NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Rituximab for the treatment of relapsed chronic lymphocytic leukaemia

This briefing presents the key 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 this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to:

- provide further information on the methods for identifying and selecting relevant studies
- provide additional clinical trial data including the number of scheduled and completed tumour assessments in each trial arm, the allocation concealment method, the number of people censored for progression-free survival (PFS) and overall survival, reasons for loss to follow-up, results of subgroup analyses for *del(17p)*-positive people, quality of life FACT-G subscores, the total amount of rituximab exposure in each arm
- outline the methods used in the Q-TWIST analysis
- clarify the parameters used in the model
- describe the differences in drug doses and costs used among the REACH trial, the economic model and the planned licensed dose
- explain the reason for using a 25-year lifetime horizon instead of 15 years as used in the appraisal of rituximab for first-line chronic lymphocytic leukaemia (CLL)
- provide further information on the function and parameters of the survival curves and provide a survival curve for no treatment or standard UK treatment
- clarify the incidence and costing of adverse events
- provide a sensitivity analysis varying both the costs and health effects of adverse events
- provide a deterministic sensitivity analysis assuming no overall survival benefit.

Licensed indication

In February 2009 rituximab in combination with chemotherapy was granted a marketing authorisation for the first-line treatment of previously untreated chronic lymphocytic leukaemia (CLL). NICE guidance on rituximab for first-line treatment of CLL (TA174; July 2009) recommends rituximab in combination with fludarabine and cyclophosphamide (FC) as a treatment option in people for whom FC is considered appropriate. It also states that rituximab in combination with chemotherapy agents other than FC is not recommended.

Rituximab has recently received an extension to its marketing authorisation. In addition to its indication for untreated CLL, rituximab is now also licensed in combination with chemotherapy for the treatment of relapsed and refractory CLL. The revised marketing authorisation states that only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.

Key issues for consideration

Clinical effectiveness

- Does the Committee consider that the population of the REACH trial was representative of people with relapsed or refractory CLL who would be eligible for rituximab in routine clinical practice?
- In routine clinical practice:
  - Will the subgroup of people with *p53* mutation be considered for rituximab treatment?
  - Will rituximab be combined with treatments other than FC?
  - Will rituximab be combined with chlorambucil for people with lower performance status, in whom FC is considered inappropriate?
- Does the Committee consider that the gains in PFS and response rates observed with rituximab will lead to a modelled gain in overall survival?

- What is the Committee's view of the importance of adverse effects of rituximab plus fludarabine and cyclophosphamide (R-FC) on people's symptoms and quality of life?

Cost effectiveness

- Does the Committee consider that FC is the appropriate comparator for R-FC in the economic analyses?
- Does the Committee consider that the manufacturer has appropriately adjusted the FC dose in the model to reflect that FC is usually administered orally in clinical practice rather than intravenously as in the REACH trial?
- Does the Committee consider that the utilities attached to the PFS and progressed health states are appropriate?
- Is the approach of aggregating people from both trial arms in the progressed health state and assuming they have a uniform probability of transition to death appropriate?
- Does the Committee consider that an assumption of overall survival gain (as used in the economic analyses) is appropriate?
- In the economic model has the manufacturer appropriately handled the adverse event data from the REACH trial, including cases of hepatitis B?
- Does the Committee consider that the methods of costing rituximab in the economic model are appropriate?
- Does the Committee consider that the manufacturer has demonstrated the clinical and cost effectiveness of rituximab as per the marketing authorisation:

  - in combination with any chemotherapy
  - for relapsed and refractory CLL
  - for people previously treated with rituximab or other monoclonal antibodies?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	The manufacturer stated that the submission addressed the clinical and cost effectiveness of rituximab for the treatment of people with relapsed or refractory CLL.
Intervention	The submission considered rituximab in combination with chemotherapy. In the economic model, rituximab is combined with fludarabine and cyclophosphamide (R-FC) given in 6 cycles of rituximab at a dose of 375 mg/m^2 body surface area for the first cycle and 500 mg/m^2 for cycles 2–6.
Comparators	The manufacturer stated that the submission considered the following comparators: fludarabine combination therapy, chlorambucil, and cyclophosphamide plus doxorubicin plus vincristine plus prednisolone (CHOP). In the economic model, the comparator is fludarabine plus cyclophosphamide (FC): Fludarabine (oral): 6 cycles at a dose of 25 mg/$m^{2.}$. Cyclophosphamide (oral): 6 cycles at a dose of 150 mg/m^2. The manufacturer stated that FC is the most common fludarabine combination therapy used in clinical practice.
Outcomes	The primary endpoint in the clinical trial was progression-free survival (PFS). Secondary outcomes included overall survival, event-free survival, disease-free survival, duration of response, time to new treatment, response rates, and quality of life. Quality of life was assessed using the Functional Assessment of Cancer Therapy – General questionnaire (FACT-G). Adverse events were reported for rituximab and FC arms.
Economic evaluation	The manufacturer's model included three health states: PFS, progressed or death. The model was developed over a lifetime time horizon (25 years). This required extrapolation of the primary endpoint, PFS, beyond the end of REACH trial follow-up. Costs are estimated from the perspective of the NHS.

