. Table 3 uses the original PFS HR (0.55) as reported by the manufacturer, whereas in Table 4 an amended PFS HR is used (0.719) obtained from using the meta-regression equation supplied by the authors of the recent JAMA paper[8] which estimated the degree of bias associated with the early reporting of clinical trials.

In both Table 3 and Table 4, a full range of the combined effects of varying the duration of effect of maintenance therapy and the proportion of PFS gain converting to OS gain is presented.

All results in Table 4 indicate ICERs greater than £39,000 per QALY gained. In Table 3, ICERs only fall below £30,000 per QALY gained if it is assumed that RTX therapy delivers continued alteration of PFS risk of more than 3 years.

Table 1 Revised base case economic results using ERG corrections to model methods and parameter values

	Cost per patient		QALYs per patient		Increment		ICER
Model scenario / alteration	RTX mtce	Observation	RTX mtce	Observation	Cost	QALYs	Cost/QALY gained
1) Revised submitted base case	**£69,949**	**£52,308**	**8.376**	**7.207**	**£17,641**	**1.169**	**£15,088**
2) ERG revised RTX costs	£70,633	£52,308	8.376	7.207	£18,324	1.169	£15,673
3) Discounting method corrected	£71,158	£52,781	8.493	7.305	£18,377	1.188	£15,472
4) Timing of RTX doses corrected	£68,780	£52,308	8.376	7.207	£16,472	1.169	£14,088
5) Accurate proportion receiving second- line treatment	£70,032	£52,350	8.382	7.210	£17,682	1.172	£15,086
6) Recalculated PFS utility values	£69,649	£52,308	7.756	6.734	£17,641	1.022	£17,261
Combined (1)-(6) ERG revised base case	**£70,666**	**£52,823**	**7.871**	**6.830**	**£17,843**	**1.041**	**£17,136**

mtce=maintenance

Table 2 Sensitivity of economic results to four additional model issues

	Cost per patient		QALYs per patient		Increment		ICER
Model scenario / alteration	RTX mtce	Observation	RTX mtce	Observation	Cost	QALYs	Cost/QALY gained
ERG revised base case	**£70,666**	**£52,823**	**7.871**	**6.830**	**£17,843**	**1.041**	**£17,136**
6) Mean age increased to 62.5, with age- stratified PFS hazard ratios	£66,049	£48,983	7.407	6.437	£17,065	0.970	£17,584
7) Increase PFS hazard ratio in trial by 30.7% for early reporting bias[8]	£71,262	£52,823	7.501	6.830	£18,439	0.672	£27,454
8a) RTX effect lasts only 28 months	£71,262	£52,823	7.412	6.830	£19,162	0.582	£32,922
8b) RTX effect lasts only 36 months	£71,714	£52,823	7.516	6.830	£18,890	0.686	£27,542
8b) RTX effect lasts only 48 months	£71,335	£52,823	7.653	6.830	£18,512	0.823	£22,488
9a) 70% of PFS gain converts to OS gain	£68,581	£52,823	7.656	6.830	£15,757	0.826	£19,078
9b) 80% of PFS gain converts to OS gain	£69,364	£52,823	7.736	6.830	£16,541	0.907	£18,240
9c) 90% of PFS gain converts to OS gain	£70,143	£52,823	7.817	6.830	£17,319	0.987	£17,544

mtce=maintenance

Table 3 Exemplification of results with mean patient age adjusted to 62.5 and using the reported PFS hazard ratio = 0.55 (PRIMA original)

