[redacted]

21st March 2011

Jeremy Powell
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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]

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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)

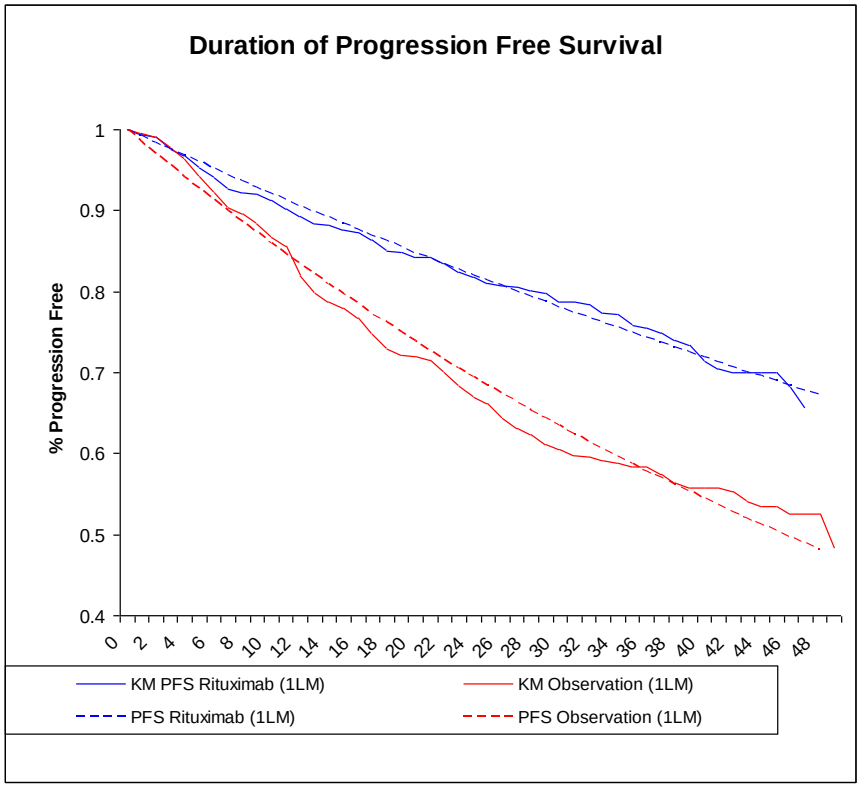
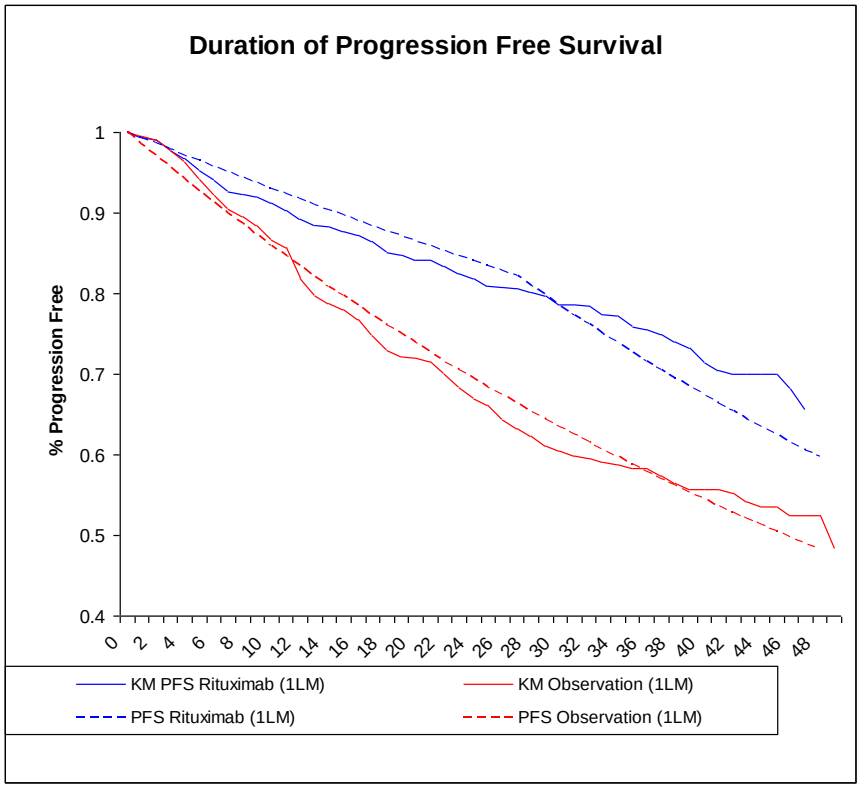


Figure 2: Sensitivity analysis with treatment duration 28 months and 70% PFS to OS Conversion rate (Gompertz)



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..