Note: see pages 17 and 18 of the ERG report for details of the original NICE scope

1.2 Evidence Review Group comments

1.2.1 Population

The ERG noted that eligible people with CLL in the scope and manufacturer's submission were those with relapsed or refractory CLL but that an eligible person was not defined in the submission. It commented that it would have expected to see criteria defining eligibility such as prior treatments, whether people were refractory to certain treatments and disease severity.

The ERG stated that in the main trial in the manufacturer's submission (REACH), people with refractory CLL were defined as those whose CLL was refractory to alkylators (for example cyclophosphamide plus doxorubicin plus vincristine plus prednisone [CHOP], cyclophosphamide plus vincristine plus prednisone [CVP], chlorambucil) and that people with CLL refractory to fludarabine were excluded. Therefore, the ERG considered that the REACH trial population was not representative of all people in the UK with relapsed and refractory CLL who would be eligible for rituximab (most of whom will have been previously treated with fludarabine). The ERG also noted that the scope specifies that people with *p53* mutation should be considered as a subgroup if evidence allows, however the REACH trial included only a small proportion (8%) of these people.

1.2.2 Intervention

The ERG commented that the draft summary of product characteristics (SPC) provided by the manufacturer does not specify whether rituximab can be given for second or subsequent relapse or the maximum number of times it can be given for relapse.

1.2.3 Comparators

The ERG considered that the comparison of FC with R-FC in the REACH trial was appropriate because these are both options for people who have relapsed. It commented that some people may be more likely to receive

rituximab plus CHOP (R-CHOP) or rituximab plus CVP than R-FC as second-line treatment. However, the ERG identified no randomised studies of these treatments.

1.2.4 Outcomes

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

1.2.5 Economic evaluation

The time horizon in the economic model was 25 years. Results were also provided with a time horizon of 15 years (in response to clarification questions), which the ERG considered to be more appropriate.

1.3 Statements from professional/patient groups and nominated experts

Patient and professional consultees confirmed that FC combination therapy is the standard treatment for people with CLL who have a good performance status. Chlorambucil monotherapy is generally used for people who do not have a good performance status. However, professional consultees stated that the addition of rituximab to FC has recently emerged as an internationally accepted first-line treatment for people with CLL and a good performance status. Therefore, people with relapsed or refractory disease suitable for rituximab treatment, are likely to have received rituximab previously as part of first-line therapy.

The consultees commented that the role of rituximab in people who have relapsed after first-line treatment with R-FC is yet to be resolved. Treatment for these people may include R-FC plus mitoxantrone or R-CHOP. Treatment for people not fit enough to receive repeat FC may include rituximab plus bendamustine. They also stated that it may be appropriate to use rituximab in people who have had a response to first-line treatment with R-FC but relapsed in a short period of time (that is, refractory disease). However, the consultees indicated that there was disagreement on the duration of this time period.

The consultees noted that rituximab plus FC and other chemotherapy combinations had been used in other countries for many years, and that rituximab is also used to treat other haematological conditions, as well as rheumatoid arthritis and lupus. Therefore the side effects of rituximab are well known. Aside from the usual side effects that are associated with chemotherapy (such as neutropenia and thrombocytopenia), patient consultees commented that the possibility of an initial infusion reaction was an additional disadvantage of rituximab treatment.

The consultees considered that adding rituximab to chemotherapy (for first-line and subsequent treatment of CLL) resulted in longer remission, which led to better overall health and quality of life. They commented that it would be difficult to show a benefit in overall survival with rituximab because the natural history of CLL is one of long survival and subsequent therapies, including rituximab, are used at disease progression. Therefore PFS is accepted internationally as a more meaningful outcome than overall survival.

The consultees considered the rituximab regimen to be more difficult to administer than the alternative FC regimen because rituximab requires intravenous (IV) infusion with day-case hospital admission. The cost and time required to travel to hospital or a chemotherapy centre for treatment are important considerations for people having this treatment. Experts also noted that the use of rituximab would have implications for the capacity of day units.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The evidence of clinical effectiveness in the manufacturer's submission was obtained from a single phase III randomised controlled trial (RCT), REACH. Further evidence was also provided from non-comparative studies.

