

Rituximab for the First-Line Treatment of Chronic Lymphocytic Leukaemia

Response to Appraisal Committee's Preliminary Recommendations:
Roche Products Limited.

20 April 2009

i) Do you consider that all of the relevant evidence has been taken into account?

Roche agrees that all current relevant clinical evidence specifically for the first-line treatment of CLL has been taken into account; however the nature of the licence granted by the EMEA for rituximab in this disease area and its implications have not been considered fully. The EMEA have endorsed a rituximab+ chemotherapy licence, allowing a physician to add rituximab to any suitable underlying chemotherapy regime and we feel the implications of this are worthy of further consideration by the Evidence Review Group.

It is well established that a significant proportion of CLL patients requiring treatment for the first time will not be suitable for a combination including fludarabine and cyclophosphamide and a regimen based on chlorambucil would be more suitable and tolerable. As has been covered in detail in the submission and clarification questions, the combination of rituximab and chlorambucil is being actively investigated in a UK only Phase II clinical trial (UK CLL208), led by Professor Peter Hillmen. This study has now recruited 75/100 patients and the first efficacy data will be available in Q4 2009. However, even though there are no data currently available from this study, the clinical effectiveness of the combination of rituximab + chlorambucil has effectively been validated by the licence given by the European Medicines Agency.

In clause 4.4, the appraisal consultation document states:

"The Committee concluded that there was considerable uncertainty about the clinical benefit associated with adding rituximab to chemotherapy regimens other than fludarabine and cyclophosphamide."

Roche feel that this conclusion is flawed and there cannot be 'considerable uncertainty' as the licence specifically allows rituximab to be combined with any chemotherapy. The EMEA would not have endorsed the licence as it stands if they felt there was any doubt surrounding the clinical effectiveness of combining rituximab with any chemotherapy regime.

The CHMP assessment report (EMA/135353/2009¹) specifically notes after consideration of the evidence that:

" Similar positive benefits were seen for rituximab added to a range of other cytotoxic chemotherapy regimens in patients with CLL. These were data mainly presented as publications but in the CHMP opinion is sufficient evidence to support the broad indication..."

This implies that rituximab in combination with any suitable chemotherapy has a favourable risk/benefit ratio and that the regulators were convinced that the magnitude of benefit would be seen with any base chemotherapy regime, *without needing to see comparative Phase III data with every different cytotoxic drug.*

Roche appreciates that there is not a completed large multi-centre Phase III study of rituximab+chlorambucil compared to chlorambucil alone which can be clinically and economically dissected, however consistent benefits of adding rituximab to a variety of underlying chemotherapy regimes have been seen in numerous Phase III studies in low-grade lymphoproliferative disorders. It is also unclear whether it would be possible to run and recruit a further randomised study in which there was no antibody in one arm (i.e. R-chlorambucil versus chlorambucil alone), as the benefits of R-chemotherapy in low grade B-cell diseases have been conclusively demonstrated, and some investigators would potentially find it difficult to randomise a patient into a study where there was clearly one inferior arm.

It should be noted that CLL is a very similar disease to other low-grade B-cell cancers and they share very similar natural histories and treatment goals (i.e. relapsing/remitting, usually incurable, good evidence that obtaining a good a remission as possible is very important prognostically). Therefore, it is pertinent to consider the wealth of Phase III data in follicular lymphoma, which have investigated rituximab plus numerous different underlying regimes. There are four key Phase III trials:

1. **GLSG'00:** rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) compared to CHOP.²
2. **OSHO-39:** rituximab plus MCP (mitoxantrone, chlorambucil and prednisolone) compared to MCP.³
3. **FL2000:** rituximab plus CHVP+ α IFN (cyclophosphamide, etoposide, doxorubicin, prednisolone and alpha-interferon) compared to CHVP+ α IFN.⁴
4. **M39021:** rituximab plus CVP (cyclophosphamide, vincristine and prednisolone) compared to CVP.⁵

A detailed review of these studies here is beyond the scope of the question, however these studies have all consistently shown that irrespective of the base regime, rituximab adds significant efficacy with manageable toxicity. It is clinically plausible to extrapolate this to CLL: the combination of rituximab plus any chemotherapy (including chlorambucil) would be clinically effective. It is important to note that study OSHO-39 used a chlorambucil containing regime (i.e. rituximab and chlorambucil have been used in combination before in low grade B-cell malignancy). There is also Phase II data that specifically has reported on the combination of chlorambucil and rituximab in low-grade lymphomas (first-line and relapsed)⁶. Martinelli and colleagues investigated this combination in 29 patients with low-grade lymphoproliferative disorders (including 2 patients with relapsed CLL/SLL). As expected, they noted excellent efficacy (overall response rate 89%, with a CR rate of 63%), with manageable toxicity, as has been seen with other rituximab combination regimes.