Model scenario / alteration		Cost per patient		QALYs per patient		Increment		ICER
		RTX mtce	Observation	RTX mtce	Observation	Cost	QALYs	Cost/QALY gained
ERG revised base case		**£70,666**	**£52,823**	**7.871**	**6.830**	**£17,843**	**1.041**	**£17,136**
28 months effect	70% PFS converts to OS	£66,227	£48,983	6.829	6.437	£17,244	0.392	**£43,934**
	80% PFS converts to OS	£66,607	£48,983	6.869	6.437	£17,624	0.432	**£40,822**
	90% PFS converts to OS	£66,986	£48,983	6.908	6.437	£18,003	0.471	**£38,234**
36 months effect	70% PFS converts to OS	£65,740	£48,983	6.911	6.437	£16,756	0.474	**£35,327**
	80% PFS converts to OS	£66,198	£48,983	6.959	6.437	£17,215	0.522	**£33,000**
	90% PFS converts to OS	£66,655	£48,983	7.006	6.437	£17,672	0.569	**£31,067**
48 months effect	70% PFS converts to OS	£65,098	£48,983	7.022	6.437	£16,114	0.585	**£27,558**
	80% PFS converts to OS	£65,662	£48,983	7.080	6.437	£16,679	0.643	**£25,939**
	90% PFS converts to OS	£66,224	£48,983	7.138	6.437	£17,291	0.701	**£24,595**

mtce=maintenance

Table 4 Exemplification of results with mean patient age adjusted to 62.5 and PFS hazard ratio = 0.719 (PRIMA adjusted for mean early reporting bias)

Model scenario / alteration		Cost per patient		QALYs per patient		Increment		ICER
		RTX mtce	Observation	RTX mtce	Observation	Cost	QALYs	Cost/QALY gained
ERG revised base case		**£70,666**	**£52,823**	**7.871**	**6.830**	**£17,843**	**1.041**	**£17,136**
28 months effect	70% PFS converts to OS	£66,639	£48,983	6.701	6.437	£17,656	0.264	**£66,870**
	80% PFS converts to OS	£66,897	£48,983	6.728	6.437	£17,913	0.291	**£61,617**
	90% PFS converts to OS	£67,154	£48,983	6.754	6.437	£18,171	0.317	**£57,289**
36 months effect	70% PFS converts to OS	£66,356	£48,983	6.749	6.437	£17,373	0.312	**£55,640**
	80% PFS converts to OS	£66,661	£48,983	6.781	6.437	£17,677	0.344	**£51,438**
	90% PFS converts to OS	£66,964	£48,983	6.812	6.437	£17,981	0.375	**£47,948**
48 months effect	70% PFS converts to OS	£65,994	£48,983	6.813	6.437	£17,101	0.376	**£45,271**
	80% PFS converts to OS	£66,360	£48,983	6.851	6.437	£17,376	0.414	**£42,019**
	90% PFS converts to OS	£66,725	£48,983	6.888	6.437	£17,742	0.451	**£39,319**

mtce=maintenance

5 MANUFACTURER'S MODEL REVISIONS AND ADDITIONAL ANALYSES

5.1 Modifications to submitted model

The version of the manufacturer's decision model used to carry out the requested additional analyses does not incorporate any of the amendments identified by the ERG in their report (as described in sections 2.1-2.5 above).

5.2 Scenarios and adaptations

In order to carry out the analyses requested by the Appraisal Committee the manufacturer has developed three scenarios within their model, and has carried out a number of alterations to allow the relevant parts of the model to reflect the changes requested.

Scenario 1: This allows a revised base case analysis to be carried out, but with the mean age of patients increased to 62.5 years. As mentioned above, the age-adjustment only affects the background mortality rate applicable to all patients; it does not implement the age-related HR for PFS described above (section 3.1).

Scenario 2: This allows a 2-way estimation of cost effectiveness for combinations of the duration of treatment effect (four options are available: 28, 36, 48 and 72 months), and the proportion of PFS gain which translates to eventual OS gain (70%, 80% and 90%). In addition to the age change in *Scenario 1*, differential PFS HRs are employed depending on the assumed duration of RTX effect: 0.48 for 28 months; 0.513 for 36 months; 0.552 for 48 months; and 0.55 for 72 months. In order to achieve the desired PFS:OS ratio, it is necessary to increase (or decrease) the model mortality rate for patients in progressive disease by applying a multiplier to both treatment arms.

Scenario 3: This scenario attempts to replicate observations by the ERG concerning the trajectory of cumulative PFS hazard plots from the PRIMA[1] trial which suggest the limitation of RTX treatment effect to 28 months. This involves changing from Gompertz to exponential modelling of PFS, using a 2-phase exponential model for the comparator (observation) arm.