REACH trial

The REACH trial was a randomised multicentre, open-label, parallel-group study of FC versus R-FC in people previously treated with chlorambucil monotherapy (with or without prednisolone), fludarabine monotherapy, or alkylator-containing therapy (such as CHOP or CVP). Other inclusion criteria included life expectancy greater than 6 months and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. People were excluded if they had previously been treated with FC concurrently or sequentially, interferon, rituximab or another monoclonal antibody or their CLL was fludarabine refractory.

People with fludarabine-refractory CLL were excluded from the REACH trial because it was considered that there would not be many people in this group, their CLL would have a poor prognosis and they would be unlikely to benefit from further fludarabine-based therapy. People who were previously treated with rituximab (or other monoclonal antibodies) were also excluded from the REACH trial because it was considered that there would not be many people in this group and because no monoclonal antibodies were approved for first-line treatment of CLL at that time.

The trial included a total of 552 people with a median age of 63 years. Most people (59%) had Binet stage 2 disease and 60% were ECOG performance status 0. Of the people in the trial 82% had had prior single-agent chemotherapy and 18% had had multi-agent chemotherapy, 56% were alkylator sensitive, 26% were alkylator refractory and 16% had been treated with fludarabine. Characteristics were generally evenly distributed between groups; 24 people (9%) in the FC arm and 18 people (7%) in the R-FC arm had a *del(17p)* mutation (see manufacturer's submission pages 58–59).

People in the trial were randomised to six cycles of FC treatment (fludarabine [25 mg/m^2] and cyclophosphamide [250 mg/m^2] on days 1, 2 and 3 of each cycle), or six cycles of R-FC (FC plus rituximab 375 mg/m^2 on day 0 of cycle

1, rituximab 500 mg/m^2 on day 1 of cycles 2–6). All treatments were administered by IV infusion and treatment cycles were 28 days.

The primary endpoint of the REACH trial was PFS, and secondary outcomes included overall survival, event-free survival, disease-free survival, duration of response, time to new treatment, response rates and quality of life. The trial was planned to last for 8 years; however, at the time of data cut-off for the submission, the median follow-up was 25.3 months.

At data cut-off, the median PFS in the R-FC group was 30.6 months compared with 20.6 months in the FC group (see table 1).

Table 1 Progression-free survival (median follow-up 25.3 months)

	FC (n = 276)	**R-FC (n = 276)**
Median PFS (months)	20.6	30.6
p-value (log-rank test)	0.0002	
HR, non-stratified, unadjusted (95% CI)	0.65 (0.51 to 0.82)	
p-value (Wald Test)	0.0002	
HR, stratified, unadjusted (95% CI)	0.66 (0.51 to 0.84)	
p-value (Wald Test)	0.0008	
FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide; PFS, progression-free survival; CI, confidence interval; HR, hazard ratio		

Median overall survival was 51.9 months in the FC group and was not reached in the R-FC group, with a non-stratified unadjusted hazard ratio of 0.83 (95% confidence interval 0.59 to 1.17, p = 0.2871). The proportion of people achieving a best overall response (partial or complete) was 69.9% of the R-FC group and 58.0% of the FC group (p = 0.0034, table 2). The median duration of response (in people with a best response or complete response) was 39.6 months in the R-FC group compared with 27.6 months in the FC group (p = 0.0252). See page 86 of the manufacturer's submission.

Table 2 Best overall response rates (median follow-up 25.3 months)

	FC (n = 276)	**R-FC (n = 276)**
Overall response rate	58.0%	69.9%
Complete response rate	13%	24.3%
Partial response rate	44.9%	45.7%
Stable disease	22.1%	17.0%
Progressive disease	5.4%	2.5%
Missing	14.5%	10.5%
FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide		

There were no significant differences between the study arms in quality of life (assessed by FACT-G) at any stage of assessment (after cycles 3 and 6 and at 12 months' follow-up).

Subgroup analyses were performed for 48 subgroups (including groups by ECOG score, Binet stage, cytogenetic abnormality and time since first diagnosis). For most subgroups there was a tendency towards a reduced risk of disease progression or death for the R-FC group compared with the FC group; however, hazard ratios were close to 1 and were not statistically significant (see manufacturer's submission pages 98–104).

Almost all people in the REACH trial experienced at least one adverse event. Rates of adverse events were similar in the two trial groups (table 3). However, slightly more people in the R-FC group (80%) experienced a grade 3 or 4 adverse event compared with the FC group (74%). There were also more people in the R-FC group (51%) who had their treatment modified or interrupted for safety reasons than in the FC group (39%). The most common grade 3 or 4 adverse events, with at least a 2% higher incidence in the R-FC arm compared with the FC arm, were neutropenia, febrile neutropenia, granulocytopenia and hepatitis B infections.

