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Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia

Produced by West Midlands Health Technology Assessment Collaboration

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This report should be referenced as follows:

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Abbreviations

AE	Adverse event
BCSH	British Committee for Standards in Haematology
CHOP	Cyclophosphamide, doxorubicin hydrochloride, vincristine (also called oncovin), prednisolone) combination
CLL	Chronic lymphocytic leukaemia
CR	Complete response
CVP	Cyclophosphamide, vincristine (also called oncovin), prednisolone combination
ERG	Evidence review group (at Birmingham university)
FACT-G	Functional Assessment of Cancer Therapy – General
FC	Fludarabine and cyclophosphamide combination
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
iv	Intravenous
KM	Kaplan-Meier (survival curve)
OS	Overall survival
PD	Progressive disease
PR	Partial response
PFS	Progression free survival
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
R-FC	Rituximab with fludarabine and cyclophosphamide combination
SD	Stable disease
SPC	Summary of product characteristics
STA	Single technology appraisal

1 SUMMARY

1.1 Scope of the submission

The scope was to assess the clinical effectiveness and cost-effectiveness of rituximab in addition to combination therapy for patients with relapsed chronic lymphocytic leukaemia (CLL).

1.2 Summary of submitted clinical effectiveness evidence

Clinical evidence was derived from a single open label unpublished RCT (the REACH trial) of rituximab and fludarabine with cyclophosphamide (R-FC) versus fludarabine with cyclophosphamide (FC) in 552 patients with relapsed CLL. Patients in the trial were relatively young and none were refractory to fludaribine. The trial demonstrated an increase in progression-free survival of 10.2 months (P = 0.0287) with a hazard ratio of 0.65 (P = 0.0002) in favour of R-FC (investigators' assessment - less favourable results were provided by an independent assessment from the clinical trial report). The clinical data for an estimate of overall survival was not complete, with 77.5% and 75.4% of patients still alive in R-FC and FC arms respectively at the time of cut off.

Best overall response rates and duration of response were statistically superior in the R-FC arm relative to the FC arm. Non randomised uncontrolled evidence was provided on fludarabine-refractory patients.

1.3 Summary of submitted cost effectiveness evidence

A de novo cost effectiveness model was submitted that conformed in structure to the model previously submitted to NICE for the assessment of the cost effectiveness of rituximab as first line treatment in combination therapy or CLL.

Estimates of resource use were mainly based on the REACH trial, costs were taken from standard sources. Estimation of health gain was based on extrapolation of Weibull fits to observed progression-free survival, modelling of overall survival that generated an overall survival advantage for R-FC, and previously employed health utility values. The model delivered a base case

deterministic ICER of £15,593/QALY, and in PSA the probability of greater than 90% that R-FC was cost effective at a threshold of £30,000/QALY.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

Although based on a single RCT, the evidence that R-FC delays disease progression in comparison to FC is convincing. It is likely this delay is associated with significant health-related quality of life gain for patients, although this is difficult to quantify through lack of suitable empirical evidence.

The model submitted was similar to that used for the recent submission on rituximab in first line treatment of CLL.

1.4.2 Weaknesses

A major driver of the economic model is overall survival. A major weakness of the submitted evidence is the limited information available from the REACH trial on overall survival, but that which is available suggests little difference between the two arms. In the economic model, R-FC is estimated to deliver an overall survival benefit relative to FC, and this benefit accrues from the very start of the model. This is not compatible with observed data from the REACH trial. Evidence of overall survival benefit from R-FC versus FC is weak. The overall survival curves for the intervention and control are essentially identical to about 2.5 years (i.e. 2 years after completion of rituximab treatment). The survival trace for the FC arm is likely to become increasingly susceptible to bias as time progresses; this is because of crossover of relapsed FC patients to rituximab treatment, which will be based on clinical grounds (probably involving more robust patients) so that patients remaining at risk in the survival analysis are unlikely to be representative of all live patients.

One weakness in the model presentation was the number of sheets in the Excel workbook that were hidden from view and that could not be revealed. There were also some errors of logic that became apparent during the project.

Most of the ones that were spotted appeared to make little difference to the results but there may be others with unknown consequences.

1.4.3 Areas of uncertainty

There is considerable uncertainty associated with estimates of overall survival both in the clinical effectiveness section and also as modelled in the economic section. The utility values attached to health states (progression-free and progressed) although arguably the best available, are not based on empirical evidence and their accuracy is very uncertain.

Another area of uncertainty is the cost of relapse therapy with rituximab (£8,332) compared to the cost of first line therapy with rituximab (£11,617) as given in the recent submission on rituximab for first line treatment for CLL.

1.5 Key issues

- The evidence for clinical effectiveness rests on a single open label unpublished RCT (REACH)

- The output from the manufacturer's economic model is sensitive to the assumption of an overall survival advantage for the rituximab arm over the comparator. Convincing randomised evidence for the existence of an overall survival advantage is lacking. When no overall survival advantage is assumed, and under all other base case assumptions, the ICER changes from £15,593/QALY to between £40,000 and £42,000/QALY.

- When no overall survival advantage for the rituximab arm is assumed, the economic model output becomes sensitive to the differential in utility between the non-progressed and the progressed state. There is a lack of empirical evidence about the utility of patients in these states.

- The manufacturer's base case economic analysis depends on investigators' assessment of progression which may be more susceptible to potential bias than the blinded independent assessment. The median time to event for the rituximab arm in the investigators

assessment was 932 days and in the independent assessment was [redacted]. The median time to event for the comparator arm in the investigators assessment was 627 days and in the independent assessment was [redacted]. So the difference was 10.2 months in the investigator's assessment but [redacted] in the independent assessment. However, when parametric fits were made to the independent analysis results only small differences in the resulting ICERs were observed and the direction of change was not consistent.

- Apart from overall survival, the other main factors found to influence cost effectiveness were the use of alternative curve fits for progression-free survival, the use of independent assessment of progression, vial wastage issues and retiming of rituximab costs. None of these alone made a large difference on cost effectiveness. When combined, with overall survival, the cost effectiveness moved from £15,593 (base case) to between £44,669 and £48,385.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The underlying health problem is relapsed/progressed and refractory chronic lymphocytic leukaemia (CLL). Newly diagnosed CLL was the topic of a previous STA (Single Technology Appraisal(Main et al. 1-101)). The submission gives details on CLL generally (p22), but there is no definition of 'refractory' and 'relapsed'. The following definitions for relapsed and refractory CLL were identified by the ERG (Evidence Review Group) in the 2008 guidelines for the diagnosis and treatment of CLL from the International Workshop on CLL(Hallek et al. 5446-56), which update the 1996 National Cancer Institute Working Group guidelines, and are reproduced below:

- Relapsed CLL: Relapse is defined as a patient who has previously achieved the criteria for a complete response or partial response, but *after* a period of 6 or more months, demonstrates evidence of disease progression.

- Refractory CLL: Refractory disease is defined as treatment failure (stable disease, non-response) or disease progression *within* 6 months of the last anti-leukaemic therapy.

Relapse (progression) can occur at any of the main stages used to classify CLL patients (Binet stage A, B and C). The description of the different stages is taken from the submission (Table 4, p23) and reproduced here:

Table 4 submission: Binet stages

	Features	**% of patients (at diagnosis)**
Binet Stage		
A	<3 lymphoid areas involved	60
B	>3 lymphoid areas involved	30
C	Haemoglobin <10g/dl or platelets, 100 X 10^9/L	10

There is brief information on p24 of the submission on prognostic factors relating to cytogenetic abnormalities. This is relevant as prognosis and most appropriate treatment option may vary depending on prognostic factors. The most well recognised prognostic marker is loss or mutation of the p arm of chromosome 17 (del17p), which is where p53 is encoded. p53 is a protein involved in tumour suppression and del17 is associated with decreased survival and clinical resistance to fludarabine treatment.(Rosenwald et al. 1428-34;Guidelines on the diagnosis and management of chronic lymphocytic leukaemia 294-317) A small proportion (8%) of patients in the REACH trial (which forms the bulk of the evidence in this appraisal) had del17.

The epidemiology section of the submission (4.1.2 on p22) reports the incidence rate of CLL as 3/100,000, which varies according to age and sex. This rate refers to initial diagnosis of CLL rather than to rates of relapsed (progressed) or refractory patients, which is the population of interest in this appraisal. Median age at diagnosis is reported as between 65 and 70, again this relates to initial diagnosis of CLL rather than relapsed (progressed) or refractory patients.

Relapse incidence rates, proportion of patients becoming refractory and median age at relapse were difficult to identify in the literature. Molica (1999)(Molica, Levato, and Dattilo 1094-99) estimates that 33% of those diagnosed with early stage A will risk progression of disease stage by 5 years and require treatment. By 10 years the risk of progression is reported to be 50%. However, these figures do not take into account patients with more severe stages of disease.

In section 8.2 of the submission (eligible patients) on p213, the proportion of newly diagnosed patients that will never need treatment is estimated at 33%, with 67% requiring treatment either immediately or eventually. Of these 67%, 66% will progress or not respond at all in a one-year time period. These figures are from a study undertaken by the consultancy Genactis on behalf of Roche and were not verifiable by the ERG. Consultation with the ERG's clinical expert (JM) suggests that the proportion of patients progressing in a one year time period is nearer 30-40%, though this estimate is based on clinical impression only. The vast majority of patients who are treated will eventually progress.(Ghia, Ferreri, and Caligaris-Cappio 234-46)

We have not been able to identify an estimate for median age at relapse; clearly this will lie above the median age at initial diagnosis of 65-70. Our clinical expert (JM) has suggested that the median age of patients in the REACH trial, which consists only of relapsed/refractory patients appears to be somewhat low at a mean age of 61.7 and median age of 63 (range 35-83). The mean/median age of a relapsed/progressed population is more likely to be in the upper 60's age range. (Representativeness of the REACH trial population is discussed in more detail in section 4.1.5).

2.2 Critique of manufacturer's overview of current service provision

CLL is treated with cytotoxic drugs including alkylating agents (chlorambucil, cyclophosphamide and bendamustine), antimetabolites or purine analogues (fludarabine or cladripine), mitoxantrone (an anthracycline) and prednisolone

(a corticosteroid). Drug combinations are also used, such as FC (fludarabine and cyclophosphamide), CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine (also called oncovin), prednisolone) and CVP (cyclophosphamide, vincristine (also called oncovin), prednisolone). These drugs are also referred to as chemotherapy to distinguish them from treatment with monoclonal antibodies (biological therapy, immunotherapy) such as rituximab or alemtuzumab.

The submission describes treatment guidelines according to the 2009 ESMO (European Society for Medical Oncology) clinical recommendations(Eichhorst et al. Abstract 2126), which suggest the following options for second line (palliative) and subsequent treatments:

- Fludarabine, FC or cladribine after chlorambucil

- Fludarabine, FC, FC+mitoxantrone +/- rituximab or alemtuzumab in fludarabine-refractory patients or relapse after Fludarabine-based therapy

- Alemtuzumab in chemotherapy-refractory patients

- Bendamustine +/- monoclonal antibodies after chlorambucil or purine analogue-based therapy

- High-dose therapy followed by autologous or allogeneic progenitor cell transplantation remains investigational

- Allogeneic progenitor cell transplantation is the only curative therapy so far and is indicated in high risk and/or refractory disease

There are no NICE guidelines on the treatment of relapsed/refractory CLL (any intervention). The British Committee for Standards in Haematology (BCSH) guidelines on the diagnosis and management of chronic lymphocytic leukaemia from 2004(Guidelines on the diagnosis and management of chronic lymphocytic leukaemia 294-317) suggest the following (NB these guidelines are in the process of being updated and do not take into account the results of several trials that were still ongoing at the time):

-Further course of chlorambucil for those patients who relapse after an initial response to low dose chlorambucil

- Fludarabine for patients refractory to low dose chlorambucil; CHOP for those patients in whom fludarabine is unsuitable
- Re-treatment with fludarabine in patients who responded to fludarabine more than 1 year ago
- FC in patients who progress within 1 year following treatment with fludarabine

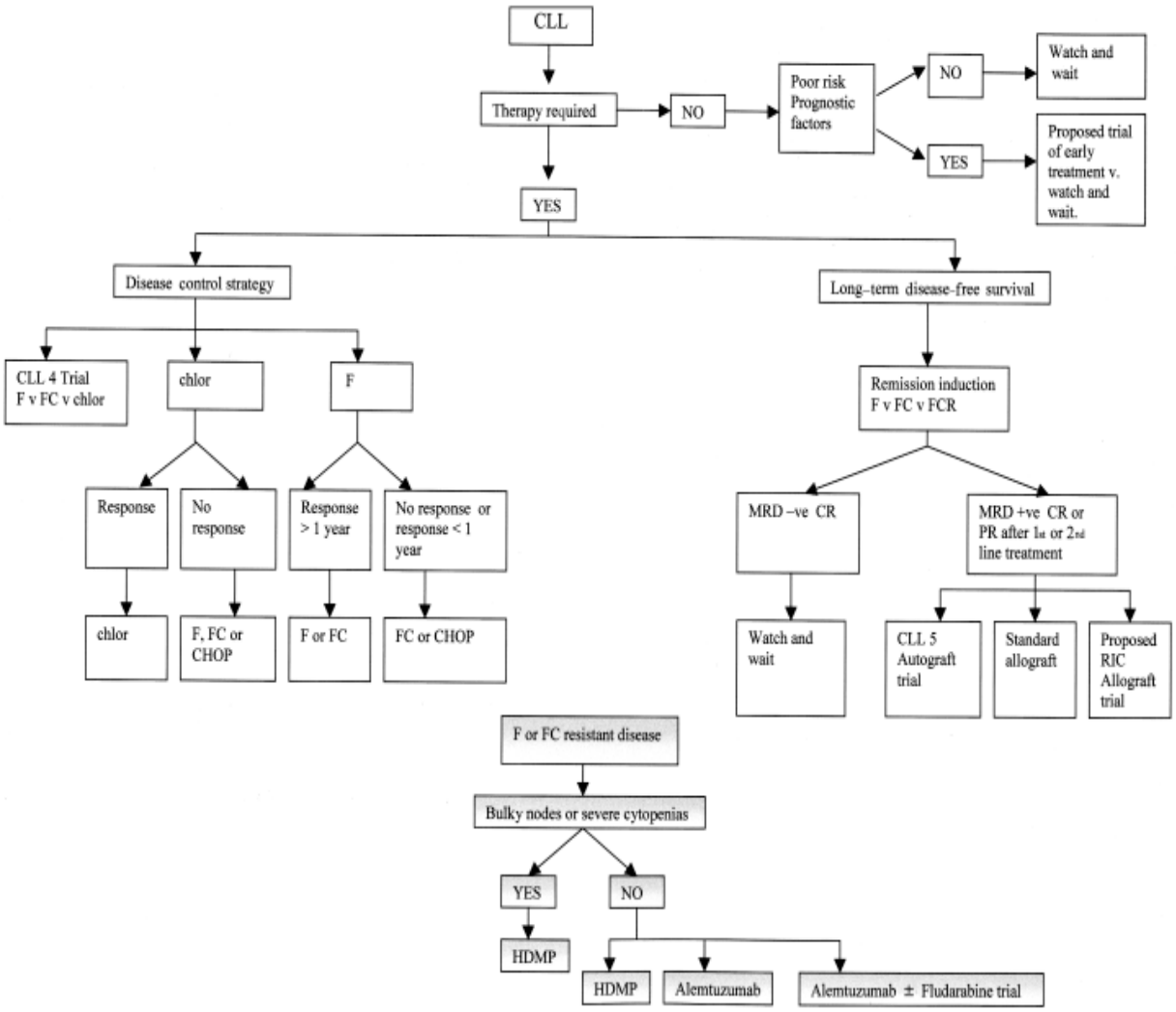
Patients who are fludarabine refractory currently have a poor prognosis and the following options are recommended:

- High-dose methyl prednisolone (particularly where there is bulky lymphadenopathy and/or p53 abnormalities)
- Alemtuzumab in patients previously treated with alkylating agents and trefractory to fludarabine
- Rituximab monotherapy is not recommended; RF or RFC may be effective in refractory CLL and warrants further evaluation

There are further recommendations regarding transplantation, which are not further discussed here.

