NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Rituximab for the first-line treatment of chronic lymphocytic leukaemia

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to:

- **confirm how missing response data were handled in the clinical trial and whether patients were eligible to cross over**
- **provide further clinical trial data, including the number of treatment cycles received, mean dose of treatments administered, rate of cross-over between treatment groups and significance tests for the differences in the rates of grade 3 and 4 adverse events**
- **provide further details about the mixed treatment comparison including the search strategy used to identify trials, methods used to conduct the mixed treatment comparison, a mixed treatment comparison 'network' diagram, reported progression-free survival rates and a copy of the WinBUGS code**
- **provide justification for the assumption in the model of a similar adverse-effect profile for chlorambucil as for fludarabine and cyclophosphamide (FC)**
- **provide a one-way sensitivity analysis to show changes in the incremental cost-effectiveness ratio (ICER) based on the differential mortality rates assumed between progression-free survival and progressed health states**
- **comment on the clinical and cost effectiveness of the combination of rituximab and chlorambucil in comparison with chlorambucil**
- **provide further clinical effectiveness data and economic analysis for the subgroup of people with CLL and the *p53* deletion/mutation.**

Licensed indication

Rituximab (MabThera, Roche) is indicated for the first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Key issues for consideration

Clinical effectiveness

- Does the Committee consider that participants in the CLL-8 trial are representative of people with CLL in routine NHS clinical practice?
- In UK clinical practice:
  - Will the subgroup of people with CLL and the *p53* mutation be considered for rituximab treatment?
  - Will rituximab be combined with treatments other than FC?
  - Will rituximab be combined with chlorambucil for older/frail people for whom treatment with FC is considered inappropriate?
- Does the Committee consider that gains in progression-free survival and response rate observed with rituximab treatment will lead to gains in overall survival?
- What is the Committee's view of the importance of complete response rates as a surrogate for overall survival?
- What is the Committee's view of the indirect comparisons between rituximab with FC (R-FC) and other comparators not investigated in the head-to-head randomised controlled trial (RCT)?
- What is the Committee's view of the importance of adverse effects of the R-FC on patients' symptoms and quality of life?

Cost effectiveness

- Does the Committee consider that FC and chlorambucil are appropriate comparators for R-FC in the economic analyses?

- Has the manufacturer appropriately adjusted the economic analyses to reflect that FC is usually administered orally in routine NHS clinical practice rather than intravenously as in the clinical trial?
- Does the Committee consider that the utilities attached to the progression-free survival and progressed health states are appropriate?
- Is the approach of aggregating people from both trial arms in the progressed state and assuming they have a uniform probability of transition to death appropriate?
- What does the Committee consider to be an appropriate assumption about gain in overall survival for use in the economic analyses?
- Does the Committee consider that the manufacturer has demonstrated the clinical and cost effectiveness of rituximab in combination with any chemotherapy, as per the marketing authorisation?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	The manufacturer considered that approximately one third of people with CLL will never need treatment and will die with, rather than of, their disease. A further third will need treatment immediately and the remainder will need treatment eventually. The population in the submission was limited to people with untreated CLL who require treatment, as defined by standard criteria published by The National Cancer Institute.
Intervention	The submission reflected the licensed indication for rituximab: rituximab in combination with chemotherapy.
Comparators	The submission included fludarabine combination therapies and chlorambucil as comparators. The pivotal, phase III randomised study (CLL-8) provided a direct comparison of fludarabine and cyclophosphamide (FC) and FC combined with rituximab (R-FC). The comparison of rituximab with chlorambucil was informed by an indirect comparison.
Outcomes	The clinical effectiveness outcomes included in the submission were progression-free survival, overall survival, event-free survival, disease-free survival, response rates, duration of response, time to new CLL treatment, health-related quality of life and adverse effects of treatment.
Economic evaluation	A Markov model with three health states (progression-free survival, progressed or death) was developed over 15 years (life time horizon).
Subgroups	A subgroup of people with CLL and the *p53* deletion/mutation that accounts for around 5% of the population in the submission was included in the clinical-effectiveness evidence, as specified in the scope.

