NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Rituximab for the first line treatment of chronic lymphocytic leukaemia

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

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
Leukaemia CARE	Leukaemia CARE is very pleased to see that rituximab is being recommended for first line use in the treatment of Chronic Lymphocytic Leukaemia in combination with fludarabine and cyclophosphamide as an option for people for whom fludarabine in combination with cyclophosphamide is considered appropriate. Furthermore we feel that under the general headings of; - 1) Do we consider that all of the relevant evidence has been taken into account? 2) Do we 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? 3) Do we consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? 4) Are there any equality related issues that need special consideration that are not covered in the ACD? We feel that these questions have all been answered satisfactorily.	Comments noted, no changes to the FAD required.
	As a general comment in addition to these, we would like to add that we are aware that physicians treating patients with CLL would also like the option of using rituximab in combination with chlorambucil on certain specific occasions, and that this option is specifically excluded here. There is an on-going trial looking at this particular combination that is due to finish in September 2009. Once sufficient robust data has been accumulated from this study (should be available within a year of the study concluding), we (Leukaemia CARE) would like to encourage NICE to review this HTA with a view to including R-chlorambucil as another treatment option.	The Committee discussed the ongoing trial of rituximab in combination with chlorambucil and the expected availability of new data. It concluded that the appraisal should have an early review date to allow consideration of this data. See FAD sections 3.26, 4.15, 7.1.

Consultee	Comment	Response
Royal College of Pathologists	Although it is uncontroversial that we should currently not be using rituximab in combination with chlorambucil outside of trials, this situation is likely to change within a relatively short time frame. However, the wording of the ACD is quite strong and will prevent rituximab being used with other chemo even when supporting data become available, and this would not be in the interests of CLL patients. With the ACD phrased as it is, I think NICE have a responsibility to revisit the topic as soon as the R-chlorambucil data are available.	The Committee discussed the clinical and cost effectiveness evidence currently available for the combination of rituximab and chlorambucil, including ongoing trials. The Committee concluded that an early review date for the appraisal was appropriate to allow consideration of the data from ongoing trials. See FAD sections 3.26, 4.4, 4.12 - 4.15, 7.1.
Royal College of Nursing	No comments	Comments noted, no changes to the FAD required.
Department of Health	In our view, this is a reasonable decision to allow the use of rituximab with fludarabine and cyclophosphamide (F&C) as first line therapy in CLL.	Comments noted, no changes to the FAD required.
	F&C is certainly acknowledged as the best currently available first-line combination treatment in CLL for the younger group. Current evidence suggests that the addition of rituximab increases the rapidity and depth of the response.	Comments noted, no changes to the FAD required.
	We believe however that there are some provisos. The panel appear to have extrapolated from progression-free survival into overall survival. Whilst this may be the case, it has yet to be proven. In chemotherapy trials, comparing F&C with oral chlorambucil shows increased CR rate and PFS, but this did not translate into improved OS. However, a short course of treatment with improved response improves quality of life so that is perhaps, in the younger group a rationale for treatment. We believe that it is also the case that a better CR can then be followed with some form of stem cell transplant, and the results again are likely to be better because of the reduction in residual disease at the time of the transplant.	The Committee considered whether gain in progression free survival could lead to a gain in overall survival. The uncertainty in gain in overall survival was also explored through a sensitivity analysis in the economic modelling. The Committee was persuaded that although the gain in overall survival was associated with uncertainty, rituximab could be considered an appropriate use of NHS resources. See FAD sections 4.3, 4.9, 4.11.

Consultee	Comment	Response
Department of Health (continued)	In the non-malignant setting (autoimmune disease), there appears to be some evidence of an increased rate of progressive multi-focal encephalopathy, with the combination of rituximab and cyclophosphamide. There has already been an FDA alert for rituximab alone and the association of PML, and there is increasing evidence that the additional immune suppression caused by cyclophosphamide exacerbates this. You may be aware that there is currently an exercise, trying to catch this data. We feel that it would be helpful if the company could carry out some post-marketing surveillance in this area, particularly if use will inevitably increase following confirmation of the appraisal.	Comments noted, no changes to the FAD required. The collection of post-marketing safety data should be considered a matter for the EMEA and other regulatory authorities.
	In our view, it is disappointing that the combination of rituximab with chlorambucil in the elderly has not been accepted We feel that this is the group which has the highest incidence of CLL, and that F&C is not an appropriate treatment. Chlorambucil will contain the disease, but is rarely associated with CR and the potential benefits that PFS may bring of the potential impact on OS that you seem to accept. We consider that rituximab is a relatively toxic-free drug to administer. In combination with chlorambucil, it would be potentially highly acceptable, and tolerated by the elderly. We feel that it is misfortunate that they will not be offered this possible effective treatment".	The Committee was aware that a proportion of people requiring treatment for CLL would not be suitable for FC chemotherapy and would normally be treated with chlorambucil. The Committee discussed the clinical and cost effectiveness evidence currently available for the combination of rituximab and chlorambucil, including ongoing trials. The Committee did not consider that the currently available evidence was sufficient to recommend the use of rituximab in combination with chlorambucil as an appropriate use of NHS resources. However, it concluded that an early review date for the appraisal was appropriate to take into account ongoing data collection. See FAD sections 3.26, 4.4, 4.12 - 4.15, 7.1.
CLL Supporting Association, part one	i) Do you consider that all of the relevant evidence has been taken into account? *We believe that the available relevant evidence for first line treatment with Rituximab has been considered.*	Comments noted, no changes to the FAD required.