The licence implies that the magnitude of effect (efficacy/safety and risk/benefit) of adding rituximab would be broadly consistent for any chemotherapy regime. Thus it is possible to economically model R-chlorambucil against chlorambucil alone. The threshold analysis considered in the economic section of the original submission suggested that only a *considerable* decrease in the clinical effectiveness of the rituximab + chemotherapy regimen (compared to R-FC) would result in a cost-ineffective combination (p149-150 “Scenario Analysis: Considerations for R-chemo”; original Roche NICE submission).

In addition to this, we provide here a simple model of R-chlorambucil versus chlorambucil based on the original model structure described in the submission. This model is based on the accepted assumption (as described above) that the relative treatment effect of adding rituximab to any base chemotherapy regime is transferable, but the baseline risks of the relevant population must be taken into account (which the original threshold analysis did not). The following adjustments were made to create this comparison:



- The age of the cohort was increased to 70, reflecting the older patient population likely to be prescribed chlorambucil over a fludarabine-based regime. This impacts the background mortality rate only.
- The chlorambucil arm (built originally for the R-FC v. chlorambucil comparison using data from the mixed treatment comparison described in the original submission) was used in order to ensure that baseline risk in the model was adjusted for the older, frailer population reflected among those who are generally prescribed chlorambucil over fludarabine-based therapy. This arm was based on the results of the chlorambucil arm in the UK CLL4 study ⁷ which reflects the most up-to-date published analysis of the real-life effectiveness of this drug in this population.
- A Rituximab + chlorambucil arm (R-chl) was created based on the chlorambucil arm (chl) by applying an adjustment factor to the PFS Weibull function to ensure that the hazard ratio observed in the CLL-8 trial for R-FC versus FC over the trial follow-up duration (44 months) was matched (HR=0.595 (CI 0.473 -0.748)). That is, the effective base case hazard ratio for R-chl versus chl applied in this model is 0.595, the same used for the R-FC versus FC model.
- The drug and administrative costs associated with R-chlorambucil were included in this arm.
- All remaining model inputs and assumptions (e.g. assumption of the monthly probability of progression to death, health care utilisation costs for bone marrow transplants and blood transfusions reported in the R-FC vs FC model, utility values, etc.) were maintained in the R-chlorambucil vs chlorambucil comparison.

- Due to updates to our model following submission to NICE, the model presented here includes two additional changes to chlorambucil drug and administration costs which do not impact on the incremental costs of the R-chl vs chl analysis (as they impact both arms in the same ways). However, for completeness, these additional adjustments are described below:
 - In the original model, the cost of chlorambucil was inadvertently set to zero. This was not highlighted by NICE or the ERG during their review. It has now been set to the appropriate BNF value as provided in Table 37 of the original submission (£23.41 per cycle).
 - This version of the model also adjusts for the drug and administrative costs of chlorambucil in the first 12 months of this markov model, using the FLOOR and MOD functions in *Excel*. Because chlorambucil is provided in 28 day cycles, but the model uses a month (30.4375 days) cycle, the number of days of chlorambucil required in each month was adjusted accordingly, with a notable decrease in the cost associated with the final (12th) month of chlorambucil drug and administrative costs.