1.2 Evidence Review Group comments

1.2.1 Population

The study population was considered to be appropriate. However, the subgroup of people with CLL and the *p53* deletion was only considered in relation to progression-free survival and not assessed in the cost-utility model.

1.2.2 Intervention

The intervention in the submission reflected the anticipated marketing authorisation. The ERG noted that the evidence in the manufacturer's submission from the clinical trial related to intravenous administration of FC instead of oral administration which is normally used in UK clinical practice.

1.2.3 Comparators

The ERG considered that the main comparators used in the cost-utility analysis: FC and chlorambucil, were appropriate. It noted that the mixed treatment comparison provided estimates of clinical effectiveness comparing R-FC with additional comparators, including alemtuzumab, fludarabine monotherapy and bendamustine.

1.2.4 Outcomes

The ERG considered that the outcomes in the submission were appropriate.

1.2.5 Economic evaluation

The ERG agreed that the 15-year time horizon would reflect a life time analysis due to minimal survival beyond this time period.

1.3 Statements from professional/patient groups and nominated experts

Patient and professional groups confirmed that FC is the standard treatment used in UK clinical practice, and that chlorambucil is used for older or frail people or those with renal insufficiency.

Experts noted that complete remission prolongs survival and expected that if rituximab increased the rate of complete remission, this would lead to increased overall survival. However, it was considered that it would be difficult to demonstrate the increased overall survival as trials were of short duration and subsequent therapies, including rituximab, were used at disease progression. Consultees commented that treatment of CLL is usually started

when symptoms appear, and that increased response rates mean better relief of symptoms and improved quality of life for people with CLL. An increased duration of remission sustains this quality of life and is valued by people with CLL. Experts were uncertain of the role of rituximab in the management of people with CLL whose prognosis is poor, such as those with *p53* deletion, for whom other treatment protocols may provide better alternatives.

Experts did not consider that rituximab is a new agent and noted that there is wide experience with its use. Infusion reactions are not uncommon, but clinically significant adverse events are rare. Rituximab is usually administered in the day-case setting. The need for pharmacy time for preparation of the infusion and day-case time for administration are important considerations. Capacity of facilities is limited within the NHS and chemotherapy administration is increasing.

2 Clinical-effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The clinical-effectiveness evidence in the manufacturer's submission relates to a single phase III trial, CLL-8. Further evidence is provided from phase II, non-comparative trials including 6-year follow-up data from a cohort treated with R-FC (see page 92 of the manufacturer's submission). The CLL-8 trial was a multi-centre, open-label, parallel group study of R-FC versus FC in previously untreated people with CLL. Participants had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and Binet stage B or C (people with Binet stage A CLL were included in the trial until a protocol amendment, at which point recruitment of people with Binet stage A CLL was stopped). Details of the ECOG performance status criteria and the Binet staging are included in appendices 1 and 2 on pages 97 and 98 of the ERG report.

A total of 810 people (median age 61 years) were randomised to receive either FC or R-FC. Demographic characteristics and disease characteristics, such as the presence of stage B symptoms and prognostic markers such as cytogenetic abnormalities, were well balanced between the trial groups. Trial participants were randomised to six cycles of treatment, with an interim staging after three cycles. People with progressive or stable disease at interim staging received alternative treatments as determined by their clinicians. Non-responders in the control group did not cross over but were eligible to receive rituximab-containing regimens. People with a partial or complete response at the interim staging received all six cycles of treatment. Each cycle of 28 days consisted of FC chemotherapy (fludarabine [25 mg/m^2] and cyclophosphamide [250 mg/m^2] on days 1, 2 and 3) with or without rituximab (375 mg/m^2 on day 0 of cycle 1, 500 mg/m^2 on day 1 of cycles 2–6). All trial treatments were administered intravenously.