Consultee	Comment	Response
CLL Supporting Association, part one (cont)	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? *In our position as lay people we feel unable to comment fully on the detailed statistical evidence on cost effectiveness. However, the clinical effectiveness of the technology has been shown in both North America and Western Europe. The resource impact and implications for the NHS appear to be accurate.*	Comments noted, no changes to the FAD required.
CLL Supporting Association, part one (cont)	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? *We consider that the provisional recommendations will form a basis for the preparation of guidance to the NHS, although we have not seen the implementation tools as stated in 5.3 (p24) of the ACD.*	Comments noted. Implementation tools will accompany the publication of the guidance.
CLL Supporting Association, part one (cont)	iv) Are there any equality related issues that need special consideration that are not covered in the ACD? *We have highlighted the needs of patients living in rural areas and associated transport difficulties. However these remain constant irrespective of the addition of this technology.*	Comments noted. The guidance applies to all people and does not distinguish between people based on residence. The marketing authorisation for rituximab indicates that it should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available. See FAD section 2.1.

Consultee	Comment	Response
CLL Supporting Association, part one (cont)	Item 7.2: Proposed date for review of guidance *We feel that the proposed review date in March 2012 will not give sufficient time to assess fully the impact of this technology on increasing time of remission, or on increasing overall survival.* *Table 70, page 158 (the manufacturer's submission) estimates that it will be 2011 before the full uptake of patients eligible for this technology will be achieved.* *We would suggest that 2014 (i.e. 5 year assessment of efficacy) might be more meaningful.*	Comments noted. Other consultees considered that the guidance should be considered for review when data for the use of rituximab in combination with chlorambucil becomes available. The Committee considered that an early review date was appropriate to allow consideration of the data for rituximab in combination with chlorambucil. See FAD sections 3.26, 4.15, 7.1.
CLL Supporting Association, part two	We wish to make the following comments: The CLLSA would like to see health related quality of life data for CLL patients be routinely collected in clinical trials and look forward to the Utility Measurement Study (section 8) results being published. In particular data being collected when people are enjoying a good remission. Warnings by the FDA in the USA about infusion related deaths deal with the situation of patients receiving Rituximab in settings that in general would not be found in the UK. However we would seek assurance that the guidance from NICE will emphasise the need for the delivery of the technology to be undertaken in Oncology Units with experience in giving this drug and full awareness of dealing with infusion reactions.	Comments noted, no changes to the FAD required. Comments noted. The marketing authorisation for rituximab indicates that it should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available. See FAD section 2.1.
Roche	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.	Comments noted. The Committee recognised that the marketing authorisation for rituximab for CLL included the addition of rituximab to any chemotherapy regimen. See FAD sections 2.1, 4.4, 4.14.

Consultee	Comment	Response
Roche (continued)	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.	The Committee was aware that a proportion of people requiring treatment for CLL would not be suitable for FC chemotherapy and would normally be treated with chlorambucil The Committee specifically considered the CLL-208 trial. See FAD sections 4.4, 4.7, 4.14-15.
	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 is stands if they felt there was any doubt surrounding the clinical effectiveness of combining rituximab with any chemotherapy regime.	The Committee considered the evidence of clinical effectiveness of adding rituximab to a range of chemotherapy regimens. The Committee considered that there was uncertainty in the relative additional benefit of adding rituximab to other chemotherapy regimens. This has been clarified in the FAD. See FAD sections 4.4, 4.12.