6 ERG COMMENTS ON MANUFACTURER'S ADDITIONAL ANALYSES

The results generated by the manufacturer of RTX appear to be generally positive for RTX maintenance therapy in that most ICERs are below £30,000 per QALY gained. However, the ERG remains unconvinced by the modified model: the ERG had previously attempted to carry out a similar exercise, but concluded that the structure of the model did not allow sufficient flexibility to accommodate some realistic scenarios. In particular, in some instances target PFS:OS ratios could not be achieved with positive mortality rates, and therefore the ERG adopted an alternative approach of adjusting model results outside the framework of the submitted model to ensure that all variables were mutually consistent.

However, if the ERG corrections (section 2 above) are implemented, the age-related HR adjustment (section 3.1 above) is applied, and the excluded second-line CTX costs (section 5.1) are re-instated, the differences between the ERG and manufacturer estimated ICERs are not great (of the order of about £5,000).

The results of the sensitivity analyses presented above (Tables 2 – 4) indicate that there are two issues of primary importance to establishing a realistic ICER value on the basis of currently available evidence:

- is the HR for PFS reported from the PRIMA[1] trial (0.55) considered reliable, or should the adjusted estimate for early-reporting trials based on a published meta-regression[8] (0.719) be used instead?

- what is the most credible estimate for the duration of RTX effect (which is given for less than 2 years) in the range from 28 months (ERG proposed estimate) to 72 months (manufacturer's base case)?

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8 APPENDIX: IMPLEMENTATION OF ERG MODEL AMENDMENTS

Details of the changes made to the submitted model to implement each change are shown below.

Revised cost of rituximab maintenance therapy

Normal distributions of BSA were used (Females mean BSA 1.7129 m^2 , SD 0.1751, Males mean BSA 1.9452 m^2, SD 0.1738), and the Female to Male proportions set to 52.36%:47.64%.

The amended cost was implemented by adding a multiplier term to the formulae in the range AE6:AE365 of the 'New Therapy' worksheet as follows:

** IF(Mod1=0,1,'Model Inputs'!$I$28)*

where Mod1 is a binary switch variable to activate the modification, and 'Model Inputs'!$I$28 contains the ratio of £1,281.52 to £1,222.39.

Correction to discounting method

On the 'model Inputs' worksheet, cell C61 was named as "d_c" and cell C62 as "d_u".

Formulae in columns E, I, N, R, W, AA, AC on worksheets 'New Therapy' and 'Comparator' were amended to replace all references to "(1+disc_u)^B*n*" to read "(1+d_u)^A*n*" for *n* = 6 to 365.

Formulae in columns AD, AE, AF, AG, AH, AJ, AM on worksheets 'New Therapy' and 'Comparator' were amended to replace all references to "(1+disc_c)^B*n*" to read "(1+d_c)^A*n*" for *n* = 6 to 365.

A binary switch variable (Mod2) was created to control the operation of this amendment (0 = original logic, 1 = revised logic).

Correction to timing of rituximab doses

A table was constructed on the 'New Therapy' worksheet to represent the correct pattern of RTX doses by monthly model period in the range AW6:AX29, showing doses given in months 1, 2, 4, 6, 8, 10, 12, 13, 15, 17 and 19.

In the formulae in columns AD and AE of the 'New Therapy' worksheet the expression IF($B*n* > 23, 0, 1) was replaced by

IF(Mod3=0,IF($B*n* > 23, 0, 1),VLOOKUP(B6,$AW$6:$AX$29,2)

where Mod3 is a binary switch variable to activate the modification, and *n* = 6 to 365

Correction to proportion of patients receiving second line chemotherapy

On the 'Transition Probabilities' worksheet, the formula in cell D10 has been amended to read

=IF(Mod5=0,1-SUM(E16:E18),445/503)

and the formula in cell D11 has been amended to read

=IF(Mod5=0,1-SUM(F16:F18),414/512)

where Mod5 is a binary switch variable to activate the modification

Correction of utility values in PFS states

The revised utility value for PFS1 was calculated as:

70.825% (complete response) * 0.79 + 29.175% (partial response) * 0.77

The revised utility value for PFS2 was calculated as:

34.7% (complete response) * 0.79 + 65.3% (partial response) * 0.77

These values were introduced into the 'Model Inputs' worksheet cells E54 and E56 by simple substitution using a binary switch variable.