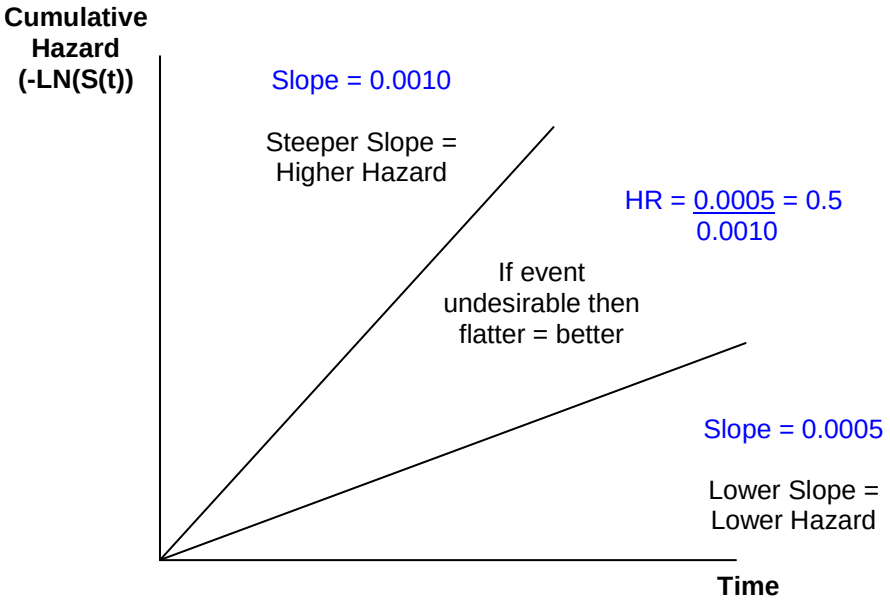
During the 2nd Committee meeting, the ERG representative proposed a new hypothesis that the duration of treatment effect offered by rituximab maintenance was limited to only 28 months based upon the cumulative hazard plots from the PRIMA study (see Figure 5 below). Roche have considered carefully the 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.

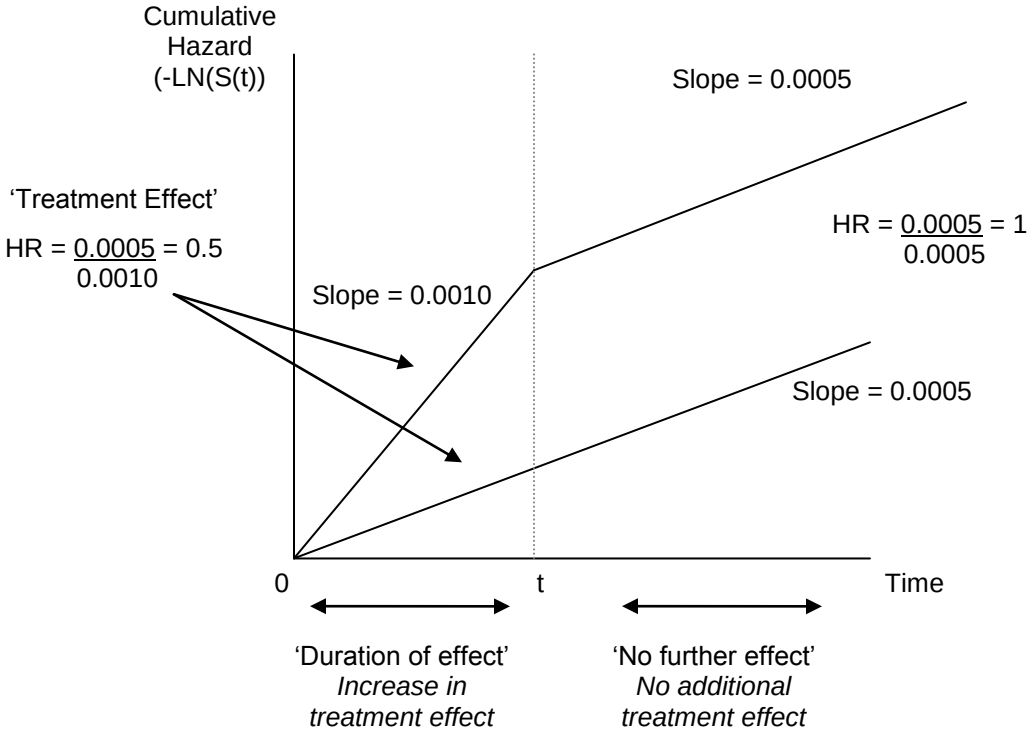
Figure 3: Example of cumulative hazard plots (1)