The primary endpoint was progression-free survival. Secondary outcomes included event-free survival, overall survival, disease-free survival, duration of response, time to new CLL treatment and overall response rate. Quality of life data were collected using the Spitzer Quality of Life Index and the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30 (EORTC-QLQC30), but the results of the analysis of these data are not available. In addition to the interim staging after the third cycle, further response assessments were completed at the end of the sixth/last cycle and a final staging at least 8 weeks later. At the pre-planned interim analysis of the trial there was a significant difference in progression-free survival between the treatment groups and the trial was halted. This became the main analysis with a median follow-up of 20.7 months (see table 1). The median progression-free survival in the R-FC group was 39.8 months compared with 32.2 months in the FC group ($p < 0.0001$) with an unstratified hazard ratio (HR) of 0.56 (95% CI 0.43 to 0.72, $p < 0.0001$). Median overall survival was not reached in either group with an unstratified HR of 0.64 (95% CI 0.41 to 1.0, $p = 0.0487$). Partial or complete response

was observed in 86.1% of the people in the R-FC group compared with 72.7% in the FC-group (table 2).

With a longer duration of follow-up (median 25.4 months), the difference in overall survival was not maintained (HR 0.72, 95% CI 0.48 to 1.09, p = 0.1252). However, the data remained highly censored (most people not having reached the outcome of interest, i.e. death), with survival rates of 88% for people in the FC arm and 91% for people in the R-FC arm. A further analysis after a median follow-up of 25.5 months reported an overall response rate of 95% in the R-FC group and 88% in the FC-group (p < 0.0001). The improvement in the response rate between the interim and later analyses is attributed to 'late complete response', where complete response only becomes apparent a few months after the last cycle of treatment and after the final staging defined in the study protocol.

Table 1 Progression-free survival results (median follow-up 20.7 months)

	FC	**R-FC**
N	407	403
Median PFS – days (95% CI)	981.0 (935 to 1069)	1212.0 (1098 to 1400)
p-value (log-rank test)	p < 0.0001	
Unstratified HR (adjusted) (95% CI)	0.56 (0.43 to 0.72)	
p-value (Wald Test)	p < 0.0001	
Stratified HR (unadjusted) (95% CI)	0.53 (0.41 to 0.68)	
p-value (Wald Test)	p < 0.0001	
CI, confidence interval; FC, fludarabine and cyclophosphamide; HR, hazard ratio; PFS, progression-free survival; R-FC, rituximab with fludarabine and cyclophosphamide		

Table 2 CLL-8 response rates (median follow-up 20.7 months)

	FC	R-FC	Difference in response rates (%) [95% CI]	p-value
N	407	403	–	–
Overall response rate N (%)	296 (72.7%)	347 (86.1%)	13.38 [7.8 to 19.0]	< 0.0001
Complete response rate N (%) [95% CI]	70 (17.2%) [13.7 to 21.2]	145 (36.0%) [31.3 to 40.9]	18.78 [12.7 to 24.9]	< 0.0001
Partial response rate N (%) [95% CI]	226 (55.5%) [50.6 to 60.4]	202 (50.1%) [45.1 to 55.1]	−5.40 [−12.4 to 1.6]	0.1234
Stable disease N (%) [95% CI]	31 (7.6%) [5.2 to 10.6]	19 (4.7%) [2.9 to 7.3]	NR	NR
Progressive disease N (%) [95% CI]	31 (7.6%) [5.2 to 10.6]	14 (3.5%) [1.9 to 5.8]	NR	NR
Missing N (%)	49 (12.0%)	23 (5.7%)	–	–
CI, confidence interval; FC, fludarabine and cyclophosphamide; NR, not reported; R-FC, rituximab with fludarabine and cyclophosphamide				

The evaluation of treatment benefit in the subgroups was limited by the small number of participants (see manufacturer's submission page 68). The improvement in progression-free survival and overall survival with rituximab was sustained across subgroups, except in people older than 70 years and those people diagnosed less than 6 months before entering the study. In subgroups based on Binet stage, the best outcomes for progression-free survival and overall survival were seen in stage A disease, and no statistically significant benefit was seen in stage C disease (HR 0.88, 95% CI 0.58 to 1.33, p = 0.54). One possible explanation of this result is that for this subgroup of people there was an imbalance in prognostic biomarkers between the trial groups. For the 46 participants with the *p53* mutation, the unadjusted HR for progression-free survival was 0.6 (95% CI 0.31 to 1.19).