The flowchart below is taken from the BCSH 2004 UK guidelines(Guidelines on the diagnosis and management of chronic lymphocytic leukaemia 294-317):

Figure 1 Treatment options in CLL



Treatment options in CLL. CLL4 trial and CLL5 autograft trial are current UK trials. Proposed UK CLL Forum trials are: (i) poor risk stage A CLL; (ii) Alemtuzumab ± fludarabine for patients resistant to fludarabine; and (iii) reduced intensity conditioning Allograft Study. Treatment strategy for patients who are refractory or become resistant to fludarabine or fludarabine + cyclophosphamide therapy is shown in shaded boxes.
chlor = chlorambucil; F = fludarabine; FC = fludarabine + cyclophosphamide; RIC = reduced intensity conditioning; HDMP = high-dose methyl prednisolone; CHOP = cylophosphomide, adriamycin, vincristine, prednisolone; FCR = fludarabine, cyclophosphamide and rituximab.

It should be noted that this flowchart was based on evidence available in 2004 and does not take into account more recent evidence. The CLL4 trial has been completed and recommends that FC should be considered the standard treatment.(Catovsky et al. 230-39). Recent NICE guidance on rituximab as first line treatment for CLL is also not taken into account.(National Institute for Health and Clinical Excellence)

There are other international guidelines (e.g. 2008 report from the International workshop on CLL updating the National Cancer Institute-Working Group 1996 guidelines(Hallek et al. 5446-56)) but these will not be discussed further here for brevity.

Consultation with our clinical expert (JM) suggests that, in the UK, most patients receive fludarabine or FC as first line treatment, then, on progression, may receive CVP or CHOP. If an application for off-licence use is successful, R-CVP or R-CHOP may be given. Chlorambucil is predominantly reserved for very frail or elderly patients unable to tolerate F(C). Alemtuzumab is not very widely used as it is associated with more side effects than rituximab, although it may be appropriate when previous treatments have failed. First-line treatment (such as fludarabine or FC) may be repeated in patients who have remained progression free for a significant period of time and then progress. Patients who progress within a shorter time period (6-12 months) would be considered refractory to that treatment and an alternative second line treatment used. The choice of first and second line treatment is decided on a patient-by-patient basis and there is regional variation. The decision at which stage of disease to (re-) initiate treatment is also subject to variation depending on treatment policies, and the treating clinician. There is disagreement between clinicians as to when to start treatment and which drugs to use for which patients.

The CLL support organisation (from scope comments) states that patients should be tested for a working p53 pathway before any treatment, as choice of treatment may depend on the presence/absence of a working p53 pathway. The submission, however, states that no additional tests or investigations are required to select CLL patients for treatment with rituximab. Testing for prognostic markers such as del17 is not routinely offered in the UK, and the presence or absence of genetic abnormalities alone does therefore not directly influence treatment options. The 2004 BCSH Guidelines(Guidelines on the diagnosis and management of chronic lymphocytic leukaemia 294-317) state that evidence that the application of prognostic factors improves clinical outcome in asymptomatic stage A patients is currently lacking. There are no

specific recommendations in these guidelines for testing relapsed/progressed patients. Testing of genetic prognostic markers is currently more likely to be undertaken as part of a clinical trial. The test used is FISH (Fluorescence In Situ Hybridisation), which costs £100 for 11q23 and 17p13 deletions, or £250 for a more comprehensive analysis (West Midlands Regional Genetics Laboratory(West Midlands Regional Genetics Laboratory)).

3 Critique of manufacturer's definition of decision problem

The table below is from the submission, p13-15. Our comments on population, intervention, comparator and outcomes follow.

NICE scope (updated)	Decision problem addressed by manufacturer
Population Patients with relapsed/refractory CLL **Subgroups to be considered** If evidence allows, the appraisal should consider sub-groups based on the following: P53 presence and p53 mutation or deletion.	**Population** It is anticipated that the licence will reflect patients with both relapsed and so-called 'refractory' disease, so the full population would be correctly defined as '**patients with relapsed/ refractory lymphocytic leukaemia**'. Thus the population considered in the submission will be slightly broader than in the final scope issued by NICE, reflecting the nature of the anticipated licence. (NB 'refractory' was added in the updated NICE scope) **Subgroups to be considered** It is anticipated that the marketing authorisation will not exclude patients with p53 deletion/mutation. There are patients with p53 abnormalities included in the clinical trials appraised in this submission and data will be analysed accordingly.
Intervention Rituximab (in combination with chemotherapy)	**Intervention** The licence will allow addition of rituximab to any chemotherapy. As in the first-line submission, the available data suggests that irrespective of the chemotherapy, rituximab adds efficacy with manageable toxicity.
Comparator Chlorambucil, fludarabine combination therapy, cyclophosphamide, doxorubixin, vincristine, prednisone (CHOP) combination, stem-cell transplant	**Comparator** The comparators considered in this submission are fludarabine combination therapy, chlorambucil, and CHOP. The pivotal, Phase III randomised study (REACH) provides a direct comparison of the most common fludarabine combination therapy used in practice (fludarabine and cyclophosphamide – FC) versus FC combined with rituximab – R-FC. Although there are alternative treatment options for previously treated CLL patients, due to differing patient

	characteristics of those who receive different chemotherapies, it would be inappropriate to compare R-FC versus chemotherapies other than FC (for example, R-FC compared to chlorambucil or R-FC compared to CHOP). This is because fludarabine-based combination therapy is usually administered to younger and/or fitter CLL patients, whereas chlorambucil is often reserved for the more frail and elderly. Similarly, CHOP is often reserved for patients in whom fludarabine is contraindicated. Instead, for each chemotherapy comparator, the appropriate intervention arm should be rituximab in combination with the comparator chemotherapy (i.e. R-chlorambucil versus chlorambucil; R-CHOP versus CHOP). There is no data currently on the combination of rituximab with chlorambucil in relapsed/refractory CLL. One phase II trial for R-CHOP in fludarabine refractory patients is used as the basis for a simple cross trial comparision provided in section 6.8. In addition, a wealth of phase II data is included in this submission demonstrating the efficacy and tolerability of rituximab in combination with <u>any</u> base chemotherapy regime. In the final scope, NICE have noted that stem-cell transplant could be considered as a comparator. However, we do not feel that this would be appropriate. In the United Kingdom in 2008, only 47 transplants were carried out for CLL (British Society of Blood and Marrow Transplantation, BSBMT).These are always done in very specific patients who are often younger and have a suitable donor for an allograft. There is no generalisable clinical decision point currently where a physician has to decide between a transplant and (rituximab based) chemotherapy. A transplant is done in very few patients (less than 0.5%), and therefore should not be considered a comparator for this submission.
Outcomes The outcome measures to be considered include overall survival, progression-free survival, response rates, adverse effects of treatment and health-related quality of life	**Outcomes** These outcomes are covered in the submission. The Functional Assessment of Cancer Therapy – General (FACT-G), was used as a tool to capture health-related quality of life in the REACH study. This data will be presented. A further analysis to evaluate the impact of rituximab on patients' QoL, a Quality adjusted time Without disease Symptoms or treatment Toxicity (Q-TWiST) was applied to REACH data. In the economic analysis, predicted time in each health state was weighted using CLL utility scores from the literature (Hancock et al, 2002) to account for patient quality of life and to estimate QALYs. An observational study estimating the health-related quality of life profiles of UK patients with CLL is underway. Interim results can be made available to NICE upon request.

3.1 Population

Eligible CLL patients are described in the NICE scope and the manufacturer submission as those who have relapsed or are refractory. An eligible patient group for treatment with rituximab was not defined *a priori* in the submission (no further clarification on inclusion criteria were received upon request). We would have expected to see an eligible patient group defined by criteria such as prior treatment(s), whether they were refractory (and to which treatment) and disease severity (Binet stage).

In REACH (the main included trial for this submission, discussed later), eligible refractory patients were those refractory to alkylators (CHOP, CVP, chlorambucil), whilst those refractory to fludarabine were excluded. The justification given by the manufacturer is that such patients are relatively uncommon, have a poor prognosis and are unlikely to benefit from further fludarabine based therapy. So randomisation of fludarabine resistant patients to further fludarabine therapy (with cyclophosphamide) was of concern. However, they also state that additional efficacy data became available after the trial had commenced which demonstrated that R-FC is a useful therapeutic option for fludarabine refractory patients (see also table in section 4.1.5 "Were the inclusion and exclusion criteria appropriate?").

The REACH trial is therefore not representative of all UK rituximab - eligible relapsed/refractory CLL patients. The submission draws on evidence from non-randomised studies to make a case for the use of rituximab in fludarabine refractory patients (see 4.2.1 Summary of results). REACH did include patients who had received fludarabine as first-line treatment but did not progress quickly and are thus not classified as refractory.

The NICE scope specifies that patients with p53 mutation should be considered as a separate sub-group if evidence allows. The REACH trial included a small proportion (8%) of patients with a p53 mutation.

Other genetic mutations that may affect prognosis are listed in Table 1. These prognostic markers may overlap, with between 20-25% of cases discordant

for at least one marker; a clear hierarchy in terms of prognostic power has yet to be established.(Ghia, Ferreri, and Caligaris-Cappio 234-46)

Table 1 Prognostic factors in CLL((Ghia, Ferreri, and Caligaris-Cappio 234-46;Guidelines on the diagnosis and management of chronic lymphocytic leukaemia 294-317))

More favourable mutation	Less favourable mutation
Unmutated 17p	del17p
Unmutated 11q	del11q
del13q (as sole genetic abnormality)	Unmutated 13q
Mutated igVH gene	Unmutated igVH gene
<20-30% CD38 expression	>20-30% CD38 expression
No ZAP-70 expression	ZAP-70 expression

Twenty sub-groups were reported in REACH (for PFS and best overall response (BOR), p101), including sub-groups with the prognostic markers listed in Table 1. The submission states that the combination of ZAP-70 positive and an unmutated IgVH gene (in 37% of patients) represents the worst prognostic combination. This group was also looked at in sub-group analysis. However, the submission does not investigate any genetic subgroups with regard to cost-effectiveness.

3.2 Intervention

In this appraisal – the use of the term first line treatment (ie palliative treatment) is also being used synonymously with the first treatment people receive, because there is no curative drug treatment available as yet for CLL. The intervention is rituximab (MabThera). The SPC (summary of product characteristics)(European Medicines Agency) states that:
"MabThera is indicated for first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy. The recommended dosage of MabThera in combination with chemotherapy is 375mg/m2 body surface area administered on day 1 of the first treatment cycle followed by 500mg/m2 body surface area administered on day 0 or each subsequent cycle for 6 cycles in total. The chemotherapy should be given after MabThera infusion."

NICE guidance(National Institute for Health and Clinical Excellence) for first line use of rituximab in CLL, issued in June 2009, states that:

"1.1 Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia in people for whom fludarabine in combination with cyclophosphamide is considered appropriate.

1.2 Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of chronic lymphocytic leukaemia."

The NICE guidance for first-line treatment thus focuses on a narrower group of patients compared to the SPC, i.e. only those for whom fludarabine in combination with cyclophosphamide is considered appropriate.

Rituximab is currently not licensed for use in relapsed/refractory patients in the UK. There is however a statement of positive opinion(European Medicines Agency) from the Committee on Medicinal Products for Human Use (CHMP) for a variation to the terms of the marketing authorisation. A draft SPC for MabThera has been submitted by Roche, which details the population and recommended dose:

"MabThera in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including MabThera or patients refractory to previous MabThera plus chemotherapy."

"The recommended dosage of MabThera in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375mg/m2 body surface area administered on day 1 of the first treatment cycle followed by 500mg/m2 body surface area administered on day 0 or each subsequent cycle for 6 cycles in total. The chemotherapy should be given after MabThera infusion."

There is no information on whether rituximab can be given for a second or subsequent relapses, or on the maximum number of times it can be given for

relapses. Clinical opinion (JM) suggests that rituximab is likely to be given as 1-2 treatment courses of 6 cycles at most.

Adverse events associated with rituximab are not specifically addressed in the decision problem. The SPC(European Medicines Agency) states that very common (≥1/10) adverse events associated with CLL patients treated with rituximab include bacterial and viral infections (including bronchitis), neutropenia, leucopenia and thrombocytopenia, infusion related reactions, angioedema, nausea, pruritis, rash, alopecia, fever, chills, asthenia, headache and decreased IgG levels. Infectious events occurred in approximately 30-50% of patients during clinical trials in patients with CLL. Common (≥1/100 to < 1/10) adverse events include but are not limited to sepsis, pneumonia, anaemia, myocardial infarction, arrhythmia, respiratory disease, urticaria and tumour pain. Very rare cases of progressive multifocal leukoencephalopathy have been reported.