The results of the R-chlorambucil versus chlorambucil comparison are therefore based on the same baseline risk associated with patients who would traditionally receive chlorambucil as reflected in the CLL4 trial – with only an effect modification for the addition of rituximab by assuming the hazard ratio is the same across chemotherapy regimes. As assumed in the original threshold analysis, the incremental cost of adding rituximab to chlorambucil is not very different from adding rituximab to FC (£11,570 for R-chlorambucil versus £11,617 for R-FC). As concluded in the threshold analysis, as the incremental costs do not differ significantly, it is the incremental benefit which deserves our attention. While we assumed that the **relative** treatment effect would not differ between across chemotherapy regimens (by utilizing HR = 0.595 observed in CLL-8 for this R-chl v. chl analysis), due to the worse baseline risk of the older, frailer patients treated with chlorambucil, the **absolute** treatment effect is smaller in this example (incremental QALYs of 0.51 for R-chl v. chl compared to 0.88 QALYs gained observed in the R-FC v. FC comparison). This resulted in a higher, but still cost-effective, ICER of £22,490 per QALY gained (compared to £13,189 per QALY in the R-FC v. FC comparison).

Table 1. Base case results for R-chlorambucil versus chlorambucil.

Cost-utility results	R-chlorambucil	chlorambucil	Incremental
Mean Life Years (yrs)	4.02	3.39	0.63
Mean QALYs	2.86	2.35	0.51
Mean Total Cost	£24,894	£13,324	£11,570
Cost per Life Year Gained (£)			£18,335
Cost per QALY Gained (£)			£22,490

To incorporate the uncertainty in the magnitude of treatment benefit achieved by the addition of rituximab to chlorambucil, a PSA was conducted by varying the same parameters in the original submission (for R-FC v. chl) and including as well the 95% confidence interval on the CLL-8 hazard ratio (CI 0.473 -0.748) using a normal distribution. The scatter plot and cost-effectiveness acceptability curve are provided

below. Base on 1,000 simulations, the probability of R-chl not surpassing a threshold of £20,000 per QALY gained in 18.6% and the probability of not surpassing a threshold of £30,000 per QALY gained is 99.7%. Thus we have demonstrated, using the above analysis, that, as well as R-FC, R-chlorambucil is very likely to result in a cost-effective option for 1st line CLL patients.

Figure 1: Scatter plot of cost per QALY for R-chlorambucil vs. chlorambucil (example:1,000 Monte Carlo simulations)