Table 3 Adverse events - number of patients (%)

Adverse event	FC (n = 272)	R-FC (n = 274)
Any adverse events	260 (96%)	270 (99%)
Grade 3/4 adverse events	200 (74%)	219 (80%)
Serious adverse events	130 (48%)	137 (50%)
Fatal adverse events	26 (10%)	36 (13%)
Adverse events leading to treatment discontinuation	69 (25%)	72 (26%)
Adverse events leading to dose modification/interruption	105 (39%)	141 (51%)
Total deaths	68 (25%)	62 (23%)
Treatment-related deaths	14 (5%)	19 (7%)
FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide		

Non-comparative studies

Twenty non-comparative studies were included in the submission to support the use of rituximab with chemotherapy regimens other than FC and also to support its use in two groups who had been excluded from the REACH trial, people with fludarabine-refractory CLL and people previously treated with rituximab.

The study designs, populations and results are summarised in appendix B of this document. Of the 20 studies, only those that relate to the use of rituximab in combination with chemotherapy regimens are included in the appendix (n = 13). Seven studies used rituximab outside the terms of the marketing authorisation (rituximab monotherapy or rituximab in combination with non-chemotherapy regimens). Five studies provided evidence on rituximab for fludarabine-refractory CLL and six studies provided evidence in people previously treated with rituximab (some studies provided evidence for both subgroups).

One study (Hillmen et al. 2007) included in the list of non-comparative studies was a randomised phase II study but it did not allow for statistical comparison to be made between treatment groups. In this study, 52 people with relapsed

or refractory CLL (of whom 6 had fludarabine-refractory CLL) were randomised to receive fludarabine, cyclophosphamide, and mitoxantrone with or without rituximab (see appendix B for results).

The largest non-randomised study provided in the submission was a single-arm, open-label phase II study of 284 people with relapsed or refractory CLL (MDACC study). Results for 177 people were published in Wierda et al. (2005) and additional unpublished data for the total 284 patients were provided in the manufacturer's submission. The median number of prior treatments was 2 (range: 1–10). Half (51%) of the group had previous treatment with both a purine analogue (such as fludarabine) and an alkylator. One hundred people (35%) had received rituximab previously and 54 people (19%) had fludarabine-refractory CLL.

The overall response rate was 56% for people with fludarabine-refractory CLL compared with 79% for people with fludarabine-sensitive CLL. Kaplan–Meier survival curves for time to progression and overall survival showed no significant differences between people with fludarabine-refractory and fludarabine-sensitive CLL, or between people who had received prior rituximab therapy and those who had not. People who had not received fludarabine previously had a longer time to progression than those who had not (see appendix 4 of the manufacturer's clarification response). Additional results are described in table 4.

Table 4 Results of the MDACC study (follow-up 42 months)

Outcome	**All people (n = 284)**	**Fludarabine-refractory CLL (n = 54)**	**Fludarabine-sensitive CLL (n = 230)**	**Rituximab pre-treated (n = 22)[a]**
Overall response rate	74%	56%	79%	64%
Complete response rate	30%	7%	36%	18%

[a] Taken from Weirda et al. (2005) Updated response data for people who had prior rituximab therapy were not provided in the manufacturer's submission.

2.2 Evidence Review Group comments

The ERG commented that the evidence for effectiveness in this appraisal was based largely on a single trial (REACH), which is unpublished and therefore not peer reviewed or had its findings scrutinised. The ERG commented that data from this trial were immature because the median follow-up period was 2.1 years and the trial was planned for 8 years.

The ERG noted that inconsistent search strategies had been used for different databases. It also commented that no formal inclusion and exclusion criteria for selecting relevant randomised and non-randomised studies were provided (for example, eligible patients, interventions). However, the ERG found no additional studies that should have been included.

The ERG considered that the REACH trial had adequate randomisation and allocation concealment. However, it noted that the trial was open-label and therefore assessments might be biased. The ERG also noted that there was less difference in PFS between the trial groups when assessed by the blinded, independent panel than the unblinded study investigators [redacted].

The ERG stated that, compared with the UK population who would be eligible for rituximab, people in the REACH trial were relatively young and 10% had mild stage disease (Binet stage A). This is a stage at which UK patients are not commonly treated. It also noted that people with fludarabine-refractory CLL were excluded from the REACH trial although they could now be eligible for rituximab according to the extension of the marketing authorisation. Although supplemental non-randomised evidence was provided showing a benefit of R-FC in people with fludarabine-refractory disease, this was based on a small number of people.