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).

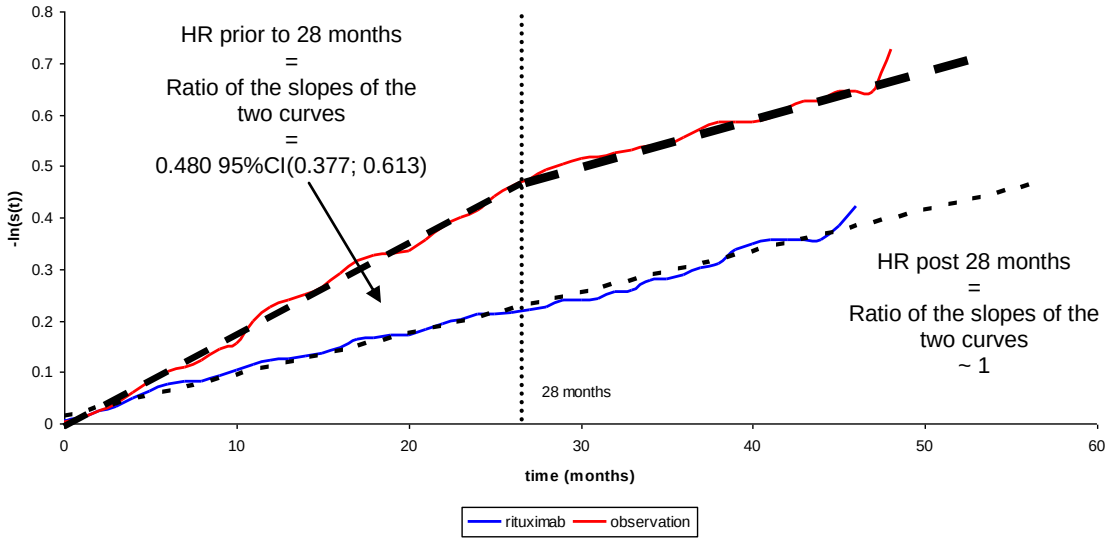
Figure 4: Example of cumulative hazard plots (2)



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)