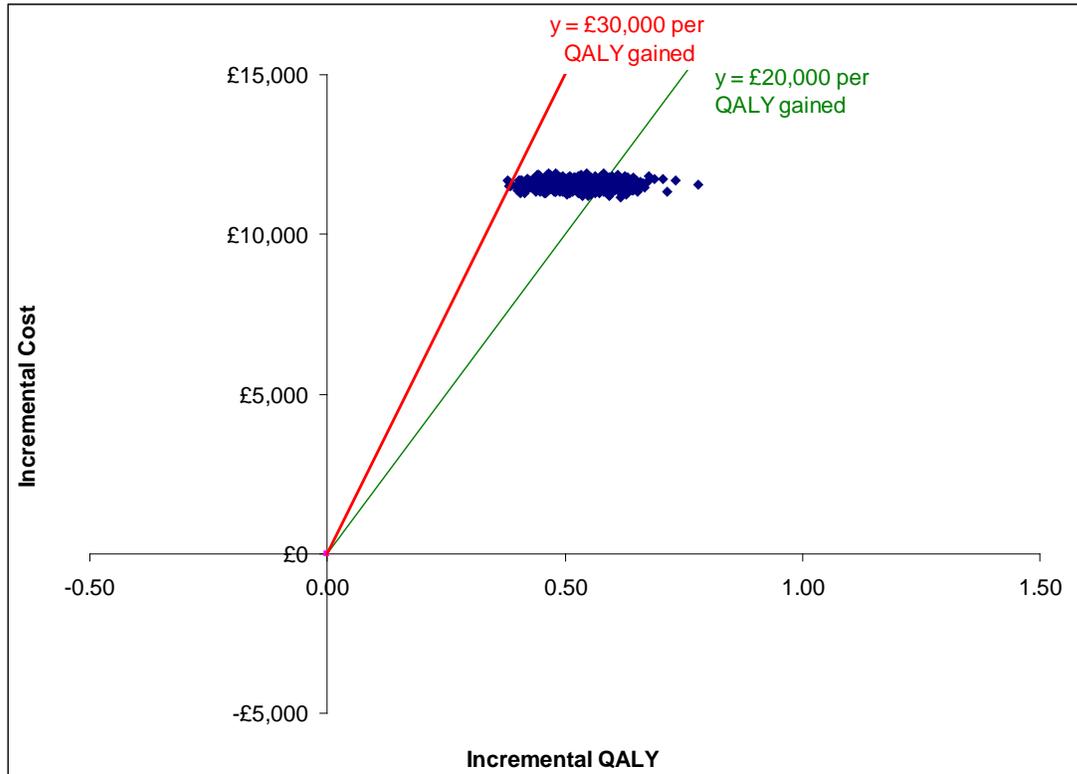
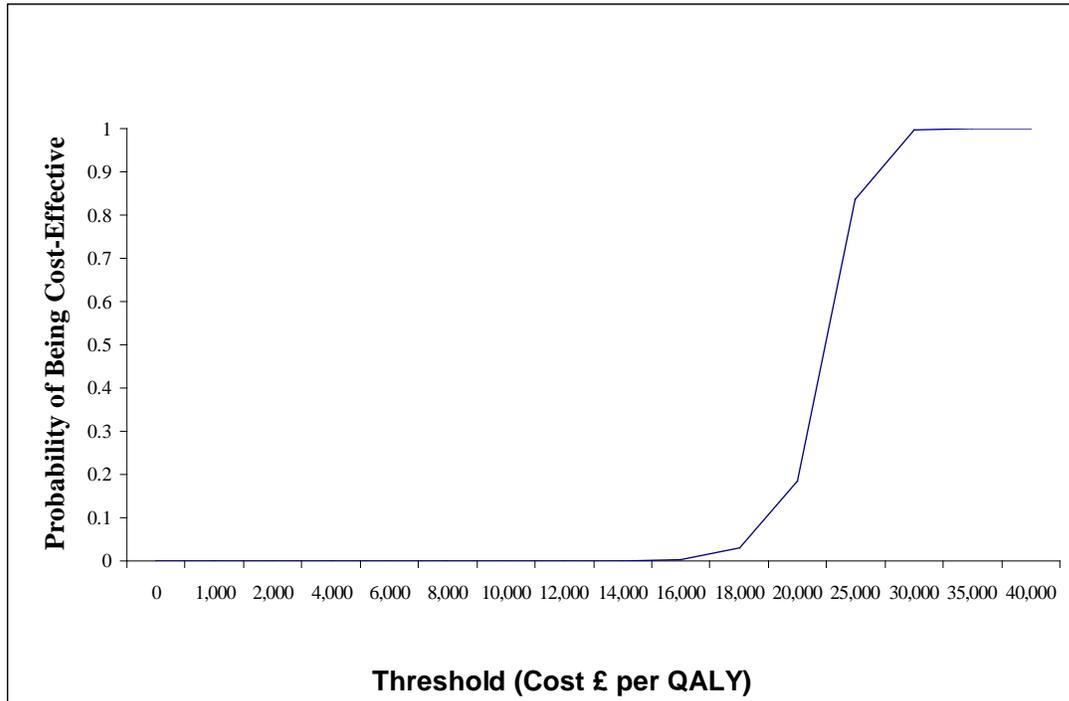


Figure 2: Cost-effectiveness acceptability curve of R-chlorambucil vs. chlorambucil (example: 1,000 Monte Carlo simulations)