The ERG accepted that there was evidence from the REACH trial that treatment with R-FC resulted in longer PFS compared with FC. It commented that median overall survival times could not be compared since this point had not been reached in the R-FC arm. The ERG considered that there was no evidence to support the assumption of an overall survival benefit in the R-FC group compared with the FC group.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The Markov model in the manufacturer's submission compared R-FC with FC across three health states, PFS, progressed and death. All people were assumed to start in the PFS health state and at the end of each cycle; they either remained in PFS, or moved to the progressed health state or died. From the progressed health state, people could only remain in that state or die. Transition probabilities between all health states were taken from REACH trial results (median follow-up of 2.1 years) extrapolated to a 25-year time horizon to follow most of the cohort to death. Transition probabilities from PFS to death were taken from the trial or the age-specific background mortality (from the Office of National Statistics), whichever was greater. People in the progressed health state were assumed to have equal risk of death regardless of treatment group so the transition probability from the progressed health state to death was the same for both the R-FC and FC groups. This assumption was based on no significant treatment effect being observed in the REACH trial for post-progression survival.

The manufacturer provided a revised base case in its clarification response, using different drug cost estimates from those used in the original submission. This resulted in a small increase in the incremental cost-effectiveness ratio (ICER) (from £14,240 to £15,593 per QALY gained). Only these revised base-case estimates are reported here (see page 27 of the manufacturer's clarification response). The calculation of drug doses and costs was based on

the planned dose from the REACH trial protocol (which is in line with the marketing authorisation) and reduced by the proportion of people expected to progress or die each month. This was done to allow for approximation of the actual observed dose in the REACH trial. For all treatments, dose calculations were based on a body surface area of 1.86 m^2 (the average for people in the REACH trial), and assumed drug wastage. Using these assumptions, the total (undiscounted) drug cost of rituximab in the economic model was £9078. The total cost of fludarabine was £2569 for the R-FC arm and £2510 for the FC arm. The total cost of cyclophosphamide was £21 for the R-FC arm and £20 for the FC arm (see page 29 and appendix 2 of the manufacturer's clarification response).

In the REACH trial, FC was administered by IV infusion. However, because oral administration is common practice in the UK, FC was assumed to be administered orally in the revised model. An IV to oral dose multiplier was used to account for differences in bioavailability between the two administration routes. The efficacy of oral and IV FC was assumed to be the same. Drug administration costs were sourced from NHS Reference Costs 2007/08. These included £201 per cycle for prescription of oral FC and £307 per cycle for IV infusion of rituximab (at which time people would also be given oral FC). Therefore, the additional cost of adding rituximab to FC is £106 per cycle (see table 69, page 190 of the manufacturer's submission).

A utility score was applied to each health state in the model, 0.8 for PFS, 0.60 for the progressed health state and 0 for death. These were obtained from a 2002 health technology assessment of fludarabine for the first-line treatment of CLL. The estimates were not preference based, and were estimated by the authors of the report from condition-specific health-related quality of life data. The manufacturer described an ongoing utility study which is designed to obtain more robust values for the UK CLL population. The study results have not yet been published. However, an interim analysis was provided to NICE after the deadline for submission. The report included 34 people, of whom 32

were progression free and two had progressed disease. The results counter-intuitively suggested higher mean EQ-5D utility scores for people in the progressed than in the progression-free health state. The mean EQ-5D utility scores were 0.80 for the progression-free group and 0.85 for the progressed disease group.

In the model, it was assumed that only grade 3 and 4 adverse events incur costs. Furthermore, only some grade 3 or 4 adverse events were assigned a cost, specifically, those assumed to require intervention that was not already captured in the model. For example, anaemia would require a blood transfusion and this resource use was already included in the trial and in the model. The health effects of adverse events were not included in the model.

The results for the manufacturer's revised base-case estimates are reported in table 5.

Table 5 Revised 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	5.207	4.536	0.671
Mean QALYs	3.744	3.158	0.585
Mean total cost	£21,140	£12,012	£9128
Cost per life year gained (£)	–	–	£13,608
Cost per QALY gained (£)	–	–	£15,593
FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide; QALY, quality-adjusted life year			

A probabilistic sensitivity analysis suggested that the likelihood of the ICER for R-FC compared with FC being below £20,000 per QALY gained was 75%. The likelihood of the ICER being below £30,000 per QALY gained was 94%. The manufacturer completed a number of one-way sensitivity analyses (see page 79 of the manufacturer's clarification response). The highest ICER reported was £23,790 per QALY gained, which resulted from changing both

the probability of progression to death reducing the difference in the utilities for the PFS and progressed health states.

3.2 Evidence Review Group comments

The ERG commented that the model structure in the manufacturer's submission followed that used in the assessment of rituximab for first-line treatment of CLL and that no transition from the progressed to the PFS health state was possible. It was concerned that this has the effect of combining all people after progression into a single state. This means that it is not possible to improve quality of life from further treatment while in the progressed health state. However, people with CLL receive a series of treatments, so they may have periods of time following relapse and further treatment when they move into the PFS health state because of their further treatment.