In the CLL-8 trial, 77% of people in the R-FC arm experienced a grade 3 or 4 adverse event compared with 62% in the FC arm. The main adverse events were related to haematological toxicity, with neutropenia, leucopenia, febrile

neutropenia and pancytopenia having a 2% higher incidence in the R-FC group, and thrombocytopenia, anaemia and pyrexia having a 2% higher incidence in the FC group. There were no differences in the rate of other adverse events in both arms.

A mixed treatment comparison was conducted because there was no head-to-head evidence comparing rituximab with comparators other than FC. This analysis included chlorambucil, alemtuzumab, fludarabine and bendamustine. In addition to the CLL-8 trial, a further seven trials were identified and used to create a network (see figure 4 on page 56 of the ERG report). The studies were combined using a fixed effect model because there was no apparent gain in goodness of fit when a random effects model was used. This suggested a lack of heterogeneity between the studies (the credibility interval of the residual deviances for both models overlapped each other for all outcomes). For progression-free survival a Cox regression model was assumed and log hazards for progression-free survival summarised across trials. For response rates, odds ratios and relative risks were combined.

The mixed treatment comparison showed that chlorambucil had the shortest progression-free survival and it was used as the reference treatment. The HRs for other treatments were compared with chlorambucil. The mean HR was 0.24 for R-FC, 0.43 for FC, 0.59 for alemtuzumab and 0.86 for fludarabine. The HR for progression-free survival of R-FC compared with the other treatments is given in table 3. It was not possible to calculate an HR comparing R-FC with bendamustine.

Table 3 Relative efficacy (HR) of R-FC for progression-free survival against comparators

R-FC versus treatment with:	Mean HR	Median HR	Lower bound	Upper bound
Chlorambucil	0.24	0.24	0.17	0.34
Fludarabine	0.28	0.28	0.20	0.38
Alemtuzumab	0.42	0.41	0.26	0.66
FC	0.56	0.56	0.43	0.72
FC, fludarabine and cyclophosphamide; HR, hazard ratio; R-FC, rituximab with fludarabine and cyclophosphamide				

Chlorambucil was also associated with the lowest complete response rate and formed the reference treatment for this outcome. The mean odds ratios for complete response in comparison with chlorambucil were 31.6 for R-FC, 6.2 for bendamustine, 23.2 for alemtuzumab, 11.5 for FC and 3.1 for fludarabine. Complete response data for R-FC compared with the other treatments are shown in table 4.

Table 4 Relative effect on percentage of patients with complete response

R-FC versus other comparators	OR				RR			
	Mean	Median	Lower bound	Upper bound	Mean	Median	Lower bound	Upper bound
Chlorambucil	31.6	30.3	17.5	53.4	16.1	15.7	10.8	23.3
Bendamustine	1.9	1.5	0.3	5.4	1.4	1.3	0.6	2.8
Fludarabine	10.4	10.1	6.3	16.4	5.7	5.6	4.0	7.8
Alemtuzumab	2.1	1.8	0.4	6.0	1.5	1.4	0.6	3.1
FC	2.8	2.7	2.0	3.8	1.9	1.9	1.5	2.3
FC, fludarabine and cyclophosphamide; OR, odds ratio; R-FC, rituximab with fludarabine and cyclophosphamide; RR, response rate								