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

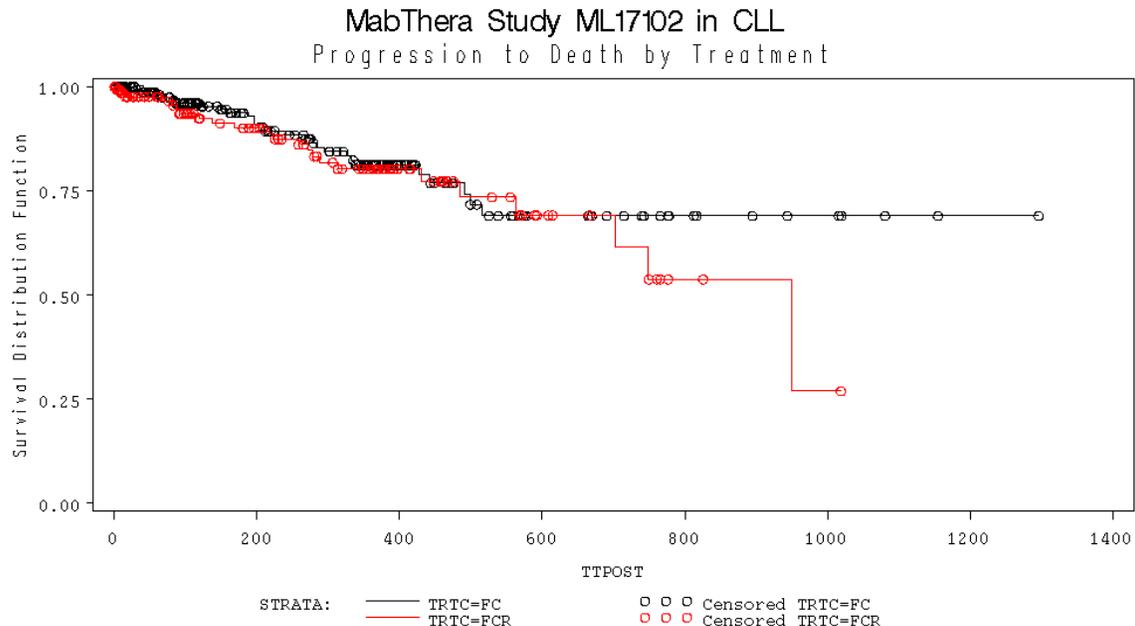
With regards to the interpretation of the clinical evidence, Roche feel that the analysis of the Phase III study (R-FC versus FC) has been fair and representative, and specifically agree on the fact that the committee have highlighted that both i.v. and oral methods of administration of FC would be appropriate in practice. Roche feel that clause 4.4 is not an accurate analysis of all available information and points around this have been discussed in question one above.

Roche broadly supports the interpretation of the cost-effectiveness evidence in the ACD. However, there is one factual error Roche would like to highlight, and the subsequent language used in the ACD following this error:

In the last sentence of Section 3.11, it is stated that in the progressed state, a single probability from the trial was applied as there was a non-significant difference in overall survival between the two groups in the trial. However, the use of a single population was based on the non-significant difference in survival following progression between the two groups in the trial. This was based on the sub-population of patients in CLL-8 who had experienced at least one day of progression as observed in the trial. It followed in Section 3.20 of the ACD that the ERG has indicated that Roche's assumption of a constant hazard of death after progression "may not be appropriate". However, given the

available data and the modeled uncertainty around this estimate, Roche believes that this is the most appropriate modeling method available given the empirical evidence. In section 7.2.6.8 of the original submission, Roche provided a Kaplan-Meier curve for patients who have progressed stratified by protocol treatment regimen (R-FC or FC) in Figure 16. This figure is reproduced below.

Figure 3. Post Progression Survival by Treatment (CLL-8, July 2008 cut)



By the clear overlapping nature of these curves, it was determined that a reasonable assumption would be to assume an equal risk of death for R-FC and FC patients following progression. Because **the log-rank was non-significant**, the progression to death population was modeled as a single population with the mean time to death converted to a constant hazard of dying.

Given this data, it would be inappropriate to assume, as the ERG has in Section 3.22 of the ACD, that a decrease in the probability of death to the FC arm by 57% compared to the probability of death in the R-FC arm would be appropriate or clinically plausible. Roche appreciates that these assumptions by the ERG were made for the purpose of stress testing the model, and not to determine a more appropriate base case, however we would still like to state our reasons to believe these methods are not suitable. A reduction in the monthly probability of dying while in progression of 57% in the FC arm suggested by the ERG equates to a 76% increase in the monthly relative risk of dying having been treated in PFS with R-FC versus FC alone. Such a large difference would probably be statistically significant and suggest that patients are being harmed by having been given the R-FC drug combination. This is illustrated by the below figures for cumulative deaths based on the original model assumptions (Figure 4) and based on the ERG's 57% reduction in FC mortality relative to R-FC assumption (Figure 5). Not only does this violate the assumption of proportional hazards but nothing in the clinical trial or in clinical practice substantiates this assumption.