The ERG stated that the details of drug doses and costs in the submission were unclear. After a request for clarification, further information was provided (see appendix 6 of ERG report). The ERG commented that it could not be sure that all figures were correct because not all calculations could be verified.

The ERG commented that not all adverse events were assigned costs in the model which meant that the adverse event costs in the FC arm (£555) were higher than those of the R-FC arm (£504) of the REACH trial despite more grade 3 and 4 adverse events in the R-FC arm. In addition, there were six cases of hepatitis B in the R-FC group and none in the FC group. This adverse event was not assigned a cost in the model.

The ERG completed a series of exploratory analyses most of which had a negligible effect on the base-case ICER (highest ICER £20,110 per QALY gained). These included adjusting rituximab costs and adverse events costs, and using PFS curves based on independent assessment of progression (the manufacturer's base case used PFS curves based on non-blinded investigator assessment of progression from the REACH trial, but a blinded, independent assessment was also performed at the interim analysis).

The most significant effect on the manufacturer's base-case ICER was seen when assuming no overall survival benefit from treatment with R-FC compared with FC (but keeping the PFS curves unchanged to maintain the PFS advantage). The ERG used two different methods of removing the overall survival advantage. One was to use the risk of death from the rituximab arm and apply it to the FC arm and the other was to use the risk of death from the FC arm and apply it to the rituximab arm. The resulting ICERs ranged from £31,009 to £47,963 per QALY gained (depending on which method of removing the survival benefit was used and which PFS curve was chosen), compared with £15,593 in the base case.

The ERG explored the effects of halving and doubling utility differential between PFS and progressed health states so that the PFS and progressed utilities were as follows: 0.9 and 0.5 respectively in one analysis and 0.75 and 0.65 in another analysis. The resulting ICERs ranged from £13,017 to £17,306 per QALY gained. However, the ERG noted that when no overall survival benefit was assumed, the ICERs became sensitive to changes in assumptions about utility. Assuming no overall survival advantage and a utility difference of 0.1 between the PFS and progressed health states, the ICER increased to £81,135 and £84,889 per QALY gained, depending on the method used to remove the survival advantage (see ERG report page 75).

3.3 Further considerations following premeeting briefing teleconference

Equality and diversity

No equality and diversity issues were identified at scoping or in the manufacturer's submission.

4 Authors

Sally Gallaugher and Zoe Garrett with input from the Lead Team (Dani Preedy and Matt Stevenson).

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 West Midlands Health Technology Assessment Collaboration:

- Dretzke J, Barton P, Kaambwa B, et al. Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia. September 2009.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Roche Products

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

- Chronic Lymphocytic Leukaemia Support Association
- 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)

Appendix B: Non-randomised evidence of rituximab-containing regimens

Studies of rituximab for the treatment of fludarabine-refractory chronic lymphocytic leukaemia

Study details	Participant characteristics	Intervention	Results
Lamanna et al. (2006)[Error! Bookmark not defined.] Single-arm, phase II study	n = 46 • Previously treated CLL (n = 32), other low-grade B-cell neoplasms (n = 14) • 65% male; median age: 62 years • Median number of previous treatments: 2 (range: 1–7) • Previous treatments: – fludarabine (78%) of whom 8 were fludarabine refractory – alkylating agents (78%)	R-PC	**All people with CLL (n = 32)** • Overall response: 75% • Complete response: 25% • Median survival: 44 months **People with fludarabine-refractory CLL (n = 8)** • Overall response: 75% • Complete response: 12%
Tam et al. (2007)[Error! Bookmark not defined.] Retrospective analysis Follow-up: not stated	n = 99 • Fludarabine-refractory CLL (100%) • 77% male; median age: 58 years • Median number of previous treatments: 4 (range: 1–15) • Previous treatments: – fludarabine and alemtuzumab refractory (59%) – fludarabine refractory and ineligible for alemtuzumab (41%)	Intensive rituximab-based combinations (n = 9) Non-intensive combinations (including R-FC, rituximab plus alemtuzumab, rituximab plus methylprednisolone; n = 19)	**People with fludarabine-refractory CLL who were treated with rituximab-based regimens (n = 28)** • Overall response: 25% • Complete response: not stated
Tsimberidou et al. (2008)[Error! Bookmark not	n = 51 • Fludarabine-refractory CLL (n = 30) or	Rituximab plus oxaliplatin, fludarabine,	**People with fludarabine-refractory CLL (n = 30)**