Severe cytokine release syndrome may occur in patient with high levels of circulating malignant cells, can be provoked by giving rituximab and in extreme cases is associated with acute respiratory failure and death. Patients with a high number of circulating malignant cells may be at higher risk of severe cytokine release syndrome and should only be treated with rituximab with extreme caution. A reduced infusion rate or split dosing over two days should be considered for the first and subsequent cycles if the malignant cell count is still high.

3.3 Comparators

The NICE scope specifies the following comparators: chlorambucil, fludarabine combination therapy (FC), cyclophosphamide, doxorubixin, vincristine, prednisone (CHOP) combination and stem-cell transplant.

The submission states that chlorambucil, FC and CHOP will be considered. Stem-cell transplants have been excluded in the submission, the reason given for this is that at present very few patients receive this treatment in the UK. The BCSH guidelines suggest that autologous transplantation should be

considered in specific patients in the context of an RCT. We have identified no RCTs comparing rituximab with stem cell transplantation.

The comparison of FC versus R-FC in REACH is appropriate, as either of these options may be considered in patients who have progressed. However, some patients may be more likely to receive (R-) CHOP or (R-) CVP as second line treatment. There is no available evidence from an RCT on the efficacy of rituximab in combination with CVP or CHOP (or chlorambucil).

Alemtuzumab could have been included as a comparator, as this monoclonal antibody is licensed for treatment of (untreated and previously treated) CLL. However, clinical opinion (JM) suggests that it is not widely used in the UK due to its toxicity.

Non-randomised studies have been included in the submission describing the efficacy of rituximab within other chemotherapy regimens (p37). Many of the drugs are not included in the scope specified by NICE (e.g. bendamustine, mitoxantrone, alemtuzamab, etanercept, cladribine, methylprednisolone).

3.4 Outcomes

The primary clinical effectiveness outcome was progression free survival (PFS). Secondary clinical effectiveness outcomes were: event free survival (EFS); disease free survival (DFS) in complete response (CR) patients; duration of response; overall response rate (ORR) for CR, partial response (PR) and nodular PR (nPR) patients; overall survival (OS); molecular remission; adverse events (AE); and quality of life (QoL). These outcome measures were thought to be appropriate.

QoL was measured using the FACT-G. The EQ-5D measure would have been useful as this generates a utility measure between 0-1, which could be used to calculate QALYs (quality adjusted life years) but was not used in REACH. See also section 4.1.6 for details on outcome measures.

3.5 Time frame

Survival in CLL is generally estimated to be up to 13 years in the majority of patients. Accordingly, this would be expected to be slightly lower in a relapsed/progressed population. The REACH RCT is due to follow patients for 8 years for most outcomes, one year for quality of life. At the time of this report, the cut-off point for data reporting was a median of 2.1 years. The timeframe used in the economic model is 25 years, although results are also provided for truncation at 15 years, which seems more appropriate (see sections on economic model for further details). Whilst a proportion patients with Binet stage A CLL may never need treatment and will die with the disease rather than from it, we are looking at a population, who have already received treatment and have subsequently progressed, and are likely to do so again after further treatment.

3.6 Other relevant factors

We have identified no additional relevant factors, which have not already been discussed in other sections of this report.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

Completed studies

The manufacturer's search strategy was as follows:

The specific decision problem on which the searches were focused was "rituximab in combination with chemotherapy for the treatment of patients with relapsed/refractory chronic lymphocytic leukaemia"

The following databases were searched:

MEDLINE via Dialog Datastar (MEYY) 1993 - present
MEDLINE In PROCESS via Dialog Datastar (MEIP) Latest few weeks
EMBASE via Dialog Datastar (EMYY) 1993-present
EMBASE Alerts via Dialog Datastar (EMBA) past 8 weeks

BIOSIS (for ASH abstracts) via Dialog Datastar (BIYY) 1993 - present
Cochrane Library CENTRAL Via Wiley internet - all dates
No details of issue of Cochrane Library searched are given but the ERG have assumed 2009 Issue 2

The full search strategies are detailed in appendix 2 section 9.2 of the submission. The searches were run on 18 June 2009 (MEDLINE and EMBASE) and 12 June 2009 (MEDLINE In PROCESS EMBASE Alerts and BIOSIS) 1 July 2009 (Cochrane Library)

ERG comments:

-No language limits were stated so the ERG assumes none were applied

-There were inconsistencies between strategies in terms of use of synonyms for e.g. the alternative term rituxan was not used in MEDLINE or EMBASE or BIOSIS while it was used in EMBASE Alerts and MEDLINE In PROCESS. The term mabthera was not used in any of the strategies.

- A combination of textwords and index terms were used to express the population (relapsed/refractory chronic lymphocytic leukaemia) and intervention (rituximab) which should make for a sensitive search and ensure studies were not missed. However the strategies were not transferred consistently between databases for e.g. the MeSH term for chronic lymphocytic leukaemia was omitted from the strategy as used on the Cochrane Library's CENTRAL database but was used with MEDLINE and EMBASE. The strategies for use on MEDLINE , EMBASE and CENTRAL did not allow for alternative spellings of leukaemia which could mean studies were overlooked .

- The ERG ran two versions of the search on CENTRAL to ensure relevant studies had not been missed. The ERG's more comprehensive version resulted in 21 hits on CENTRAL. A replication of the manufacturer's version located 13 trials. The ERG examined the extra references and none were found to be relevant.

- It was stated in the submission that "randomised and non randomised studies were filtered out using the same searches" but it is not clear how this

was done. The clinical trials filter only appears to have been used with MEDLINE (line 10 of strategy 1 (9.2.4)) and not with EMBASE. Presumably the search results were screened to locate randomised and non-randomised studies (as shown in flowchart figure 2 of the submission) however if the 214 refs (line 13) have already been subject to a publication type filter for clinical trials, it is unclear why was this not applied to the EMBASE set (191). 257 studies in the MEDLINE set had already been removed pre-screening – it may have been more consistent to either manually screen both sets or to apply a study filter to both sets. The ERG replicated this search to examine whether the inconsistency was likely to have resulted in omission of any relevant references and concluded this was unlikely.

Ongoing studies

The manufacturer noted that "There are no ongoing trials from which additional evidence will be available in the time period specified (i.e. the next 12 months)."

ERG Comment:

There was no record of ongoing trials registers being searched in the submission. However when this question was raised in the clarification document the manufacturer did send details of trials register searches. A search of ClinicalTrials.gov using the following terms: relapsed refractory chronic lymphocytic leukaemia (condition) and rituximab (intervention) located 29 studies. A list of the studies was provided including reasons for their exclusion/inclusion.

The ERG carried out searches of UKCRN Portfolio, Current Controlled Trials MetaRegister and ClinicalTrials.gov and 211 studies (including duplicates) were located and examined. Two ongoing trials were identified that compare rituximab and alemtuzumab. Alemtuzumab was not included as a relevant comparator in this appraisal.

- NCT00771602: A Randomized Trial of Rituximab vs Alemtuzumab vs Alemtuzumab + Rituximab as Consolidation Therapy for Patients With

Chronic Lymphocytic Leukemia (CLL) With Evidence of Residual Disease Following Prior Chemo(Immuno)Therapy

- NCT00086775: A Phase II Trial Comparing Combination Treatment With Fludarabine and Alemtuzumab to Fludarabine and Rituximab in Patients With B-Cell Chronic Lymphocytic Leukemia Requiring Treatment After First Line Therapy

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

There were no formal inclusion and exclusion criteria presented in the submission. Upon request for clarification, the following information was provided:

Randomised controlled trials: *Exclusion criteria*: not a trial; duplicates; not CLL; not a randomised controlled trial including R-chemotherapy in first line CLL; not a comparative randomised controlled trial; first-line CLL *Inclusion criteria*: all remaining trials

This information does not provide details on eligible patients, interventions and comparators with respect to the study question. A patient group for whom rituximab therapy in combination with various chemotherapy regimens might be of benefit was not defined *a priori* (see also sections 3.1, 3.2 and 3.3 on the decision problem). The submission has been mainly based on the REACH trial, which compares FC with R-FC. The REACH trial is the only trial on which the licensing information is based and the scope specifies clinical and cost effectiveness of rituximab within its licensed indication. The draft SPC does not specify a particular chemotherapy regimen. Other patient groups were considered in non-RCT studies in the submission, but again no formal inclusion and exclusion criteria were given. These included patients that were refractory to or could not tolerate fludarabine.

The submission presented flowcharts of inclusion and exclusion of studies based on the CONSORT guidelines (rather than QUOROM guidelines). CONSORT guidelines refer to the follow-up of patients through an RCT and not to the inclusion of studies in a systematic review. It is apparent that the flowcharts were not based on a formal set of inclusion and exclusion criteria. Upon request for clarification, no amended versions were supplied.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded.

The REACH trial is the only included RCT. This is an unpublished study and has not been peer reviewed.

One additional RCT, Hillmen 2007(Hillmen et al.), is described below (see section 4.1.4). The study by Robak 2007(Robak et al. 107-13) is described in the submission as a randomised phase II study. It is in fact a historically controlled study (n=46).

Twenty non-randomised, mainly uncontrolled studies were included (including Robak 2007). As there are no formal inclusion and exclusion criteria it is unclear how they were selected. The first group of studies (Table 5, p37) were described as being “the full set of phase II studies that highlight the efficacy and tolerability of rituximab in combination with a variety of chemotherapy regimes in the relevant population”. Studies grouped in tables 6 and 7 (p39, 40) were described as supporting the evidence on the efficacy of rituximab containing regimens in patients with fludarabine-refractory CLL and on the efficacy of re-treatment with rituximab-containing regimens in patients with relapsed/refractory CLL. The majority of these studies (15/20) included chemotherapy regimens not specified in the NICE scope. Data from these studies is presented in the results section of the submission, but none is used in the economic model. There was no list of excluded studies.

4.1.4 Details of any relevant studies that were not included in the submission ?

The study by Hillmen 2007(Hillmen et al.) was a randomised controlled trial comparing fludarabine, cyclophosphamide and mitoxantrone (FCM) without

rituximab versus FCM with rituximab. (Mitoxantrone is currently licenced for use in the UK but not for CLL). The RCT was included in the submission in Table 5 (p37), which lists non-randomised studies to support the evidence on the efficacy and tolerability of rituximab in combination with different chemotherapy regimens. In response to a request for clarification on why this study was not eligible for inclusion, the manufacturer stated that despite being randomised, the study was non-comparative as its design did not allow a statistical comparison between the treatment arms. This was a small trial (n=52) with a primary endpoint of response (according to NCI criteria) after two months. Results in 46 evaluable patients suggested greater numbers of patients in the rituximab arm compared to the non-rituximab arm showed complete response or complete remission with incomplete marrow recovery (10/23 versus 3/23). In showing an advantage for patients receiving rituximab, these results are consistent with REACH, although they do not provide any information on PFS or OS, and also included mitoxantrone, which was not included in the NICE scope as a comparator.

4.1.5 Description and critique of manufacturers approach to validity assessment

The submission used a standard set of questions to assess the validity of the REACH trial, which is appropriate (Table 26, p80). The manufacturer's responses together with comments made by the ERG are listed below.

Criterion	**Submission response** **REACH (BO17072)**	**ERG comments**
How was allocation concealed?	REACH was an open-label study. Placebo control for a study involving IV rituximab administration and pre-medication would have been very difficult and probably considered unethical. All Phase III rituximab studies to date have been open-label. End-points measured were objective and any potential effect obtained by infusing a placebo rituximab would have been unable to significantly confound the results.	The manufacturer's initial comments (see column to the left) referred to blinding rather than concealment of allocation. After requesting further clarification, the manufacturer stated that patients were allocated using a central interactive voice response system (ClinPhone). This appears to be an appropriate method of allocation concealment.
What randomisation technique was used?	Patients were randomized using a dynamic allocation method, which is an appropriate method for randomising a Phase III study.	This is an appropriate method. One of the advantages of dynamic randomisation is to allow several patient characteristics to be balanced between groups. However, the method has been criticised for the possibility of allowing predictability, as the assignment

		to a particular group depends on the characteristics of the participants already in that group, and so is not completely random for every patient. However, this is unlikely to have a substantial effect on results.
Was the sample size justified adequately?	Yes. See section 6.3.5	The initial sample size calculation appeared adequate. The planned sample size was 550 (recruited 552) to detect a treatment different in terms of median PFS of about 50.5% (HR=0.664) with a power of 80% at an overall alpha level of 1%. However, the power calculation did not compensate for potential loss to follow-up. Only 233/552 (42%) patients continued in follow-up (this is defined as the period starting 28 days after the last treatment cycle).
Has there been adequate follow-up?	Yes At the time of final analysis (data cut-off July 23 2008), with a median observation time of 25.3 months, the study demonstrated a highly statistically significant improvement in PFS with the addition of rituximab to FC. This PFS benefit was robust and apparent in almost all pre-specified subgroups. It is appreciated that the OS data are immature and did not demonstrate a statistically significant advantage when rituximab was added to FC. This is maybe unsurprising given median OS in CLL is 5-10 years plus OS benefits may be masked by subsequent treatment options. Nonetheless, OS data will continue to be collected with further results with a longer period of follow-up becoming available in 2010.	The trial is planned to have a follow-up period of 8 years, which is an adequate follow-up time given the median survival times of patients, and is likely to be sufficient to measure differences in progression free survival and other outcomes. Accurately measuring OS, as the submission states, would still be difficult due to confounding effects of crossovers. At the cut-off date for REACH data analysis (25.3 months median observation time), just over half of patients (57.2% in FC arm, 47.8% in R-FC arm) had experienced an event (death or progression). 75.36% and 77.54% (FC and R-FC arm) were still alive. Median overall survival had not yet been reached in the R-FC arm. Thus a large proportion of the data is censored and this needs to be taken into account when interpreting the results. See also section 4.2.1 for interpretation of the survival curves. More recent data was not available at the time of writing this report.
Assessors aware of treatment allocation?	It is likely that assessors were aware of treatment allocation in this study, however, the assessment of CLL post treatment is very objective and it is very unlikely that this will have biased results. In addition, an independent assessment of the data was performed at the interim and final analysis, where patients were in a blinded manner assessed for response and progression based on peripheral blood counts, bone marrow biopsy results, CT scans and reports of physical examination. These data, however, have not yet become available.	The trial was open-label, and patients and study investigators were aware of treatment allocation after randomisation. The reason given for this is that placebo infusions of rituximab would have to be given in the FC-arm, which is impractical. Also, infusion related reactions would be more likely to occur in the R-FC arm. He open-label nature of the study is unlikely to influence very objective outcome measures such as death, but may have an effect on determining progression and in particular QoL measures. It would have been possible to blind outcome assessors and it appears this was done through an independent assessment of response and progression. The results of this independent assessment were made available to the ERG and are discussed in the results section. The independent and blinded assessment has resulted in a less pronounced advantage of R-FC over FC in terms of PFS.
Was the design parallel group or cross-over?	Parallel-group The primary end-point of PFS would not be influenced by post-study treatment, and start of a new (i.e second line) CLL	This was a parallel-group design, which is appropriate. Crossover of patients did occur, but due to treatment failure not as part of the trial