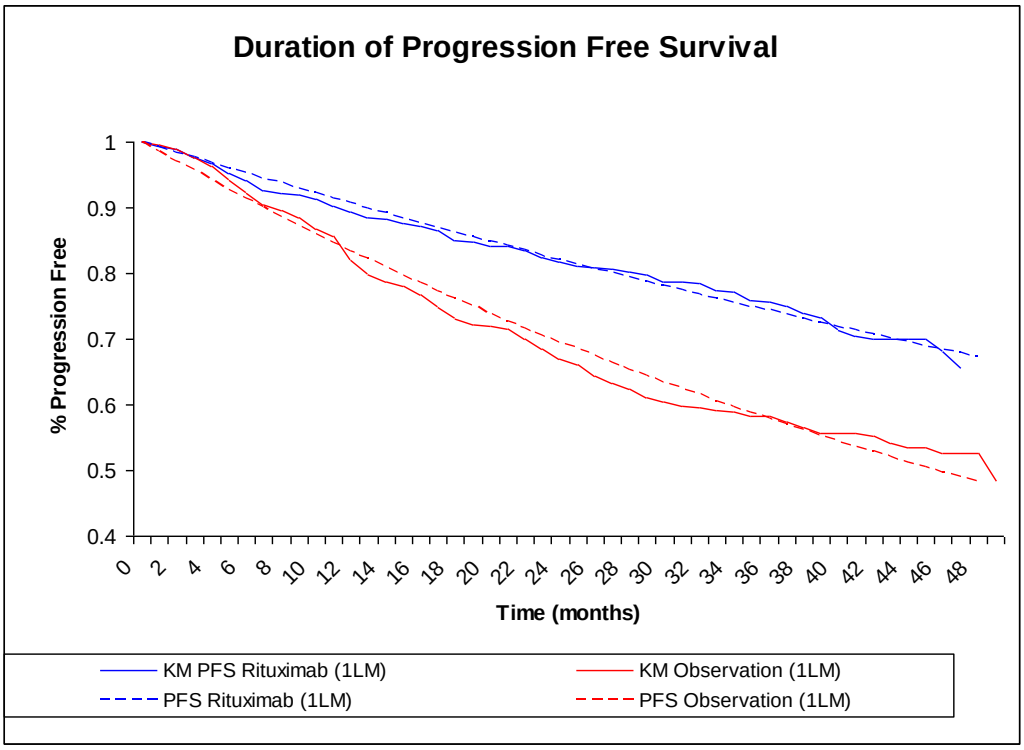
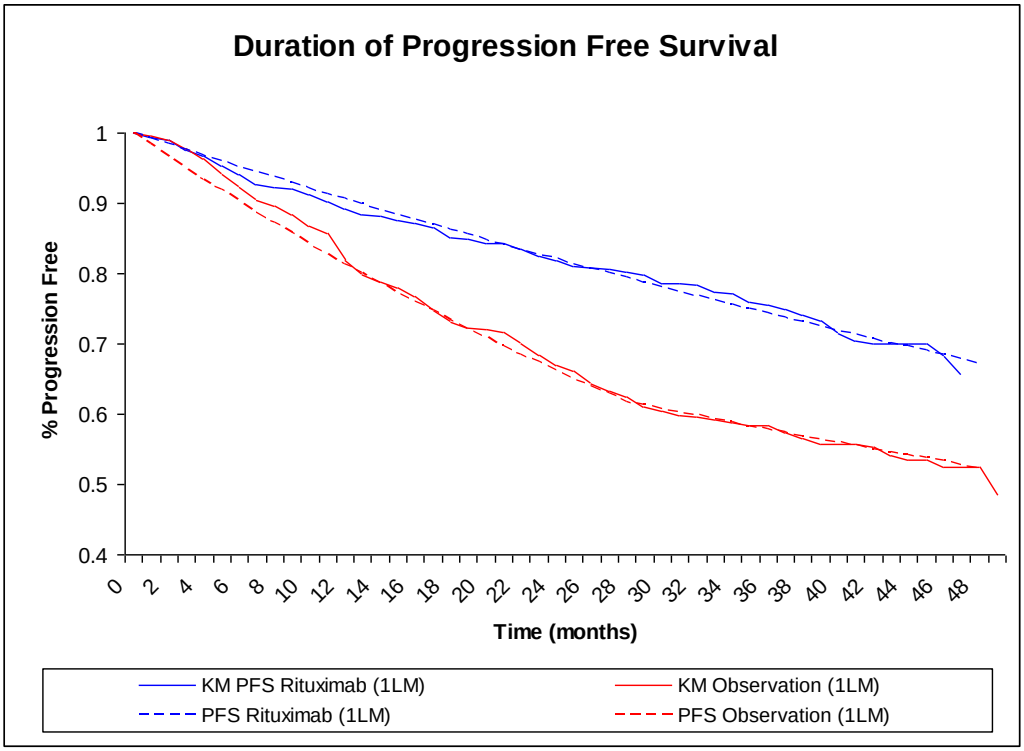


Figure 7: Sensitivity analysis: Treatment duration 28 months (Exponential)



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

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