2.2 Evidence Review Group comments

The ERG confirmed that all relevant trials had been identified in the manufacturer's submission. It considered that the CLL-8 trial was well designed and conducted, but noted that the lack of blinding to treatment group introduced the potential for bias. The ERG considered that the trial analysis was adequate, but noted that the trial was not powered to detect statistical differences in subgroups, such as people with the *p53* deletion as specified in the scope. The ERG also noted that the short duration of the trial, in

comparison with expected survival in CLL, and the use of second-line therapies at progression, including rituximab, made it difficult to detect differences in overall survival. It considered that no RCTs have shown an overall survival benefit with chemotherapy in CLL. The ERG noted that the trial population was younger and had better performance status than the people with CLL who would be seen in routine UK clinical practice. Similarly it was noted that people with Binet stage A CLL were included in the trial until the protocol amendment but would not be considered for treatment in the UK. The ERG noted the lack of utility data from the CLL-8 trial.

The ERG accepted the results of the CLL-8 trial and noted the consistency of the benefit in progression-free survival at increasing duration of follow-up. It also noted that the stratified (by country and Binet stage) and unstratified estimates of the HR for progression-free survival were similar. The ERG accepted that the trial was not powered to show differences between subgroups. However, it noted that risk reduction was most pronounced for Binet stage A and was statistically non-significant for stage C. For the *p53* deletion subgroup specified in the scope, the HR for progression-free survival was not statistically significant. For overall survival the ERG noted the initial benefit at interim analysis was not maintained with longer follow-up. The ERG also agreed with the manufacturer that the improvement in complete response rates with longer follow-up were likely due to the phenomenon of late response.

The ERG considered that all appropriate studies had been included in the mixed treatment comparison and that the analysis was appropriately conducted.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The economic analysis in the manufacturer's submission is based on a three-state Markov model that compared R-FC with FC and chlorambucil. The

model has the following health states: progression-free survival, progressed and death. Patients enter the model in progression-free survival at the start of treatment. The progressed state includes all remissions and relapses relating to second and subsequent treatments until death. The cycle length is 1 month and the time horizon 15 years, representing a life time horizon for this group of people. The model was based on the whole CLL-8 trial cohort with no further analysis of subgroups. Clinical-effectiveness data for the economic model were taken at a later cut-off date than that in the interim analysis (after a median follow-up of 26.4 months). At this point the R-FC group had a median progression-free survival of 42.8 months compared with 32.2 months in the FC group ($p < 0.001$) with an Unadjusted/Unstratified HR: 0.595 (CI 0.473-0.748) P<0.001. Extrapolation of the trial data for progression-free survival was done using a Weibull model. Transition probabilities from progression-free survival to death were taken from the trial or the age-specific background mortality, whichever was greater. For the transition from the progressed state to death, the arms of the trial were combined into a single population with a constant hazard of dying, taken from the CLL-8 trial. This assumption was justified by the manufacturer based on the non-significant survival difference between the treatment groups in the trial. To extrapolate overall survival beyond the trial period, an exponential model was used.

In the model, the drug costs for rituximab are £1397 for the first cycle of treatment and £1746 for subsequent cycles (see table 24 page 72 of the ERG report). For six cycles of treatment the total drug cost of rituximab is £10,128. These drug costs were calculated assuming a body surface area of 1.93 m^2 which reflects the average body surface area in the CLL-8 trial. The CLL-8 trial used FC administered intravenously, but it is more common to use oral chemotherapy in the UK. In the model it is assumed that the efficacy of FC is the same regardless of the route of administration, providing the dosage is adjusted to ensure equivalent bioavailability. The costs of the drug in the model are adjusted accordingly to make allowance for the difference in the route of administration. The total drug costs of fludarabine, cyclophosphamide

and chlorambucil are calculated as £2790, £22 and £286 respectively (see table 25 page 72 of the ERG report). The model included costs for supportive care that varied between the health states. This included costs for blood transfusions and bone marrow transplant in the progression-free survival state taken from the CLL-8 trial and costs for second-line therapies for the progressed disease state. In the model rituximab has a cost for intravenous administration of £430 per cycle of treatment. The cost for an appointment to prescribe oral FC chemotherapy is assumed to be £280. The administration of rituximab therefore incurs an incremental cost of £150 in the model (see table 26, page 73 of the ERG report). In the base case, all patients who respond after the third cycle are assumed to receive a complete course of six cycles of therapy. Costs are also added for the pharmacist's time for preparation of the infusion.