	treatment post randomisation was not considered an event or a reason for censoring.	design. This is relevant for OS as discussed above.
Was the study carried out in UK? **and** **How does the population compare with patients who are likely to receive R-FC in The United Kingdom?**	REACH was an international study including the UK. There are no obvious differences between the study population and non-trial patients requiring treatment for chronic lymphocytic leukaemia in the UK, except, perhaps that the study patients are slightly younger (median age of 63 compared to median age at diagnosis of 65-70 for non-trial patients). The vast majority (99%) of patients in the trial were caucasian, which would compare very favourably with a British population. Indeed the highest recruiting countries (France, Russia, Poland, and Canada), all provide a demographic of patients that would be very similar in general to The United Kingdom. Disproportionate recruitment of younger patients is a general problem in oncology clinical trials – the study had no upper age limit for participation, and the oldest patient recruited was 83.	Patients were recruited at 88 centres in 17 countries, the majority were from France (16%), Russia (14%), Poland (13%) and Canada (10%). Between 3-7% of patients were from other countries including the UK. Only 2 patients were recruited from the US. Prior treatment may differ in these countries compared to the UK. Median age at diagnosis is 65-70, so at 1st relapse is likely to be higher. The population in the REACH trial is therefore younger than expected. Older patients may be less able to tolerate side effects from rituximab. 10% of patients in REACH had Binet stage A disease. Clinical opinion suggests that in the UK stage A patients would not normally be treated unless they had a very poor prognosis, so this proportions seems very high. There are no fludarabine refractory patients in REACH (as treatment includes fludarabine), however, there are such patients within a UK rituximab-eligible population. Almost 8% of UK population are from ethnic groups other than white, so slightly more than in REACH. There is no evidence of genetic variation of disease according to ethnicity so this is unlikely to make a difference. 8% of patients in REACH had del17p. Estimates from the literature put the proportion of CLL patients with p53 mutations at between 4-15%.(Dierlamm et al. 27-35)
Was the dosage regimen acceptable and justifiable?	Currently, the licensed, approved dose for rituximab in lymphoma (whether monotherapy or given in combination with chemotherapy) is 375mg/m^2. It had become apparent from monotherapy dose finding studies in CLL (O'Brien et al, 2001), that there was an increasing response in CLL patients as the dose increased up to 2250mg/m^2. On the basis of this, groups starting Phase II studies of R-FC in CLL (specifically Keating et al. and Wierda et al. at The MD Anderson Cancer Center in The United States) felt that the lymphoma dose was not appropriate for CLL and a higher dose would be required. 500mg/m^2 was decided upon as an acceptable higher dose for CLL patients to use in combination with FC. The dosing chosen in REACH was based on the MDAAC Phase II studies. A dose reduction of 375mg/m^2 in cycle 1 was	The doses used seem appropriate, however, both fludarabine and cyclophosphamide were given as an IV infusion in REACH. This is different to UK practice where these drugs would be given orally. Where oral doses have been used in the economic model, these are based on conversions from the iv doses and are thus not actual doses used in REACH (see section 5.1.4 for further details on dosing).

	decided on to minimise any potential cytokine release/ tumour lysis that may have been triggered by the known large circulating tumour burden in CLL. This is also the licensed dosing regimen in previously untreated CLL patients as recently approved by the EMEA on the basis of compelling data from the phase III CLL-8 trial. Thus the dosing of rituximab in this study was entirely appropriate and consistent with Phase II R-FC studies in CLL. The dosing used in these Phase II studies was also rationalised and based upon a published dose-finding study as highlighted above. The dosing of fludarabine and cyclophosphamide was the same in both arms. The approved standard dose of fludarabine as monotherapy in patients with relapsed CLL is 25 mg/m^2/day for the first 5 days of each 28-day cycle (usually 6 cycles). O'Brien and colleagues evaluated the safety and efficacy of combined fludarabine (30 mg/m^2) and cyclophosphamide (300-500 mg/m^2) therapy given daily for three days over 6 cycles (4-6 week cycle duration) (O'Brien et al, 2001). A dose reduction in cyclophosphamide from 500 mg/m^2 to 300 mg/m^2 appeared effective in reducing the severity of myelosuppression. Therefore, to improve the safety profile further in the REACH study, an even lower dose of fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2/day) was used. This is the same regimen as used in the MDACC phase II studies (Keating et al, 2005; Wierda et al, 2005). The dosing of R-FC used in this study will be the approved dose in the SmPC.	
Were the inclusion and exclusion criteria appropriate?	The inclusion and exclusion criteria were entirely appropriate and consistent with accepted and validated criteria for running CLL trials. Please note that patients who were previously treated with rituximab were excluded from the study as, at the time of study planning in 2001 and 2002, patients who had received rituximab therapy in the first-line setting were considered rare. At the time (and for most of the recruitment period) no monoclonal antibodies were approved for the first-line treatment of CLL patients. Data on the use of rituximab-containing regimens after failure of first-line rituximab-containing therapy has, however, been reported in more than 200 patients in a variety of small series and case reports. These data will be discussed at length in Section 6.8 in support of guidance that will not exclude CLL patients who have previously received rituximab-containing therapy from treatment with rituximab-containing combinations at relapse, as per the anticipated licence. Patients who were refractory to fludarabine were also excluded from entry into REACH.	The inclusion and exclusion criteria were appropriate for a trial in this area. The population is however not necessarily representative of a UK relapsed/progressed CLL population (see above," *How does the population compare with patients who are likely to receive R-FC in The United Kingdom?*")

	Exclusion of these patients was based on the view that such patients are relatively uncommon (Johnson et al, 1996; Leporrier et al, 1991 Rai et al, 2000, have a poor prognosis, and are unlikely to benefit from further fludarabine-based therapy. This view was based mainly on a retrospective analysis of 147 patients with fludarabine-refractory CLL from the MDACC, available at the time (Keating et al, 2002). Since then, additional efficacy data on patients with fludarabine refractory CLL has become available from the MDACC demonstrating that R-FC is a useful therapeutic option for patients whose disease is refractory to prior fludarabine-containing therapy (Wierda et al, 2005 Wierda et al, 2006). These data are supported by data on other rituximab-containing regimens in fludarabine-refractory CLL and are discussed together in Section 6.8 in support of guidance that will reflect the anticipated licence, allowing "relapsed/refractory" patients to be eligible for treatment with rituximab in combination with chemotherapy.	
Were both arms of the study group comparable?	Yes – as detailed in section 6.3.2, patient characteristics in both arms were well balanced at baseline.	Study groups were well balanced overall across demographics, disease stage, diagnosis history, tumour assessment, haematology, standard laboratory tests, baseline prognostic factors, creatinine clearance values, previous and concomitant diseases and previous chemotherapy. Slight imbalances occurred, particularly where several smaller sub-groups of patients were being compared. This could be expected by chance. In terms of prognostic factors, patients with both more favourable and less favourable chromosomal aberrations were slightly more frequent in the FC group: del13q: 60% FC , 56% R-FC Trisomy 12: 15% FC, 11% R-FC del11q: 59% FC , 56% R-FC del17p:24% FC, 18% R-FC A higher proportion of patients in the R-FC group were CD38+, however CD38 status was not measured for all patients.
Were appropriate statistical tests used?	Yes, fully detailed in section 6.3.5.	Yes, appropriate statistical tests were used.
Was an intention to treat analysis undertaken?	Yes, as fully detailed in section 6.3.5. Efficacy analyses and economic analysis are subsequently presented for the intention-to-treat population.	Efficacy analyses were based on ITT population (defined as all patients who were formally randomised), patients were included in the analysis regardless of whether they received treatment or not. Patients who withdrew or crossed over were censored. Safety data were based on safety analysis population, defined as all patients who received at least one dose of trial treatment and had at least one safety follow-up.
Are there any confounding factors	There are not thought to be any confounding factors that attenuate the	We agree that a difference in OS will be difficult to show. At the time of analysis

that may attenuate the interpretation of the study?	interpretation of the primary endpoint and most of the secondary endpoints. For the analysis of overall survival, it is likely that subsequent treatment options will limit the ability to show an overall survival benefit in favour of R-FC, an issue that has been seen in a number of Phase III CLL studies.	(median 2.1 years) 34/69 patients in the FC arm had crossed over and received rituximab.

In summary, the REACH trial appears to have adequate randomisation and concealment of allocation. It was however, open label, and both patients and investigators were aware of the treatment received. Investigators and an independent panel acted as outcome assessors (see results section). There was less of a difference in PFS between the treatment arms when assessed by the (blinded) independent panel, which may indicate biased assessment by the (un-blinded) investigators. The trial had a planned follow-up of eight years, which appears adequate, however at the data cut-off for this report, patients had been observed for a median of 2.1 years only resulting in immature data. The median for OS had not yet been reached for the R-FC arm. There appear to be some differences between the trial population and what you would expect in an 'average' UK progressed CLL population (which is rituximab eligible). The patients in REACH were relatively young and 10% were classified as Binet stage A, a stage at which patients are rarely treated in the UK. There were no fludarabine refractory patients in REACH. It should be noted that the ERG's assessment is based mainly on the submission and the clinical trial report was not analysed in detail. REACH has not been published in the peer reviewed literature.

4.1.6 Description and critique of manufacturers outcome selection

The primary clinical effectiveness outcome was progression free survival (PFS). Secondary clinical effectiveness outcomes were: event free survival (EFS); disease free survival (DFS) in complete response (CR) patients; duration of response; overall response rate (ORR) for CR, partial response (PR) and nodular PR (nPR) patients; overall survival (OS); molecular remission; adverse events (AE); and quality of life (QoL).

CLL has a long median survival, so differences in OS may not become apparent for several years. However, the patients were probably fitter and younger than the UK population eligible for treatment. PFS is an appropriate

outcome measure, particularly as the REACH trial, on which most of the clinical evidence is based, has not yet finished (median duration of 2.1 years at time of data analysis). In addition, the crossover of patients who do not respond on FC to the R-FC arm has a confounding effect on effectiveness results and makes it increasingly difficult to gauge the difference in overall survival between the two treatment arms as time progresses. At the time of analysis (median 2.1 years) 34/69 patients in the FC arm had crossed over and received rituximab.

Time to progression can be distinguished from the time to death once progressed. However, without median overall survival data, the REACH trial cannot be used to calculate the time to death once progression has happened for rituximab compared to FC alone. The reason there was little survival data at the time of analysis is because the trial had not yet run for long enough and because patients in REACH were relatively young compared to what you would expect in an average relapsed/progressed population and are thus surviving for longer. In addition, crossover from the FC to the R-FC arm acted as a confounder.

QoL data was measured for one year only. Upon request for the rationale for this, the manufacturer replied that this was the schedule determined by the REACH study group and was endorsed by the ethics committee. QoL was measured using the FACT-G. The EQ-5D measure would have been useful as this generates a utility measure between 0-1, which could have been used to calculate QALYs (quality adjusted life years) but was not used in REACH.

4.1.7 Describe and critique the statistical approach used

The statistical approach used is described in section 4.2.1 below as it mostly refers to handling of the results from the REACH trial. As there was only one included study, no meta-analysis was possible.

4.1.8 Summary statement

Although there were some inconsistencies in the manufacturer's search strategy, the ERG did not identify additional relevant RCTs relating to the study question as defined by NICE. The decision problem in terms of eligible

study population and eligible comparators was poorly defined in the submission as there were no formal inclusion or exclusion criteria either for RCTs or non RCTs. Instead the population was defined on the basis of the REACH trial and other non-randomised studies. The ERG did not attempt to replicate the identification of relevant non-randomised studies, so we cannot be completely confident that these were selected in an unbiased fashion.

REACH is an ongoing, unpublished study. The data within REACH used for this submission was immature as a median observation time of only 2.1 years had been achieved (the trial is scheduled to run for eight years). Only data from the investigators' assessment was included in the submission, however, the independent assessment data was provided at a later date.

4.2 Summary of submitted evidence

4.2.1 Summary of results

1. REACH trial

Patients

26% of patients in REACH were alkylator refractory. The remainder were alkylator sensitive (56%) or had been treated with fludarabine (16%) or sequential alkylating agents and fludarabine (1%). 66% of patients had had monotherapy with an alkylating agent and 16% had had monotherapy with fludarabine or cladripine or both. 18% of patients had had prior multi-agent chemotherapy. Alkylator refractory was defined as (from Table 8 in the submission on p48):

Definition

- Patients' best response to first line alkylator therapy is PD/SD after a minimum of 8 (PD) to 12 (SD) weeks of single-agent chlorambucil or 2 (PD) to 3 (SD) cycles of alkylator-containing combination therapy.
- Patients have responded (PR/CR) to initial alkylator therapy but had SD as a response to the last course of alkylator therapy.
- After last exposure to first line alkylator treatment, patient has:

1) PD after having been treated with a minimum of 8 weeks or 2 cycles of alkylator therapy or 2) SD after having been treated with a minimum of 12 weeks or 3 cycles of alkylator therapy.

Eligible patients

CHOP/CVP → Best response is SD
CHOP/CVP → Progress through therapy (PD)
Chlorambucil → respond (PR/CR) to first period of treatment → followed by intermittent use of chlorambucil → no response to last period of chlorambucil ie, PD/SD whilst on therapy**.**

Patients with the del17 mutation (8%, n=42) were included in the REACH trial and considered in a sub-group analysis for PFS and BOR. This was a very small group, particularly as a large number of patients were censored (i.e. had not yet progressed or died), and results need to be interpreted cautiously.

Mean age was 61.7 (SD 9.14), median age was 63 (35-83). 57% were younger than 65. 67% were men.

Loss to follow-up/withdrawals (PFS)

At the time of the cut-off for data analysis, a total of 290/552 (53%) patients had experienced an event (death or progression). The remainder had been censored either because they had not yet had an event or had been withdrawn for another reason. As can be seen from the survival curve (next section-PFS) 196 patients are contributing to the analysis at 2 years, 87 at 3 years and 16 at 4 years. These low numbers are partly due to the fact that patients have not yet been in the trial long enough to experience an event, and have been censored. Censored patients also include those who have crossed over to the other treatment arm (34/69 patients from the FC arm who relapsed and have received subsequent therapy for CLL are known to have received rituximab). Greater uncertainty is associated with the survival curve the lower the number of patients at risk. The table below combines information from Tables 22 and 23 of the submission (p65, 66).