Consultee	Comment	Response
Roche (continued)	The CHMP assessment report (EMEA//135353/2009) specifically notes after consideration of the evidence that: *" Similar positive benefits were seen for rituximab added to a range of other cytotoxic chemotherapy regimes 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*.	The Committee considered that there was uncertainty in the relative additional benefit of adding rituximab to other chemotherapy regimens. It was not persuaded that the relative effects of the treatment or hazard ratio were transferable between various chemotherapies combined with rituximab. See FAD sections 4.4, 4.12, 4.13-14.
	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:	The Committee considered the additional phase III comparative evidence from other low-grade lymphroproliferative disorders. See FAD sections 3.24, 4.4.

Consultee	Comment	Response
Roche (continued)	1. GLSG'00: rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) compared to CHOP. 2. OSHO-39: rituximab plus MCP (mitoxantrone, chlorambucil and prednisolone) compared to MCP. 3. FL2000: rituximab plus CHVP+αIFN (cyclophosphamide, etoposide, doxorubicin, prednisolone and alpha-interferon) compared to CHVP+αIFN. 4. M39021: rituximab plus CVP (cyclophosphamide, vincristine and prednisolone) compared to CVP. 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). 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 Committee specifically considered these trials. The Committee noted that the trials listed here use chemotherapy of greater toxicity than chlorambucil and that, in common with many phase III trials, they are likely to have recruited people who were on average younger and had a better performance status. The Committee did not consider that the evidence of relative benefit from these trials could necessarily be generalised to the addition of rituximab to chlorambucil in people with CLL. See FAD sections 3.24, 4.4.

Consultee	Comment	Response
Roche (continued)	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).	The Committee, while recognising that the licensed indication for rituximab allowed its use with any chemotherapy regimen, was not persuaded that the relative effects of the treatment or hazard ratio were transferable between various chemotherapies combined with rituximab. See FAD sections 4.4, 4.12. The Committee has considered the scenario analysis and the additional economic analysis provided. See FAD sections 3.17, 4.12-14.
	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: ***Markov model was provided but not produced here (CiC)***	The Committee considered this economic analysis. The Committee, while recognising that the licensed indication for rituximab allowed its use with any chemotherapy regimen, was not persuaded that the relative effects of the treatment or hazard ratio were transferable between various chemotherapies combined with rituximab. See FAD sections 4.4, 4.12.
	o 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. o 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 which reflects the most up-to-date published analysis of the real-life effectiveness of this drug in this population.	The Committee considered this economic analysis. The Committee, while recognising that the licensed indication for rituximab allowed its use with any chemotherapy regimen, was not persuaded that the relative effects of the treatment or hazard ratio were transferable between various chemotherapies combined with rituximab. See FAD sections 4.4, 4.12.

Consultee	Comment	Response
Roche (continued)	o 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. o The drug and administrative costs associated with R-chlorambucil were included in this arm. o 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. o 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 (12^{th}) month of chlorambucil drug and administrative costs.	The Committee considered this economic analysis. The Committee, while recognising that the licensed indication for rituximab allowed its use with any chemotherapy regimen, was not persuaded that the relative effects of the treatment or hazard ratio were transferable between various chemotherapies combined with rituximab. See FAD sections 4.4, 4.12.

Consultee	Comment	Response
Roche (continued)	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 rituxmab 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 was provided but not produced here.*** 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 and 2 were provided but not reproduced here.***	The Committee considered this economic analysis. The Committee, while recognising that the licensed indication for rituximab allowed its use with any chemotherapy regimen, was not persuaded that the relative effects of the treatment or hazard ratio were transferable between various chemotherapies combined with rituximab. In addition, the Committee considered that other sources of uncertainty, such as the gain in overall survival and the assumed utility of health states, made the estimates of cost effectiveness uncertain. See FAD sections 4.4, 4.12-14. The Committee was aware of an ongoing trial that could provide additional data. It concluded that the appraisal should have an early review date to allow consideration of this data. See FAD section 4.15, 7.1.

Consultee	Comment	Response
Roche (continued)	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.	Comments noted, see response above.

Consultee	Comment	Response
Roche (continued)	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 modelled uncertainty around this estimate, Roche believes that this is the most appropriate modelling 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 was provided but not reproduced here.*** 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 and FC patients following progression.	The FAD has been amended in line with this comment. The ERG considered that the assumption in the model implied a correlation between progression free survival and overall survival that the ERG did not consider had been empirically proven. The ERG explored the effect of this assumption in a sensitivity analysis where the benefit in overall survival was removed and a probabilistic sensitivity analysis where the uncertainty in the benefit in overall survival was incorporated. The Committee considered the analysis completed by the ERG, but was persuaded that rituximab could be considered as a cost effective intervention for the first line treatment of CLL. See FAD sections 4.8 – 4.11.