Adjustment of PFS hazard ratio for a change in population mean age

The mean age and proportion of the population was calculated for each of three age-bands (under 44, 44-65 and 65+), using data supplied by the manufacturer in response to clarification requests. The odds ratios provided by the manufacturer were converted to relative risk, and a linear regression line calibrated by ordinary least squares allowing the relative risk to be estimated for any mean age.

The mean age in the PRIMA[1] trial of each age band was increased by 6.5 years, and the corresponding relative risk value estimated from the regression equation. A ratio was then calculated for each age-band estimated relative risk to the overall relative risk in PRIMA[1] (0.624) to yield a risk multiplier appropriate to each age-band as part of a population with mean age 62.5 years. The multiplier values are 0.8208 (<50.5), 1.0982 (50.5-70.5) and 1.3398 (over 70.5).

Revised model results were obtained separately for each age band, setting the mean age for the band in cell E19 of the 'Model Inputs' worksheet, and using a binary switch variable to apply the multiplier to the formula in cell N30 of the 'Gompertz' worksheet. Finally a weighted average of the model results for total costs and total QALYs from the 'Results' worksheet was calculated using the proportions of patients in each age band for both maintenance and observation arms to obtain a revised ICER estimate.

Correction for early reporting bias

A binary switch variable was created to apply the HR multiplier (1.307) to the formula in cell N30 of the 'Gompertz' worksheet.

Duration of effect of rituximab maintenance therapy

A numeric variable was created in the 'Results' worksheet to represent the number of months that RTX provides additional effect on PFS (or rather the number of months less 1). The formulae used in cells C6:C365 of the 'New Therapy' worksheet were modified for the option when t_eff=3, to refer to the chosen value in the 'Results' worksheet. This allows alternative durations of effect to be readily tested, having first set t_eff=3.

Relationship of PFS gain to OS gain

The calculations involved in revising the outcomes and costs obtained with the manufacturer's model are as follows:

<u>Undiscounted survival</u>

- a variable *R* is set to the desired proportion of PFS gain which should be converted to OS gain

- model PFS gain = ('New Therapy'!D3+'New Therapy'!H3+'New Therapy'!Q3)/12
  - (Comparator!D3+Comparator!H3+Comparator!Q3)/12

- revised OS gain = *R* * model PFS gain

- revised PPS gain = revised OS gain - model PFS gain

- revised RTX OS = Comparator!AB3/12 + revised OS gain

- revised RTX PPS = revised PPS gain + observation OS – observation PFS

Discounted survival

Based on the relationship between overall discount factors and undiscounted OS and PFS in the manufacturer's model a simple linear relationship was calibrated ($r^2 = 0.9996$) as follows:

Revised discounted survival = 0.92076 - 0.01055 * Revised undiscounted survival

This was applied to the undiscounted revised OS in the RTX arm, and the discounted PPS, discounted OS gain and discounted PPS gain calculated to match all PFS and observation model estimates.

Discounted QALYs

The revised discounted RTX QALYs in PPS were calculated by multiplying the revised discounted PPS time in the RTX arm by the utility value for patients in PPS. The revised discounted overall estimated QALYs in the RTX arm were then calculated by summing the QALYs in PFS and PPS. The QALYs gains from use of RTX were then revised as the difference between the revised RTX QALY estimates and the model observation QALY estimates.

Discounted costs

Discounted costs were revised by recalculating the discounted PPS cost per patient in the RTX arm as the discounted PPS time in the RTX arm multiplied by the average cost of supportive care in the PPS state. From this figure the overall discounted cost per RTX patient was recalculated, and the additional cost per patient due to use of RTX in the PPS and overall was recalculated.