The utilities attached to the health states were taken from a Health Technology Assessment report completed in 2002 that assessed the cost effectiveness of fludarabine as a first-line treatment for CLL. A utility of 0.8 was attached to the progression-free survival state and 0.6 to the progressed disease state. The estimates of utility were not empirically based, and were estimated by the authors of the Health Technology Assessment report. The manufacturer's submission provides details of an ongoing utility study, but this has not yet been reported (see page 125 of the manufacturer's submission). No disutility for adverse events was included in the model.

The model assumes that there are no differences in treatment-related adverse events between the R-FC and FC arms. This approach was adopted because the differential rates of neutropenia in the trial arms were not found to be associated with differential clinical consequences (e.g. febrile neutropenia) that would incur costs and disutilities. Because of the lack of clinical data for chlorambucil alone, the model assumed chlorambucil would have the same adverse-event profile as FC. The base-case results reported in the manufacturer's submission (pages 143 and 145) are reported in table 5.

Table 5 Base-case analysis for R-FC versus FC and R-FC versus chlorambucil

Cost-utility results: R-FC versus FC	**R-FC**	**FC**	**Incremental**
Mean life years	5.73	4.65	1.07
Mean QALYs	4.26	3.38	0.88
Mean total cost	£25,595	£13,978	£11,617
Cost per life year gained (£)	–	–	£10,825
Cost per QALY gained (£)	–	–	£13,189
Cost-utility results: R-FC versus chlorambucil	**R-FC**	**Chlorambucil**	**Incremental**
Mean life years	5.73	3.40	2.33
Mean QALYs	4.26	2.35	1.91
Mean total cost	£25,595	£13,345	£12,250
Cost per life year gained (£)	–	–	£5,253
Cost per QALY gained (£)	–	–	£6,422
FC, fludarabine and cyclophosphamide; QALY, quality-adjusted life year; R-FC, rituximab with fludarabine and cyclophosphamide			

Sensitivity analysis was undertaken using different parametric models for the progression-free survival extrapolation. Costs for adverse events were added, including costs for febrile neutropenia episodes as per the trial, increasing and decreasing supportive care costs for the health states by 50% and assuming utility values for the health states such that the difference in the values between the health states was 0.4 and 0.1. The assumption of similar adverse events for chlorambucil as for FC was tested by assuming no bone marrow transplants, fewer transfusions and less febrile neutropenia for the chlorambucil arm. The base-case estimates were not sensitive to utility values, monthly supportive care costs or drug administration costs (see table 29 on page 77 of the ERG report). The results were sensitive to the function used to extrapolate progression-free survival (exponential, Gompertz), but the highest ICER reported (using a Gompertz function) was approximately £22,000 per QALY gained.

Scenario analysis was completed to explore the effect of using intravenous administration of FC chemotherapy in the model using the actual doses in the trial, with reductions from the full protocol dose, as well as with the

recommended protocol dose. This analysis demonstrated that the ICER was not sensitive to assumptions about administration. A further scenario analysis modelled the cost effectiveness of rituximab in combination with chemotherapies other than FC. The results of this analysis suggested that the QALY gain from combining rituximab with chemotherapy would need to decrease to about 40% of that in the base case, all else remaining the same, for the cost effectiveness of using rituximab to increase to over £30,000 per QALY gained.

Probabilistic sensitivity analysis results suggested that when comparing R-FC with FC there was a greater than 90% probability that the ICER would not be more than £20,000. When comparing R-FC with chlorambucil, this probability was 100%.

