STA ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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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.

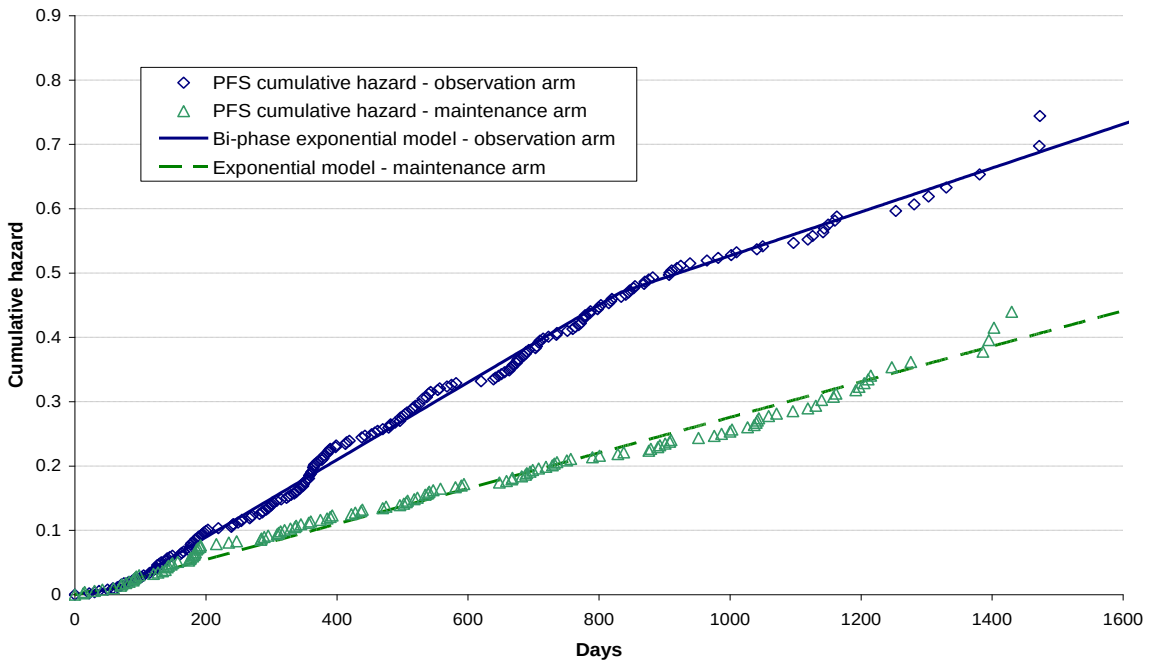

Figure 1 PRIMA PFS cumulative hazard data modelled to estimate risk parameter values

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)?

7 REFERENCES

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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.