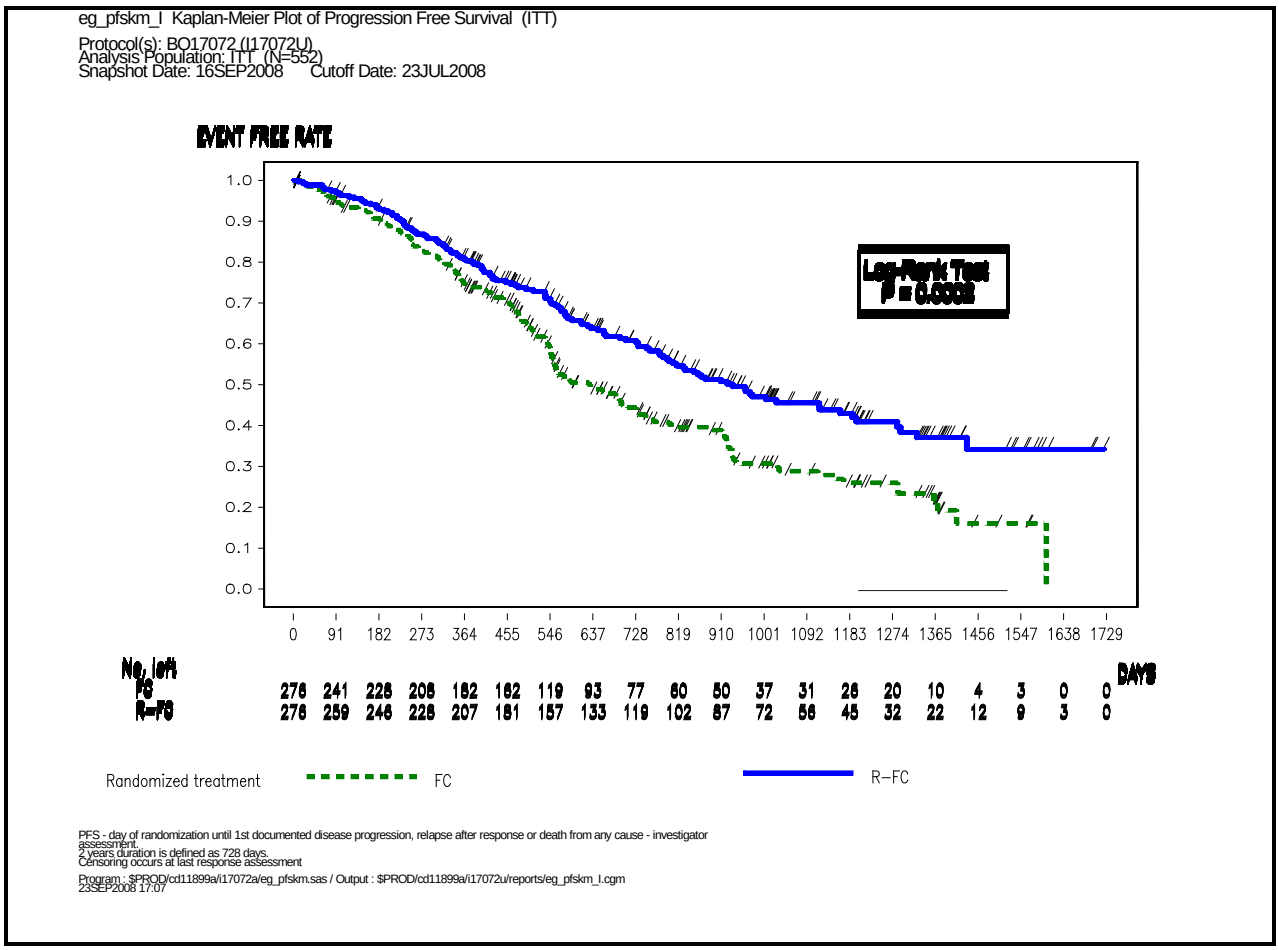
At cut-off 23 July 2008	FC	R-FC
Total with event (progressed or died)	158	132
Censored	118	144
During first 6 months: Prematurely discontinued trial treatment (mainly for safety reasons)	109 (80 of these AE or death)	95 (79 AE or death)
After approx 7 months: Withdrawn prematurely from follow-up phase (main reason insufficient therapeutic response/progressive disease)*	162 (118/258 progressive disease)	131 (96/268 progressive disease)

*follow-up phase starts 28 days after last cycle (i.e. after approx 7 months)

Progression-free survival

This was the identified primary outcome in REACH, and is the most reliably observed of the outcomes relevant to the submitted economic model. There were two sets of results, one based on the investigators' un-blinded assessment, and one based on an independent assessment of progression, which was blinded and therefore might be assumed to be less susceptible to potential bias.

The Kaplan-Meier plot below is taken from p89 of the submission and is based on the investigators' assessment:



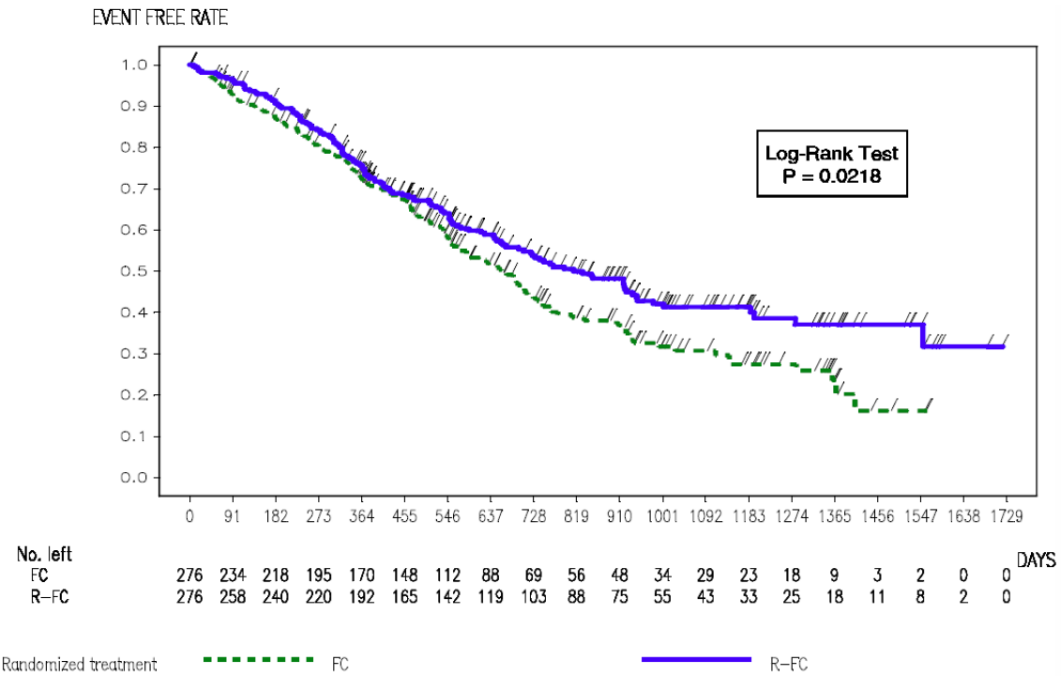
The R-FC and FC curves are similar in slope for most of the time represented but separate from each other especially during a 3 month period from 455 to 546 days (15 to 18 months) when there is a distinct kink in the FC trace. The graph does not indicate the uncertainty associated with the plots and because patient level data was unavailable the ERG was unable to remedy this. The curve for R-FC has a flat tail extending from about 45 to 57 months that is based on analysis of 10 to 20 patients only; consequently this part can be assumed to be associated with considerable uncertainty.

The investigators' assessment indicates that at the cut-off of July 2008, progression or death had occurred in 132 (47.8%) patients in the R-FC arm and 158 (57.2%) patients in the FC arm. The remainder of the patients were censored. Median time to event was 932.0 days in the R-FC arm and 627.0 days in the FC arm. This is a difference of 305 days, or **10.02 months.** The

hazard ratio (unadjusted) of 0.65 (95% CI: 0.51; 0.82) (tables 3 & 27, (p86) submission) was statistically highly significant (p 0.0002).

[redacted]

gure 1: Kaplan-Meier Plot of Progression-Free Survival (IRC Assessment, ITT)



It shows that, at the cut-off point of July 2008, progression or death had occurred in [redacted] patients in the R-FC arm and in [redacted] patients in the FC arm. Median time to event was [redacted] in the FC arm and [redacted] in the R-FC arm. This is a difference of [redacted], or [redacted].

[redacted] The hazard ratio was [redacted].

[redacted]

The results for independent and investigator assessment of PFS differed somewhat but both indicated statically significant superiority for R-FC versus FC. The results from both assessments are contrasted below.

Table 2 PFS results presented for REACH trial

	Investigator R-FC	Investigator FC	Independent R-FC	Independent FC
Number (%) with event	132 (47.8)	158 (57.2)	[redacted]	[redacted]
Number died Number progressed	30 102	25 133		
Number (%) censored	144 (52.2)	118 (42.8)	[redacted]	[redacted]
Median time to event days (months)	932 (30.6)	627 (20.6)		
Median time to event R-FC – FC	305 days; 10.02 months		[redacted]	
Hazard Ratio (95% CI) [P] R-FC versus FC	0.65 (0.51;0.82) [0.0002]		[redacted]	

* assumed as investigator assessment. ** calculated by difference

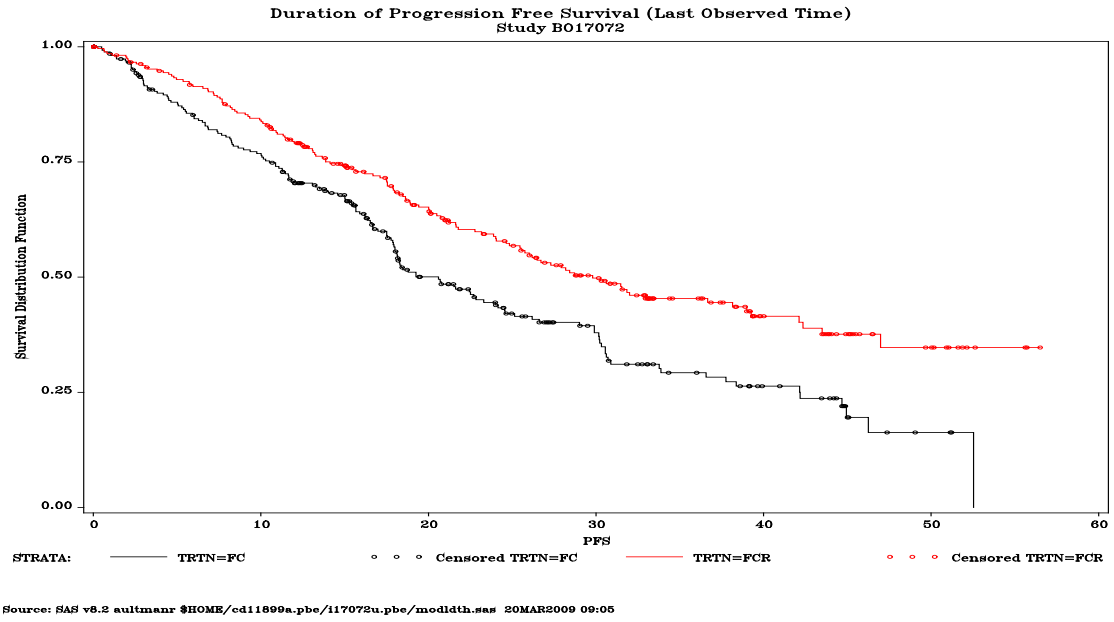
Note; slightly different investigator results presented in submission Table 60 and used in economic mopdelling

The difference between assessments appears to depend on [redacted] FC patients progressed and [redacted] FC patients censored according to the independent assessment, and [redacted] R-FC progressed and [redacted] censored in the independent assessment.

The investigator assessment of PFS was used for economic modelling. In view of the large difference in median time to event between the two assessments [redacted] the ERG considered it desirable that the independent assessment should also be examined to assess the impact that choice of assessment analysis might have on the results of economic analyses. Patient level data were not available so information was extracted from Kaplan-Meier graphs (the methods are described in Appendix 2).

A further investigator PFS analysis was presented in figure 20 of the submission (economic analysis section 7.2.6.9, with summary data in Table 60). In this version the difference in median time to event was 9.2 months (29.8 minus 20.6) and the unadjusted hazard ratio 0.673 (95% CI: 0.528 ; 0.857). The Kaplan-Meier plot accompanying this part of the submission is shown below (time axis assumed to be months):

Figure 20 Progression Free Survival of R-FC versus FC: median follow-up 2.1 years



Comment.

This figure is not referred to in the submission text. The following statement is from the accompanying economic section of the submission (7.2.6.9):

> This economic model uses patient level data for the ITT population to calculate primary efficacy, and consisted of 552 patients (276 patients in FC, 276 patients in R-FC). At the time of the clinical cut-off (July 23, 2008), the Kaplan-Meier estimated median PFS was improved by 10 months, from 20.6 months with FC to 30.6 months with R-FC.

However elsewhere on this and the next page: (ERG inserted bold font):

> Cross-over is already known to have occurred in the BO17072 study. In the FC arm, 34/69 patients who relapsed have received subsequent therapy for CLL are known to have received rituximab, either in combination with a chemotherapy regimen or as single agent (and 2 more have received another anti-CD20 antibody). This compares with 14/47 of patients who relapsed have received subsequent rituximab containing therapy for CLL in the R-FC arm.
> **Consequently, in this economic analysis of BO17072, patients who remained in PFS but crossed over to alternative CLL therapy were censored at the time of cross-over.**

The ERG found the submission somewhat unclear here about which investigator PFS analysis was actually used for modelling.