Figure 4: Cumulative time to progression and death for R-FC and FC using CLL-8 trial data (reproduction of Figure 23 from original Roche submission)

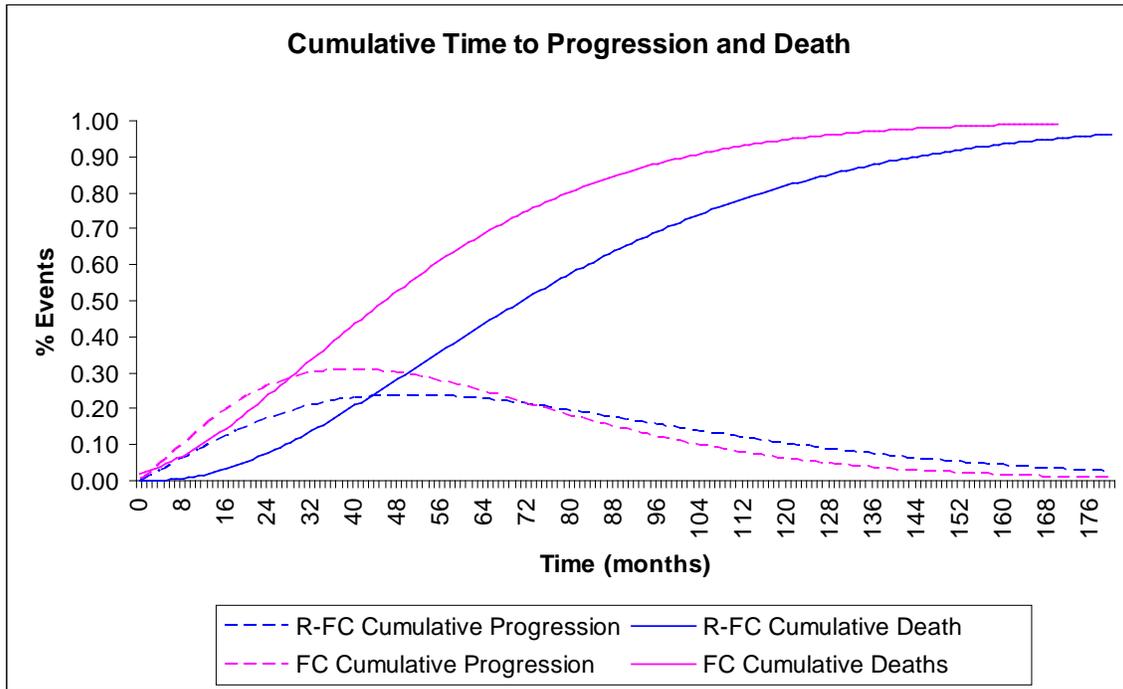
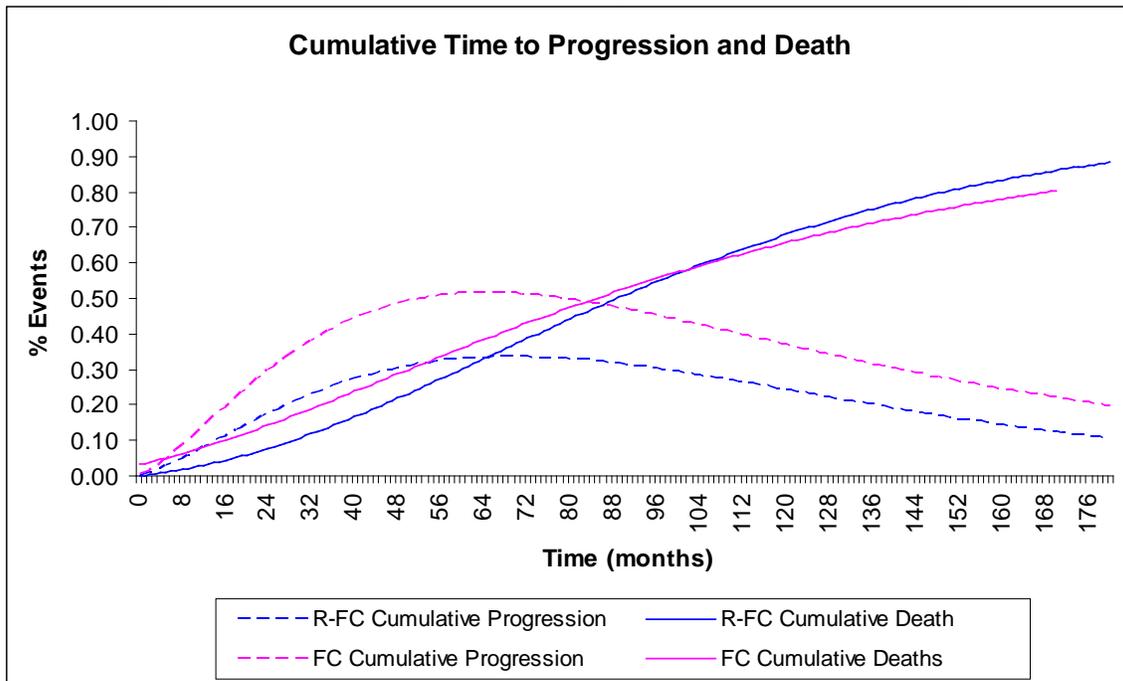