Consultee	Comment	Response
Roche (continued)	Because the log-rank was non-significant, the progression to death population was modelled 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 and based on the ERG's 57% reduction in FC mortality relative to R-FC assumption. Not only does this violate the assumption of proportional hazards but nothing in the clinical trial or in clinical practice substantiates this assumption. ***Figures 4 and 5 were provided but not reproduced here***	The ERG explored the effect of this assumption in a sensitivity analysis where the benefit in overall survival was removed and a probabilistic sensitivity analysis where the uncertainty in the benefit in overall survival was incorporated. The Committee considered the analysis completed by the ERG, but was persuaded that rituximab could be considered as a cost effective intervention for the first line treatment of CLL. See FAD sections 4.8 – 4.11.

Consultee	Comment	Response
Roche (continued)	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	The Committee, while recognising that the licensed indication for rituximab allowed its use with any chemotherapy regimen, was not persuaded that the relative effects of the treatment or hazard ratio were transferable between various chemotherapies combined with rituximab. In addition, the Committee considered that other sources of uncertainty, such as the gain in overall survival and the assumed utility of health states, made the estimates of cost effectiveness uncertain. See FAD sections 4.4, 4.12-14. The Committee was aware of an ongoing trial that could provide additional data. It concluded that the appraisal should have an early review date to allow consideration of this data. See FAD section 4.15, 7.1.

Consultee	Comment	Response
Roche (continued)	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.	The Committee considered whether the equalities legislation and the requirement for fairness meant that it should make a positive recommendation for rituximab in combination with chlorambucil for this group. The Committee was not persuaded that it could justify a positive recommendation of rituximab in combination with chlorambucil within the scope of NICE's functions. See FAD section 4.14.
	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 were provided but not reproduced here.***	See responses above.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
None	None	

Comments received from commentators

Commentator	Comment	Response
None	None	

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional 1	1	Recommendation 1.1 is very welcome news and I very much hope that patients with CLL in the UK will now finally move away from alkylating agent as first line treatment. However, not every patient would be eligible for purine analogue therapy on the basis of impaired renal function or other index of poor physiological performance. In these cases the question of which is the optimum therapy arises. I am concerned that treatment of "fragile" patients with CLL will be actively compromised for a prolonged period as a result of recommendation 1.2 In the UK there are ongoing clinical trials combining anti-CD20 antibodies and chlorambucil, the results of which should become available over the next 12-18 months. Why not wait until more clinical trial data is available before ruling out the use of combined chemoimmunotherapy based on less toxic drugs e.g. chlorambucil? By toning down this paragraph by adding a "pending data" clause would sustain the sentiment without the longer term limitation on therapy for fragile patients with CLL. A more strongly worded para 1.1 where the combination is recommended when FC therapy is the "treatment of choice" may obviate para 1.2	Comment noted, no changes to the FAD required. The Committee discussed the clinical and cost effectiveness evidence currently available for the combination of rituximab and chlorambucil, including ongoing trials. See FAD sections 4.4, 4.12 - 4.15. The Committee discussed the ongoing trial of rituximab in combination with chlorambucil and the expected availability of new data. It concluded that the appraisal should have an early review date to allow consideration of this data. See FAD sections 3.26, 4.15, 7.1.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', '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
NHS professional 1 (continued)	4	While current UK practice would be to consider exclusively rituximab in combination with fludarabine and cyclophosphamide "when FC is the treatment of choice" there are current NCRN badged clinical trials where chlorambucil is combined with antibody and available to patients when FC is not deemed to be the treatment of choice.	See response above
	6	Consideration could be given to revising the recommendation regarding combined fludarabine and cyclophosphamide in patients who cannot tolerate rituximab	See response above
NHS professional 2	1	Disagree with recommendation, which is based on data from one unpublished RCT involving a younger/fitter population to that treated in UK practice. Evidence of improved survival with addition of rituximab is not compelling use of rituxumab increases toxicity	Comment noted. The Committee considered that the trial of rituximab had demonstrated benefits to progression free survival, although the extent to which gain in progression free survival translated into a gain in overall survival was uncertain. Clinical specialists considered that the people enrolled in the clinical trial were comparable to people who would normally be treated with fludarabine and cyclophosphamide in clinical practice. See FAD sections 4.3 4.8, 4.9, 4.11.
	3	Addition of rituximab to FC regimen, did not increase overall survival in longer-term but did increase toxicity	See response above.