It is notable the benefit of R-FC versus FC for progression-free survival in relapse therapy is substantially less than that observed for R-FC versus FC in first line therapy (for details see Appendix 4)

Sub-groups (PFS, investigators' assessment)

Sub-group analyses were conducted for sub-groups of patients based on 20 categories (p100-101 of submission) resulting in 48 sub-groups. The risk of progression or death was reduced in 46/48 sub-groups for the R-FC arm compared to the FC arm. The risk of progression was increased in the R-FC arm for two categories (time from diagnosis ≥ 10 years and negative CD38 status, though the latter parameter was not measured in all patients), but the HRs were close to 1 and not statistically significant. All confidence intervals overlapped within and between categories. Tests for statistical differences between sub-groups were not performed. There was a fairly large difference of benefit according to age (HR of 0.47 (0.34-0.66) for <65, HR of 0.87 (0.56-1.33) 65-70 and HR of 0.99 (0.58-1.69), with older patients benefiting less from R-FC compared to FC. This is in line with the observation that patients with less than 10 years since diagnosis tend to benefit less. Both patients with and without del17p appear to benefit from R-FC compared to FC, though there was no significant difference between FC and R-FC for patients with the del17 mutation.

Due to the large number of sub-groups some differences seen may be due to chance. As these sub-groups were not powered to show a difference (and are based on only 2.1 years median observation time with many patients censored), any differences must be interpreted with caution and treated as exploratory investigations. This does not mean that such differences do not exist. Further evidence may be needed to look at the effect of R-FC versus FC in older patients with a long time since first diagnosis.

Subgroups (PFS, independent assessment)

Results were not significantly different to the investigators' assessment of subgroups.

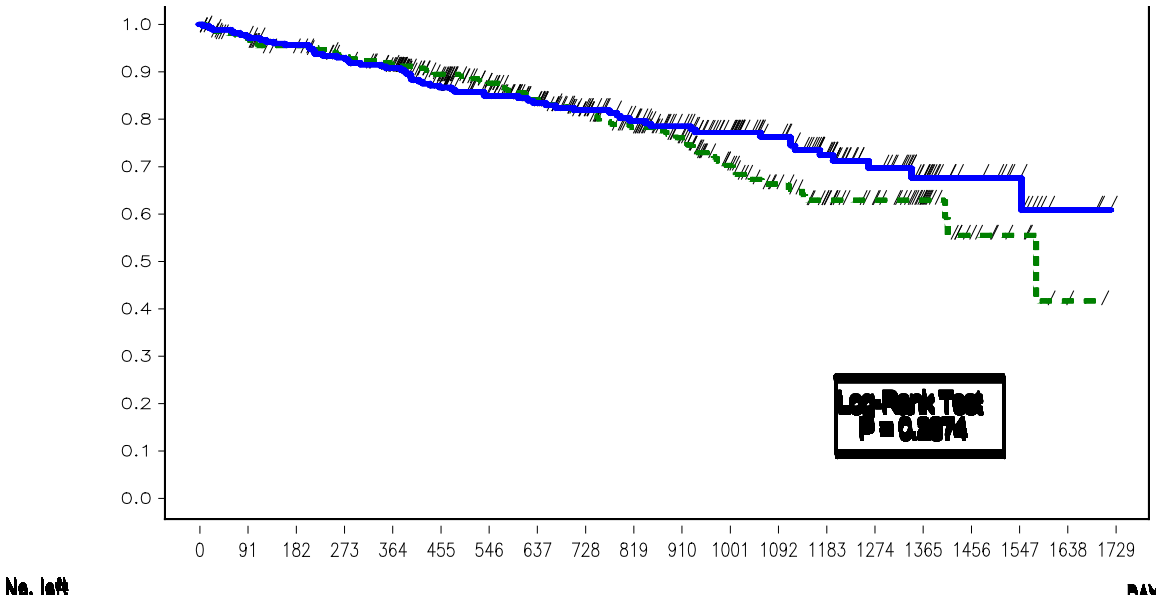
[redacted]

[redacted]

Overall survival

In the REACH trial overall survival was defined as a secondary outcome. At a cut off of July 2008, 68 and 62 patients had died in the FC and FC-R arms respectively. Median survival was not reached and the unadjusted hazard ratio was 0.83 (95% CI: 0.59 ; 1.17. P = 0.287). The Kaplan-Meier plot from the submission is shown below (dashed line = FC arm):

Kaplan-Meier Plot of Overall Survival (ITT)



Comment

There was no indication of the uncertainty associated with the curves.

Up to 910 days (2.5 years) the curves are the same for both arms; after 2.5 years the curves separate with better performance in the R-FC arm. At cut off 208 (75%) of patients in the FC arm were alive and therefore at 2.5 years at least this number had survived. The number at risk for analysis in the FC arm at 2.5 years however is only 101. Thus more than half the live patients have

been censored in the FC arm by the time the curves separate. It is possible that the 101 patients remaining in the analysis at risk may not be representative of the whole population of at least 208 FC-live patients. Patients may have been censored by reaching cut off without dying, while a further major reason for censoring is likely to be transfer to alternative treatment(s) (including rituximab for the FC arm) and this is likely to occur more in the FC arm and to be considered for patients selected on clinical grounds leading to imbalance between arms. The ERG requested clarification regarding reasons for censoring as follows:

"*The submission indicates that many patients were censored for progression free and overall survival (Figures 8 and 9 (p89, 91)). We are interested in numbers of patients censored because a) they reached the end of the trial without an event and b) because they were lost to follow-up before reaching the end of the trial. We are also interested in the reasons for loss to follow-up. Please provide further information on censoring and loss to follow-up, some example tables are provided in a separate attachment as a guide.*"

Some further information was provided about withdrawals from treatment but the numbers censored because they had reached cut off without an event was not supplied; the relevant part of the manufacturer's response is shown below:

> In terms of patients who reached the clinical cut-off date without an event (and were not withdrawn for any reason), this analysis has not been performed. If required by NICE however, this analysis can be programmed by the study statistician and forwarded on subsequent to this document.

There was insufficient time available to follow up the request.

In summary the comparison of treatment arms after 2.5 years loses some of the benefit of randomisation and is susceptible to potential bias, while the comparison up to 2.5 years shows no difference between trial arms. An alternative interpretation is that two years after completion of the six-month treatment cycle, rituximab exerts an effect on overall survival in some way, for example from an influence upon the development/evolution of unwanted cell clones in the bone marrow subsequent to end of treatment. As stated in the submission, when further data becomes available, crossover between treatment arms is likely to confound interpretation of any differences.

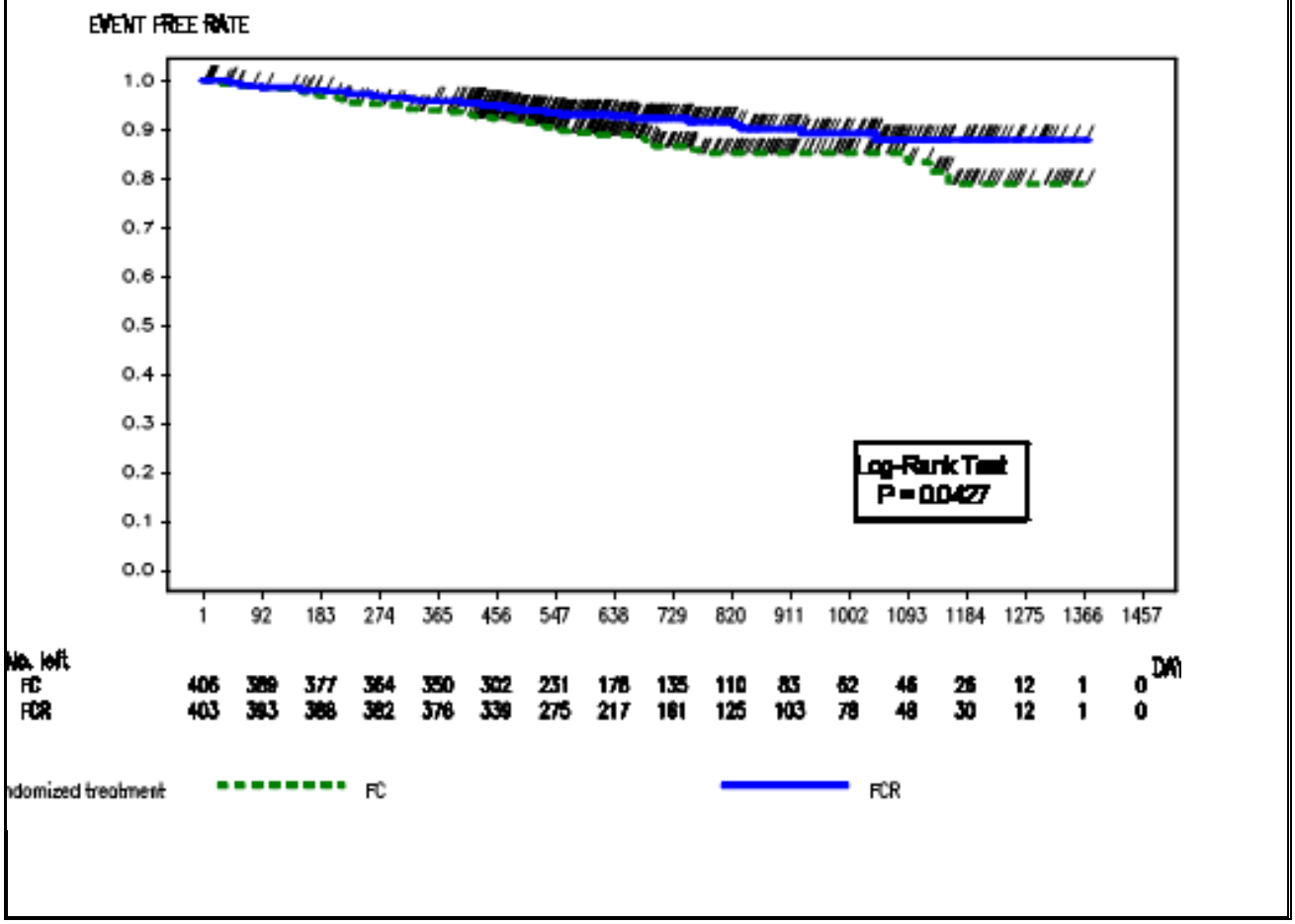
The evidence for rituximab benefit in overall survival is an important question in the context of the economic modelling presented by the manufacturer (see the economic section of this report) because the model generates an advantage for rituximab in overall survival. The ERG consider that an assumption of overall survival advantage is well supported by the evidence available from the REACH RCT.

In response to a request for clarification about the handling of overall survival in the economic model the manufacturer stated as follows:

> The final guidance associated with the 1st line CLL treatment with rituximab (TA174 Section 4.3) also suggested that the committee were persuaded by clinical evidence that an overall survival advantage was likely (though it was difficult to quantify).

This implies that because some evidence for overall survival advantage was found for rituximab in first line therapy then a similar advantage is likely to hold for relapse therapy (i.e. the present case). The ERG therefore examined the evidence from the manufacturer's submission about first line therapy (available in the public domain NICE website). In this appraisal the CCL-8 trial provided evidence. At cut off, 48 (11.8%) and 33 (8.2%) patients had died in the FC and R-FC arms respectively. The adjusted hazard ratio was 0.64 (95% CI: 0.41; 1.00. P = 0.048). The appropriate Kaplan-Meier plot of overall survival for R-FC versus FC is shown below.

Kaplan-Meier overall survival. CCL8 trial rituximab in first line therapy



Comment

There are a third more patients in this trial than in REACH. The FC and R-FC curves separate early (in favour of R-FC) and remain separate throughout the analysis. The numbers at risk diminish rapidly (even though most patients remain alive) so that by 911 days only 83 patients remain at risk in the FC arm. The evidence for an overall survival advantage from rituximab, although weak, is more substantial than in relapse therapy.

Other outcomes

Other outcomes measured in REACH were event free survival (EFS); disease free survival (DFS); best overall response (BOR) at any time prior to disease progression or subsequent treatment (BOR=complete response (CR), partial response (PR) or nodular partial response (nPR), see submission p68); duration of response; and end of treatment response (ETR).

For EFS, there was a difference of 9.4 months between treatment arms, favouring R-FC (statistically significant). The proportion of patients with a BOR of CR, PR or nPR was significantly higher in the R-FC arm compared to the FC arm (69.9% and 58.0%). The proportion of patients with a response at end of treatment was significantly higher in the R-FC arm (63.4% compared to 52.9%). The median duration of response was also significantly longer in the R-FC arm (39.6 months versus 27.6 months).

There was little difference in disease free survival (DFS) in those patients who had achieved complete response. Disease free survival was defined as the interval from first documented CR to disease progression or death in patients with a BOR of CR. 103 patients achieved a CR and were included in this analysis, two thirds of which came from the R-FC arm. Similar numbers of patients progressed or died in the R-FC and FC arm (28.4% and 27.8%) and the median time to progression or death for the R-FC and FC arms was 39.6 months and 42.2 months. This is based on relatively small patient numbers but does not show an advantage for patients who achieved a CR in the R-FC arm.

Except for disease free survival, these results are consistent with the PFS results, i.e. show an advantage for R-FC over FC. As none of these results are utilised in the economic model, they have not been analysed in detail by the ERG.

As for the PFS and OS results, a large proportion of patients will have been censored at the data cut-off point and are therefore not contributing to these results. All these results are based on the investigators' assessment and are likely to be subject to similar biases as the PFS results.

The independent assessment results were also available for these outcomes, except EFS. The proportion of patients with a BOR of CR or PR was [redacted] in the R-FC arm and [redacted] in the FC arm [redacted]. The proportion of patients with a response at end of treatment was [redacted] in the R-FC arm

[redacted]

[redacted] The median duration of response was [redacted]. For disease free survival, [redacted] patients in the FC arm and [redacted] patients in the R-FC arm achieved a CR. Of these patients, [redacted] patients in the FC arm [redacted] and [redacted] in the R-FC arm [redacted] progressed or died. The median time to disease progression or death for patients achieving a CR was [redacted] in the FC arm and [redacted] the R-FC arm. This was based on small patient numbers.

Adverse events

Safety analyses of REACH were based on the safety population, which according to the submission (p78) included all patients who had at least one dose of trial treatment and at least one safety follow-up regardless of whether they withdrew prematurely or not. These data included patients who relapsed and received subsequent rituximab therapy (34/69 patients in FC arm and 14/47 patients in R-FC arm).

In the rituximab arm, between 89% and 96% of those receiving rituximab received ≥90% of the scheduled dose. At the time of analysis, around 63.8% of patients had received 6 cycles of therapy, see information from the submission (Table 40, p109) below:

Table 40 Treatment cycles received

Summary of Number of Treatment Cycles Received (SAP)

Number Of Cycles Received	FC N=272 No.(%)	R-FC N=274 No.(%)
1	272 (100.0%)	274 (100.0%)
2	251 (92.3%)	262 (95.6%)
3	236 (86.8%)	250 (91.2%)
4	209 (76.8%)	228 (83.2%)
5	197 (72.4%)	212 (77.4%)
6	167 (61.4%)	185 (67.5%)

A cycle is counted as received in case a patient got at least one study treatment component (non-zero dose) in that cycle.