defined. Single-arm, phase I/II study Follow-up: not stated	Richter's syndrome (n = 21) • Median age: 59 years • For patients with fludarabine-refractory CLL, median number of previous treatments: 4 (range: 1–11)	and cytarabine	• Overall response rate: 33% • Complete response: 6% • 6-month survival: 89%
Wierda et al. (2005)**Error! Bookmark not defined.** Single-arm, open label phase II study	n = 177 • Relapsed and refractory CLL • Median age: 59 years • Median number of previous treatments: 2 (range: 1–10) • Previous treatments: – alkylating agents only (18%) – fludarabine alone or combination (82%) of whom 61% were fludarabine sensitive and 21% were fludarabine refractory – rituximab alone or in combination (12%) – fludarabine and cyclophosphamide (FC) (19%) of whom 30 were fludarabine sensitive and 4 were fludarabine refractory	R-FC	**All people (n = 177)** • Overall response: 73% • Complete response: 25% • Median overall survival: 42 months **People with fludarabine-sensitive CLL (n = 78)** • Overall response: 77% • Complete response: 33% **People with fludarabine-refractory CLL (n = 33*)*** • Overall response: 58% • Complete response: 6%
Wierda et al. (2006)**Error! Bookmark not defined.** Single-arm, phase II study Median follow-up: 12 months	n = 79 • Relapsed/refractory CLL (only 74 had completed treatment) • 75% male; median age: 58 years • Median number of previous treatments: 3 (range: 1–14) • Previous treatments: – R-FC (54%) – FC (13%)	Rituximab plus cyclophosphamide, fludarabine, and alemtuzumab	**All people (n = 74)** • Overall response rate: 65% • Complete response: 24% • Median survival: 19 months (all patients including non-refractory); 35+ months (complete response); 18 months (partial response); 7 months (non-responders) **People with fludarabine-refractory CLL (n = 32)**

			• Overall response rate: 51% • Complete response: 13%
CLL, chronic lymphocytic leukaemia; FC, fludarabine and cyclophosphamide; R-FC, rituximab plus fludarabine and cyclophosphamide; R-PC, rituximab plus pentostatin and cyclophosphamide			

Studies of rituximab for the treatment of chronic lymphocytic leukaemia after previous treatment with rituximab

Study details	Participant characteristics	Intervention	Results
Gupta et al. (2002)**Error! Bookmark not defined.** Retrospective analysis	n = 8 • Steroid-refractory autoimmune haemolytic-anaemia CLL • 88% male; median age: 60 years • Median number of previous treatments: 2 (range: 1-4) • Previous treatments: – steroids (n = 8) – fludarabine (n = 6) – alkylating agents (n = 5)	R-CD	**All people (n =8)** • Overall response: 100% autoimmune haemolytic anaemia responses (all 8 patients achieved remission) • 5 patients had a relapse of autoimmune haemolytic anaemia (after a median response of 13 months) and were re-treated with R-CD
Lamanna et al. (2007)**Error! Bookmark not defined.** Single-arm, phase II study	n = 21 • CLL patients previously treated with R-PC or R-FC • CLL (n = 17); other low-grade B-cell neoplams (n = 4) • 76% male; median age: 62 years • Median number of previous treatments: 2 (range: 1-6)	R-PCM	**All people evaluable for response (n = 16)** • Overall response: 94% • Complete response: 25% **People who received rituximab treatment (R-PC or R-FC) and who were evaluable for response (n = 11)** • Overall response: 91%

	• 65% of CLL patients had previously been treated with chemoimmunotherapy using PCR or R-FC		• Complete response: 19%
Tam et al. (2008)**Error! Bookmark not defined.** Retrospective analysis Median follow-up (after salvage therapy): 32 months	n = 97 • Refractory CLL • All patients were previously treated with R-FC • Taken from a series of 300 patients treated with first-line R-FC. After median of 6 years 103 had relapsed and of these 97 patients completed subsequent therapy	Salvage treatment with various rituximab-containing regimens	**All people (n = 97)** • Overall response: 49% • Complete response: 15% **People who received any rituximab-based salvage treatment (n = 80)** • Median overall survival: 32 months
Wierda et al.(2005)**Error! Bookmark not defined.** Single-arm, open-label phase II study	n = 177 • Relapsed and refractory CLL • Median age: 59 years • Median number of previous treatments: 2 (range: 1–10) • Previous treatments: – alkylating agents only (18%) – fludarabine alone or in combination (82%) of whom 61% were fludarabine sensitive and 21% were fludarabine refractory – rituximab alone or in combination (12%) – FC (19%) of whom 30 were fludarabine sensitive and 4 were fludarabine refractory	R-FC	**All people (n = 177)** • Overall response: 73% • Complete response: 25% • Median overall survival: 42 months **People previously treated with rituximab (monotherapy or combination therapy; n = 22)** • Overall response: 64% • Complete response: 18% • Median overall survival: 48 months
Wierda et al. (2006)**Error! Bookmark not defined.**	n = 79 • Relapsed/refractory CLL (only 74 had completed treatment)	Rituximab plus cyclophosphamide, fludarabine, and	**All people (n =74)** • Overall response rate: 65% • Complete response: 24%