Figure 5: Cumulative time to progression and death for R-FC and FC based on ERG assumption of 57% decrease in mortality for FC relative to R-FC patients



iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

Roche welcomes and endorses clause 1.1, to recommend rituximab in combination with fludarabine and cyclophosphamide in those patients for whom fludarabine in combination with cyclophosphamide is considered appropriate.

Clause 1.2 states:

“The use of rituximab for the first-line treatment of chronic lymphocytic leukaemia in combination with chemotherapeutic agents other than fludarabine and cyclophosphamide is not recommended.”

Following on from the points raised in our answer to question one, Roche feel that this clause should be removed and broader guidance in line with the marketing authorisation should be recommended.

If the appraisal committee feel that they are unable to endorse a broader recommendation, we feel that this clause should still be removed or reworded. The current phrasing of the clause does not explicitly make clear the nature of the licence and again implies (like clause 4.4) that there is uncertainty about the effectiveness of rituximab combined with chemotherapies other than FC, which we feel is inaccurate.

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

The narrowing of the preliminary recommendation compared to the actual marketing authorisation and licence will mean that many frailer, older patients with CLL who are not suitable for a fludarabine based regime will be unable to be treated with the combination of rituximab and chlorambucil.

It is well established and clinically clear that not all patients requiring treatment for the first time will be suitable for rituximab based treatment, but there is a significant proportion of patients who will be unable to tolerate R-FC (because of co-morbidities), but will be able to tolerate a more efficacious regime than chlorambucil alone, which will allow the opportunity for a deeper remission and better progression-free survival than would be offered by chlorambucil alone. In addition, the above analysis presented in section i) above suggests that when the model is adjusted for the baseline risk of the older, frailer patients more likely to receive chlorambucil, the addition of rituximab is likely to remain cost-effective.

It should be reiterated that we do not feel that all patients should get a rituximab-based regime, but endorsing the use of rituximab in combination with chlorambucil specifically, in addition to the existing endorsement for R-FC, will allow clinicians the flexibility of an additional approach for a number of ‘in-between’ patients (who are often older), who are too fit for the most gentle chlorambucil monotherapy, but not fit enough for fludarabine based treatment.

Summary

We believe that the arguments articulated above highlight that rituximab plus any suitable chemotherapy would be clinically effective and cost-effective, and specifically the combination of rituximab and chlorambucil would be a clinically realistic option for a number of older, frailer patients who need treatment for the first time.

REFERENCES

- ¹ CHMP variation assessment report: EMEA/135353/2009.
- ² Hiddemann W, Kneba M, Dreyling M *et al.* Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood.* 2005;106: 3752-3732
- ³ Herold M, Haas A, Srock S *et al.* Rituximab Added to First-Line Mitoxantrone, Chlorambucil, and Prednisolone Chemotherapy Followed by Interferon Maintenance Prolongs Survival in Patients with Advanced Follicular Lymphoma: An East German Study Group Hematology and Oncology Study. *J Clin Oncol.* 2007; 15: 1986-1992
- ⁴ Salles G, Mounier N, de Guibert S *et al.* Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood.* 2008 Dec 15;112(13):4824-31.
- ⁵ Marcus R, Imrie K, Belch A *et al.* CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood.* 2005 Feb 15;105(4):1417-23.
- ⁶ Martinelli G, Laszlo D, Bertolini F, *et al.* Chlorambucil in combination with induction and maintenance rituximab is feasible and active in indolent non-Hodgkin's lymphoma. *Br J Haematol.* 2003 Oct;123(2):271-7.
- ⁷ Catovsky D, Richards S, Matutes E, Oscier D, Dyer MJ, Bezares RF *et al.* Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. *Lancet* 2007; 370(9583):230-239.