The information below (Table 41, p110) taken from the submission gives an overview of AEs.

Table 41: Overview of AE incidence

	FC N = 272 No. of patients (%)	R-FC N = 274 No. of patients (%)
Any AEs	260 (96%)	270 (99%)
Grade 3/4 AEs	200 (74%)	219 (80%)
SAEs	130 (48%)	137 (50%)
Fatal AEs	26 (10%)	36 (13%)
AE leading to treatment discontinuation	69 (25%)	72 (26%)
AE leading to dose modification/interruption	105 (39%)	141 (51%)
Total deaths	68 (25%)	62 (23%)
Treatment-related deaths	14 (5%)	19 (7%)

There were slightly more grade 3 or 4 AEs, serious AEs (SAEs), fatal AEs, AEs leading to treatment discontinuation or dose modification/interruption, and treatment related deaths in the R-FC arm, and more total deaths in the FC arm. Treatment-related SAEs were observed in 36% of patients in the FC arm compared to 39% of patients in the R-FC arm.

Almost all patients experienced an AE, with patients in the R-FC arm experiencing slightly more (1468 AEs in FC arm versus 1797 AEs in R-FC arm). A more than 2% higher incidence was experienced in the R-FC arm compared to the FC arm for nausea, vomiting, constipation, neutropenia, febrile neutropenia, granulocytopenia, pyrexia, chills, cough, pruritus, urticaria, hypotension, hypertension and myalgia.

The number of grade 3/4 AEs are shown below (Table 64, p183 from submission). Overall, there were more grade 3/4 AEs in the R-FC arm (65%) compared to the FC arm (60%).

Table 64: Grade 3 and 4 adverse events

Preferred Term (MedRA 7,1)	Grade of Severity	FC Total Events	R-FC Total Events
AGRANULOCYTOSIS	3	6	4
AGRANULOCYTOSIS	4	4	9

Table 64: Grade 3 and 4 adverse events

Preferred Term (MedRA 7,1)	Grade of Severity	FC Total Events	R-FC Total Events
ALANINE AMINOTRANSFERASE INCREASED	3	0	2
ANAEMIA	3	33	30
ANAEMIA	4	6	8
ANAEMIA HAEMOLYTIC AUTOIMMUNE	3	1	0
ANAEMIA HAEMOLYTIC AUTOIMMUNE	4	3	0
ANGINA PECTORIS	3	0	1
APLASIA PURE RED CELL	3	1	0
APLASIA PURE RED CELL	4	0	2
BICYTOPENIA	3	3	0
BRONCHITIS	3	1	3
BRONCHITIS	4	0	1
CHILLS	3	0	4
CYTOMEGALOVIRUS INFECTION	3	1	0
DIARRHOEA	3	1	3
FEBRILE BONE MARROW APLASIA	4	1	1
FEBRILE NEUTROPENIA	3	26	24
FEBRILE NEUTROPENIA	4	4	10
GRANULOCYTOPENIA	3	17	26
GRANULOCYTOPENIA	4	14	37
HAEMATOTOXICITY	3	1	0
HAEMOGLOBIN DECREASED	3	2	0
HAEMOLYSIS	3	0	2
HAEMOLYTIC ANAEMIA	3	2	2
HAEMOLYTIC ANAEMIA	4	1	0
HYPOTENSION	3	0	3
HYPOTENSION	4	0	2
LEUKOPENIA	3	8	11
LEUKOPENIA	4	2	2
LYMPHOPENIA	3	2	5
NEUTROPENIA	3	130	117
NEUTROPENIA	4	91	136
NEUTROPENIC INFECTION	3	2	1
NEUTROPENIC INFECTION	4	1	0
NEUTROPENIC SEPSIS	4	5	1
PANCYTOPENIA	3	6	3
PANCYTOPENIA	4	0	4
PNEUMONIA	3	9	2
PNEUMONIA	4	3	3
PYREXIA	3	4	6
SEPSIS	3	0	3
SEPSIS	4	1	0
SEPTIC SHOCK	4	1	1
SINUSITIS	3	0	2
TACHYCARDIA	3	0	3
THROMBOCYTOPENIA	3	18	26
THROMBOCYTOPENIA	4	5	5
VOMITING	3	5	6

The AEs occurring most frequently were neutropenia (and febrile neutopenia), anaemia, granulocytopenia and thrombocytopenia.

It should be noted that there were some inconsistencies in the submission in the listing of grade 3/4 AEs. In Table 43 of the submission (p112) hepatitis B is listed as a grade 3/4 AE. There were 6 cases in the R-FC arm and none in the FC arm. However, hepatitis B is not listed in Table 64 of the submission (p183) and does thus not contribute to the costing of AEs. Another AE classified as grade 3/4 or a SAE but was not included in Table 64 was tumour lysis syndrome, which occurred in 9 (3%) of patients in the FC arm and 6 patients (2%) in the R-FC arm.

Further, the percentages listed in section 7.2.7.4, p182 (65% and 60%,) do not correspond to the percentages listed in Table 41, p110 (74% and 80%), although both detail grade 3 or 4 AEs. It is also unclear what the overlap is between grade 3/4 AEs and serious AEs is, and why SAEs are not included in Table 64 of the submission (which is the basis for costing). A table of all SAEs would have been helpful.

Despite the reporting inconsistencies, the types of AEs occurring seem to be consistent with those expected for the treatments.(European Medicines Agency)

The submission notes an observed imbalance between neoplasms (17/272 (6%) in the FC arm and 23/274 (8%) in the R-FC arm. After exclusion of non-malignant neoplasms, benign disorders, malignancies representing progressive CLL and malignancies likely to have been present before study entry, 12 cases in each treatment arm remained.

No cases of severe cytokine release syndrome were reported. These are more likely to occur in patients with high levels of circulating malignant cells. We do not know for how many patients in REACH this was the case, but it is likely that patients from the less severe end of the progressed spectrum were included.

The fact that not all patients had received all their treatment, but the safety analysis is based on all patients, may mean that the overall number of AEs is underestimated and may increase slightly as the trial progresses. We do not know how late after treatment AEs can occur. The manufacturer quotes a report, which states that the median time period from the start of rituximab treatment to the diagnosis of viral infection was 5 months. Cases of late neutropenia, occurring more than four weeks after the last infusion, have been reported.(European Medicines Agency)

Quality of life

FACT-G (Functional Assessment of Cancer Therapy – General) was measured for one year in the REACH trial. The submission states that this was ITT, but in fact patients with disease progression or those who withdrew due to AEs were lost before the 1-year time point, so it is unclear how many patients were contributing data at each time point (3 months, 6 months and 1 year). There was very little difference between treatment arms at any time point, both for summary scores and scores for sub-categories (physical, social, emotional and functional well-being; NB scores for sub-categories were provided in the response to clarification questions). This is to be expected as it appears the questionnaire was only completed by patients up to the time of an event (i.e. while they were stable and without any AEs) and is thus not very informative. FACT-G results were not incorporated into the economic model. The manufacturer has commissioned an EQ-5D based study on QoL in CLL, which is ongoing. Preliminary results from this study were requested by the ERG, however, none were made available.

A Q-Twist (quality adjusted time without symptoms of disease or toxicity of treatment) analysis was also performed in the submission. This is an alternative to the QALY (quality adjusted life year) in which utility scores are assigned to a number of pre-defined 'states' (e.g. in progression, in remission, treatment toxicity) that a patient may experience. A value in units of time is generated. In contrast to QALYs these states and their associated utility scores are not fixed, which leads to inconsistencies between studies and means that Q-Twist values cannot be compared across studies or disease

groups unless exactly the same scheme is used.(Stephens 425-26) The utilities for each state can be generated by physicians, patients or clinical investigators.(Revicki et al. 411-23) Although the concept of Q-Twist has been around for more than 20 years, it appears it is not widely used.(Stephens 425-26)

The utility values used in the submission's Q-Twist analysis were based on clinical opinion or otherwise 'assumed' (p161) and the results were as follows: patients who received R-FC gained an average of 6.38 months without disease symptoms or treatment toxicity; spent an average of 4.82 months less in relapse; and achieved an average of 3.45 months longer quality adjusted survival time without any increase in the burden of toxicity.

In the economic model health benefits were expressed solely as QALYs, therefore the results (and underlying assumptions) generated by the Q-Twist analysis have not been analysed in detail by the ERG.

2. Non randomised studies,

The majority of submitted studies (15/20) included treatment regimens not specified in the NICE scope and have not been looked at by the ERG. The remaining studies are Wierda 2005(Wierda et al. 4070-78), Wierda 2006(Wierda et al. 337-45), Eichhorst 2005(Eichhorst et al. Abstract 2126), Winkler 1999(Winkler et al. 2217-24) and Herold 2000(Herold et al. 332-35). The study by Herold 2000 included only 2 patients and is not further discussed. The remaining four studies are detailed in Appendix 5).

The largest of the relevant non-randomised studies (Wierda 2005, n=284 extended analysis) provided some evidence that R-FC was effective in patients pre-treated with fludarabine and fludarabine refractory patients, and also in patients with and without prior rituximab exposure. This was an uncontrolled study and we therefore have no alternative treatments as a comparison. Results for fludarabine refractory patients were based on small patient numbers and need to be interpreted cautiously. The study by Eichhorst (2005) looked at a R-CHOP combination given to a small number of patients (17 evaluable) with advanced disease status. There was no complete

remission in any patients, however, we do not know if this is due to the treatment being ineffective, or the patients being at a more advanced stage of disease, or, given the small numbers, due to chance. It is difficult to compare efficacy of treatments across studies due to variations in disease stage, age, pre-treatment etc. No conclusions can be drawn from the non-randomised studies regarding superiority of one rituximab-chemotherapy regimen over another. This does not mean that such differences do not exist for different patient groups.

4.2.2 Critique of submitted evidence syntheses

Nature and context of the clinical evidence

The ERG usually can refer to the Scientific Discussion Document issued by the EMEA at the time of licensing, and this provides an independent and useful summary of the manufacturer's submitted evidence regarding the effectiveness and safety of their technology. The EMEA licence statement on Rituximab for CLL is pending and a Scientific Discussion Document has not been released. The evidence for effectiveness essentially rests on the single open label REACH trial; this trial is currently unpublished and so has yet to be scrutinised in peer review and its findings remain unconfirmed. The information available to the ERG therefore consisted of the manufacturer's submission (231 pages), the manufacturer's response to requests for clarification (a further 96 pages) and the electronic full trial report for REACH supplied by the manufacturer extending to 3719 pages (30 megabytes).
No meta-analyses were performed as there is only one included trial (REACH). The non-randomised studies are tabulated and results described. There is no formal evidence synthesis.

4.2.3 Summary

There is evidence from the REACH trial that treatment with R-FC results in a longer period of progression–free survival compared to treatment with FC. The difference in median time to progression was approximately 10 months or 5 months (investigators' or independent data assessment), both of which are statistically significant. This was based on a data cut-off point of 2.1 years, at

which progression or death had occurred in 53% of patients. 47% of patients were censored, i.e. had not had an event at this time.

Median overall survival times cannot be compared for the two treatment arms as this point had not yet been reached in the R-FC arm. 75% and 78% of patients were still alive in the FC and R-FC arm respectively. There was no statistically significant difference in the OS curves at the point of data cut-off. There is no convincing data to support the assumption (used in the economic model) that on average the R-FC arm gain more overall survival benefit than the FC arm. The ERG notes that the overall survival Kaplan Meier curves only separate at 2.5 years (fig 9 submission), many months after the finish of the six months treatment cycle. There may be a biologically plausible reason for how this might happen, but we are unsure what this might be.

The REACH trial had younger patients than would normally be expected in a trial of relapsed CLL patients (median age of 63 *at relapse* in REACH compared to median age *at diagnosis* of 65-70 in general CLL population). Ten percent of Binet stage A patients (i.e. very mild disease) were included in REACH. Patients at this stage would generally not be treated in the UK unless there was evidence of progression, so it is unusual to see this proportion included in a trial of relapsed patients. The impact of having healthier patients in the RCT compared to the total UK CLL population that may be eligible for rituximab is that the healthier patients are likely to survive for longer. The median overall survival in the R-FC arm was not (yet) reached, and this may be one of the reasons why. Also, it is likely that younger and/or healthier patients would experience fewer adverse events and thus be less likely to drop out.

Sub-group analyses were performed for 48 sub-groups. R-FC was found to be more effective than FC in the majority of sub-groups in reducing the risk of progression or death. The risk of progression was increased with R-FC compared to FC in the following categories: time from diagnosis >10 years (investigators's assessment); [redacted] (independent assessment); and [redacted] (independent assessment). None of these results were statistically significant. The sub-groups were not powered to show differences

and were also only based on 2.1 years median observation time. Some differences may be due to chance as a large number of sub-group analyses were performed. However, it may be that older patients benefit less from R-FC compared to FC; further research is necessary. There were no significant differences between sub-groups based on del17 status; R-FC was more effective for del17 positive and negative patients for both assessments.

REACH was an open label study and thus patients and investigators were aware of treatment allocation. In an open label study with relatively few patients per centre clinicians are likely to know every patient individually and this may bias assessment. An independent assessment was also carried out. There was a difference in the number of patients assessed as progressed, by independent (blinded) assessors compared to the (un-blinded) investigators' assessment.

In the REACH trial, fludarabine and cyclophosphamide were given as an infusion. These drugs are usually given orally in the UK. It is unclear whether this would have an impact on the effectiveness of the drugs.

No fludarabine refractory patients were included in the REACH trial, however, these patients are likely to be eligible for rituximab. There is some evidence from one uncontrolled study (n=284) that R-FC is effective in fludarabine refractory patients, and also in patients with prior rituximab exposure. Results for fludarabine refractory patients are based on small patient numbers and need to be interpreted cautiously.

There is no evidence from RCTs on the effectiveness of other rituximab-chemotherapy combinations. One small, uncontrolled study looked at a R-CHOP combination given to patients with advanced disease. There was no complete remission in any patients. We do not know if this is due to the treatment being ineffective, or the patients being at an advanced stage of disease, or, given the small numbers, due to chance.

We have identified no evidence regarding the superiority of one R-chemotherapy regimen over another. This does not mean that such differences do not exist for different patient groups

Quality of life was measured in REACH for one year using the FACT-G questionnaire. There was very little difference between treatment arms, as the questionnaire was only completed by patients up to the time of an event (progression or AE). Results did not feed into the economic model. Preliminary results from the EQ5D study currently being undertaken by the manufacturer were not available to the ERG.