3.2 Evidence Review Group comments

The ERG commented that a limitation in the structure of the economic model was that it did not allow transitions from the progressed health state to the progression-free survival health state. The ERG considered this a limitation for modelling first-line treatment where the effects of subsequent treatments on remission were not allowed for in the model structure. In addition, the model structure aggregated all people in the progressed state, regardless of treatment group, and applied a constant hazard of death after progression. This implied a correlation between progression-free survival and overall survival that had not been empirically demonstrated, because in the CLL-8 trial the initial benefit in overall survival was not sustained at longer follow-up. The model structure also resulted in the costs for second-line treatments being applied equally to all people in the progressed state.

The ERG reviewed the choice of parametric model to extrapolate progression-free survival and agreed with the manufacturer that the Weibull model was the most appropriate. The ERG also accepted the manufacturer's approach to transition probabilities from progression-free survival to death in the model.

The ERG commented that the utility data in the model came from a source that did not use a preference-based estimation and represented non-clinical author estimates based on condition-specific data. In addition, costs for adverse events were applied equally across both arms despite the occurrence of (statistically insignificant) differences in incidence of adverse events in the trial arms.

To address areas of uncertainty around utility estimates and survival benefits, the ERG undertook some exploratory analyses. It conducted a component analysis to examine the relative contributions to utility gain from the gain in progression-free survival and the gain in overall survival. This was done by giving the same utility value to the progressed and progression-free survival health states. It showed that progression-free survival contributed to 0.24 QALYs and overall survival to 0.64 QALYs (of a total gain of 0.88 QALYs). The majority of the benefit is therefore derived from overall survival. Within the model, as a single transition probability is attached to all people aggregated in the progressed health state, the benefit in overall survival is derived almost entirely from the differential rate of transfer from the progression-free survival to progressed health state in the R-FC and FC groups.

The manufacturer was requested to provide further analysis that removed the survival advantage between the R-FC and FC groups. The manufacturer increased the probability of death in the progressed health state for the R-FC group by 315%. This resulted in a QALY gain for R-FC of 0.24 at an incremental cost of £7226, resulting in an ICER of £30,336 per QALY gained.

The ERG repeated this analysis by decreasing the probability of death in the progressed state for the FC group. A decrease in the probability of death in the FC group to 57% of the base-case level removed the difference in survival between the groups and resulted in a QALY gain of 0.24 at an incremental cost of £7228 and an ICER of £30,304 per QALY gained. The ERG identified that if it is assumed that there is no difference in overall survival between the R-FC and FC groups, the model outputs become sensitive to the assumed

utility differences between the progression-free survival and the progressed health states. If the difference in utility between the health states is reduced by 0.1 (that is from 0.2 to 0.1), the ICER increases to about £60,000 per QALY gained.

The ERG completed a probabilistic sensitivity analysis assuming no difference in overall survival between the two treatment groups. The results of this analysis suggested that the probability of R-FC being cost effective compared with FC at a threshold of £20,000 per QALY was 29% and at a threshold of £30,000 per QALY gained was 49%. However, the ERG considered that the likely survival benefit was somewhere between the manufacturer's base case and the assumption of no survival benefit. It therefore incorporated this into the probabilistic sensitivity analysis by adding an additional variable, in which the decrease in probability of death in the FC group was sampled as a uniform distribution between 1 and 0.574 (corresponding to base-case gain in overall survival and the decrease in this parameter required to remove overall survival gain in the R-FC arm). The results suggested that R-FC had a 72% probability of being cost effective compared with FC at a threshold of £20,000 per QALY gained and 88% probability of being cost effective at a threshold of £30,000 per QALY gained.

4 Authors

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by the Peninsula Technology Assessment Group (PenTAG):

- Main C., Pitt M., Moxham T et al., The clinical and cost-effectiveness of rituximab for the 1st line treatment of chronic lymphocytic leukaemia: an evidence review of the submission from Roche, January 2009

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Roche

II Professional/specialist, patient/carer and other groups:

- Chronic Lymphocytic Leukaemia Support Organisation
- UK CLL Forum
- British Committee for Standards in Haematology
- Royal College of Pathologists
- Royal College of Nursing
- Royal College of Physicians (on behalf of NCRI/RCR/ACP/JCCO)
- Hampshire PCT