Single-arm, phase II study Median follow-up: 12 months	• 75% male; median age: 58 years • Median number of previous treatments: 3 (range: 1–14) • Previous treatments: – R-FC (54%) – FC (13%)	alemtuzumab	• Median survival: 19 months (all patients including non-refractory); 35+ months (complete response); 18 months (partial response); 7 months (non-responders) **People previously treated with rituximab (R-FC; n = 43)** • Overall response rate: 56% • Complete response: 19%
Zent et al. (2008)**Error! Bookmark not defined.** Single-arm, phase II study	n = 30 • High-risk CLL • 67% male; median age: 61 years Nine patients with *del(17p)* mutation who received rituximab plus alemtuzumab initially were subsequently retreated with: alemtuzumab plus rituximab (n = 1); cyclophosphamide, fludarabine, alemtuzumab plus rituximab (n = 2); pentostatin, cyclophosphamide plus rituximab (n = 4); F-CR (n = 1); rituximab, cyclophosphamide, vincristine plus prednisone (n = 1)	Rituximab plus chemotherapy	**People re-treated with a rituximab-containing regimen after initial treatment with rituximab plus alemtuzumab (n = 9)** • Overall response: 78% • Complete response: 44%
CLL, chronic lymphocytic leukaemia; FC, fludarabine and cyclophosphamide; R-CD, rituximab plus cyclophosphamide and dexamethasone; R-PCM, rituximab plus pentostatin, cyclophosphamide, and mitoxantrone; R-FC, rituximab plus fludarabine and cyclophosphamide; R-PC, rituximab plus pentostatin and cyclophosphamide			

Additional studies of rituximab in combination with various chemotherapy regimens for the treatment of relapsed or refractory chronic lymphocytic leukaemia

Study details	Participant characteristics	Intervention	Results
Eichhorst et al. (2005)**Error! Bookmark not defined.** Multicentre, single-arm, phase II study	n = 34 • Fludarabine refractory CLL (n = 19) or CLL with autoimmune hemolytic anemia (n = 7) or Richter's transformation (n = 4) • Mean age: 66 years • Mean number of previous treatments: 2.1	Rituximab plus CHOP	**People evaluable for response (n = 17)** • Overall response: 70% • Complete response: 0%
Fischer et al. (2008)**Error! Bookmark not defined.** Single-arm, phase II study	n = 81 • Relapsed/refractory CLL • Median age: 67 years • Median number of previous treatments: 2 (range: 1-3)	Rituximab plus bendamustine	**People evaluable for response (n = 23)** • Overall response: 77% • Complete response: 15%
Hillmen et al. (2007)**Error! Bookmark not defined.** Randomised)non-comparative), phase II study	n = 52 • Previously treated, progressive CLL • 79% male; median age: 65 years • Median number of previous treatments: 2 (range: 1-6) • Previous treatments: – fludarabine (n = 31) of whom 6 were refractory or relapsed within 6 months	1. FCM (n = 26) 2. FCM plus rituximab (n = 26)	**People who received FCM plus rituximab and were evaluable for response (n = 23)** • Overall response: 70% • Complete response: 43% **People who received FCM and were evaluable for response (n = 23)** • Overall response: 57% • Complete response: 13%

Lamanna et al. (2006)[Error! Bookmark not defined.] Single-arm, phase II study	n = 46 • Previously treated CLL (n = 32), other low-grade B-cell neoplasms (n = 14) • 65% male; median age: 62 years • Median number of previous treatments: 2 (range: 1–7) • Previous treatments: – fludarabine (78%) of whom 8 were fludarabine refractory – alkylating agents (78%)	R-PC	**All people with CLL (n = 32)** • Overall response: 75% • Complete response: 25% • Median survival: 44 months
Robak et al. (2007)**Error! Bookmark not defined.** Non-randomised, phase II study Median follow-up: 16 months	n = 46 • Relapsed (72%) or refractory (28%) CLL • 59% male; median age: 59 years • Median number of previous treatments: 2 (range: 1-5)	1. RC (n = 18) 2. RCC (n = 28)	**All people (n = 46)** • Progression-free survival: 12 months (range: 4-46 months) • Overall response: 74% • Complete response: 7%
CHOP, cyclophosphamide plus doxorubicin plus vincristine plus prednisone; CLL, chronic lymphocytic leukaemia; FCM, fludarabine, cyclophosphamide, and mitoxantrone; RC, rituximab plus cladribine; RCC, rituximab plus cladribine and cyclophosphamide; R-PC, rituximab plus pentostatin and cyclophosphamide			