There were slightly more grade 3/4 and serious adverse events in the R-FC arm, which was expected given the safety profile of rituximab. Treatment related deaths were also slightly higher in the R-FC arm.

5 ECONOMIC EVALUATION

5.0.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate

The manufacturer's search strategy was as follows:

Key references retrieved during the scoping were used to develop strategy No study filters used

Databases searched:

MEDLINE via Dialog Datastar (MEYY) 1993 - present
MEDLINE In PROCESS via Dialog Datastar (MEIP) Latest few weeks
EMBASE via Dialog Datastar (EMYY) 1993-present
Cochrane Library NHS EED database Via Wiley internet - all dates
No details of issue of Cochrane Library searched are given but the ERG have assumed 2009 Issue 2
ISPOR Research Digest

Health economic databases and websites, NICE and Scottish Medicines consortium sites were also searched.

The full search strategies are detailed in appendix 3 section 9.3 of the submission All searches were conducted on 24 June 2009. A date limit of 2000-2009 was used for all databases but the Cochrane Library was searched in its entirety.

ERG comments:

The databases searched were appropriate to the question. The platform used to search MEDLINE, MEDLINE In Process and EMBASE was Dialog Datastar. All databases and websites searched are listed in table 57 of the submission on p166. Search strategies are listed in appendix 3 of the submission.

The strategy combined index terms and textwords to express the intervention and the population. However there is some inconsistency between the terms used to describe the population and intervention in the cost and clinical effectiveness searches – CLL and rituxan are omitted from the cost strategy and this could have resulted in some references being missed.

No study filters were used but appropriate index terms to locate cost effectiveness studies were employed, 24 references were located via MEDLINE and EMBASE and one via NHS EED which were ultimately all excluded. A wider use of textwords for the economic terms would have achieved a more comprehensive strategy and the ERG conducted some additional more sensitive searches to establish whether any studies were likely to have been missed. Fifty references were located after the removal of duplicates from searches of MEDLINE, EMBASE and the NHS EED and HTA databases (Cochrane). Of these none were subsequently found to be relevant.

5.1 Overview of manufacturer's economic evaluation

5.1.1 Natural history

The model submitted by Roche follows the same structure as that used in the assessment of rituximab for first line treatment of CLL. There are three states in the model: Progression Free Survival, Progressed, and Death. No transition from Progressed to PFS is possible. We share the concerns of the PenTAG group about this structure. In summary, this has the effect of combining all patients post-progression into a single state. It is therefore not possible to improve quality of life from treatment while in the Progressed state.

5.1.2 Treatment effectiveness within the submission

The main treatment is modelled by the inclusion of separate "survival curves" for progression free survival for the options with and without rituximab. These curves and their fits have been described previously in this report.

5.1.3 Health related quality of life

The model retains the non-preference based utility scores from the previous appraisal. These were taken from Hancock et al(Hancock et al.)

5.1.4 Resources and costs

The resources and costs are in line with the NICE reference case that the perspective should be UK NHS and Personal Social Service.

Doses and costs of rituximab, fludarabine and cyclophosphamide

The information on drug doses and costs provided in the original submission was unclear and contained errors. Further information has since been provided. Appendix 6 details information on doses and costs provided by the manufacturer with comments by the ERG on how the amounts were derived. We have attempted to verify all calculations, though this has not always been possible. As a result we cannot be completely confident that all figures are correct. It should be noted that the economic model uses months, whilst the cycles run in 28-day periods. A multiplier of 1.08705 is used to convert cycles into months. Whilst the total cost of six cycles does not change, this takes into account new patients starting treatment and averages the cost out over a six-month period. Further, in the REACH trial, fludarabine and cyclophosphamide were given as infusions, whilst it is common practice in the UK to give these drugs orally. An IV to oral conversion factor (multiplier) has been used, which is 24/25 for fludarabine and 150/250 for cyclophosphamide. We have not repeated the above calculations for cyclophosphamide, as the cost is very low and any slight differences are unlikely to have an impact on the overall cost-effectiveness result. The total monthly cost (from list of model parameters provided by the manufacturer) has been given as between £3.45 and £3.91 depending on scenario (including/excluding wastage) and treatment arm (FC or R-FC).

Administration issues

Some hospitals still prepare rituximab at ward level or in non-aseptic areas- ideally doses should be prepared at pharmacy based compounding facilities (See comment on scope from Baxter healthcare). Many NHS compounding centres have little spare capacity. Extra cost might be involved in increasing the workload of aseptic units (or may impact on patient safety). For rituximab, there would be a need to find space in day care units, some of which are already full. Also, there will be nursing costs involved, particularly for first infusion, as there may be infusion reactions. However, the impact on pharmacies on time and space is unlikely to be substantial (personal communication, Neil Masters, University Hospitals Birmingham, September 2009) as there is already a lot of rituximab being prepared for the treatment of other conditions,

Costs of adverse events

Not all AEs were attributed a cost with the result that, although more grade 3 and 4 AEs occurred in the R-FC arm, the costs of AEs was higher in the FC arm (£554.68) compared to the R-FC arm (£504.19). The manufacturer suggested that this was due to the high costs of pneumonias (associated with hospital stay) in the FC arm compared to the R-FC arm. The incidence of pneumonia associated with rituximab therapy is described in the SPC as common, therefore to base the costs of AEs on a higher incidence of pneumonia in the treatment arm without rituximab does not seem appropriate. Furthermore, there were six cases of hepatitis B in the R-FC arm and none in the FC arm. This was not incorporated into the costings. It should be noted that, whilst costs of AEs were incorporated into the model, no differences in treatment related adverse events were assumed between the two treatment arms and any possible impact of AEs on QoL was disregarded.

Cost of relapse therapy compared to first line therapy

In economic analyses of first line and relapse therapy, estimates on use of resources was largely based on that recorded for the CCL-8 and REACH trials respectively. The total incremental cost of first line treatment (R-FC minus FC) was £3,285 more than for relapse therapy (£11,617 compared to £8,332). The

main elements responsible for this lower incremental cost for relapse therapy were: (from table 76 relapse & table 56 first line submissions)

- £1,887 less cost for rituximab (£10,113 minus £8,226)
- £604 less cost for administration of rituximab (£1,224 minus £620)
- £422 less cost for bone marrow transplant (BMT) ([£565-£756=-£293] minus [£592-£360=£191])
- £265 less cost for blood transfusions ([£366-£498=-£132] minus [£640-£507=£133]).

Despite a small proportional reduction in use of rituximab in relapse treatment the cost of administration is reduced to a half that for first line therapy; a clear explanation for this is not obvious.

In first line therapy R-FC patients received more BMTs and more blood transfusions than did FC patients (5 and 3 BMT, 318 and 269 transfusions respectively). In relapse treatment the reverse was the case (3 and 4 BMTs, 113 and 137 transfusions).

The inclusion of BMT costs is debatably appropriate and is surprising in view of comments in various parts of the submission. Firstly it is stated that BMT in CLL is rare in the UK:

> In the United Kingdom in 2008, only 47 transplants were carried out for CLL (British Society of Blood and Marrow Transplantation, BSBMT)

Secondly, candidacy for BMT was an exclusion criterion in REACH as follows:

> …..patients who were considered to be candidates for allogeneic or autologous BMT or PBSCT as assessed by his/her treating physician.

Thirdly, the submission's view on recourse use was expressed as follows:

> While some resource data was collected in REACH, these were not always comprehensive or detailed. Resource utilisation and costs associated with subsequent treatments, drug administration and patient monitoring could be improved within the model via actual UK observational data.

Lastly, it was stated that:

> ....allogeneic transplantation is generally performed as a consolidation procedure in patients who have responded to second or subsequent line therapy and not as an alternative.

Since the R-FC arm generated higher levels of response it is surprising fewer patients received this therapy in the than in the FC arm.

5.1.5 Discounting

In line with the NICE reference case, a discount rate of 3.5% per year has been applied to both costs and benefits. The method used within the model was to convert this to a monthly discount rate. The method used is theoretically superior to the (more common) use of a "stepped" discount function whereby future costs and benefits are discounted according to the number of whole years from the start of the model.

5.1.6 Sensitivity analyses

A number of deterministic sensitivity analysis results are shown. These include varying the following factors:

- Functional form for curve representing progression free survival;
- Utility scores for health states;
- Drug costs (dose and administration);
- Supportive care costs;
- Adverse event costs;
- Assumptions about probability of progression to death.

Combinations of changes were also included, so the description of these as “one-way sensitivity analyses” is not technically accurate.

Additionally, the model was subject to probabilistic sensitivity analysis in the usual way. One thousand replications of the model were made. These were described in the manufacturer’s submission as 1,000 patients running individually through the model. This description is not correct: rather, what appears is a statistically representative sample of 1,000 estimates of population mean outcomes, which are then appropriately shown on a cost-effectiveness plane and summarised through a cost-effectiveness

acceptability curve (CEAC). The proportion of model replications giving favourable results at £20,000/QALY and £30,000/QALY is reported as the probability of the treatment including rituximab being cost-effective.

5.1.7 Model validation

The manufacturer's report (page 202) describes a process of internal validation. Despite this process, initial examination of the model revealed an error in the way in which the background death rate was calculated. The effect of the error was negligible, and was reported to the manufacturers, who have provided revised results which correct for the error. More detailed scrutiny of the model has revealed further apparent errors and questionable assumptions in the way in which the model has been built. The effect of these is described in later sections.

5.2 Critique of approach used

As noted above, the approach used is similar to that used in the appraisal of rituximab for first-line treatment of chronic lymphocytic leukaemia. We have applied the ScHARR-TAG checklist to the model: the results appear in Appendix 3.

5.3 Results included in manufacturer's submission

In response to initial clarification questions from the ERG, the manufacturers made two changes to their base case modelling. The first of these involved accepting a correction to the means of calculating background mortality, of the which the effect was negligible, but the second more substantial change is that the base case results now assume planned dosage (with wastage) rather than the actual average dosage recorded in the REACH trial. Accordingly, the results reported here are somewhat different from the results in the original manufacturer's submission. The remaining text in this section is taken directly from the manufacturer's response to questions.

Results based on changes from clarification stage of NICE appraisal for Rituximab in Relapsed/Refractory CLL

Two changes have been made: adjustment of formula associated with background mortality (use of function male2female) and change of dose scenario to planned dose with wastage (instead of actual dose).

Base case results

Costs

Table 19 indicates that rituximab given in combination with fludarabine and cyclophosphamide is associated with an additional average per-patient costs of £9,128 over the analyzed patients' lifetime period when compared to fludarabine and cyclophosphamide therapy alone.

Table 39 Total average per-patient cost for the two compared treatment groups over a lifetime period (deterministic analysis) using REACH trial data

Cost component (£)	R-FC	FC	Incremental
Mean cost of PFS	£16,396	£6,720	£9,676
Costs of Rituximab	£9,015	£0	£9,015
Administration costs of Rituximab	£620	£0	£620
Cost of Fludarabine	£2,552	£2,510	£42
Administration costs of Fludarabine	£843	£829	£14
Costs of Cyclophosphamide	£21	£20	£1
Administration costs of Cyclophosphamide	£843	£800	£43
Cost of supportive care in PFS	£1,066	£752	£315
Cost of Bone Marrow Transplantation	£565	£756	-£191
Cost of Blood Transfusions	£366	£498	-£132
Cost of Adverse Events	£504	£555	-£50
Mean cost of Progression	£4,744	£5,293	-£549
Mean Total Cost	£21,140	£12,012	£9,128

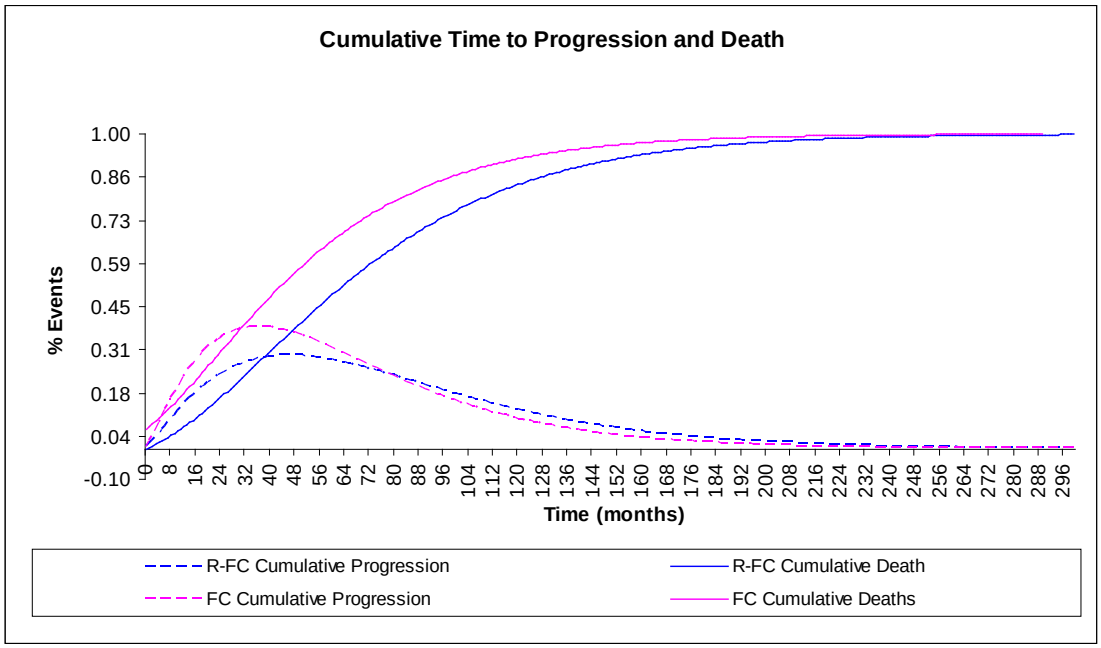
Life Years and Quality-Adjusted Life Years

Table 20 shows that the combination of rituximab plus fludarabine and cyclophosphamide results in a mean gain of 0.671 life years and 0.585 quality-adjusted life years (QALYs) when compared to Fludarabine and Cyclophosphamide alone over the analyzed lifetime period. This finding is related to a QALY gain due to a longer stay in the health state of progression-free survival (PFS) for the patients assigned R-FC than that observed for patients assigned FC alone. This is further illustrated in Figure 1 where patients in the FC arm progress quicker and have a shorter time to death than R-FC patients.

Table 40: Total mean QALYs per patient for the two compared treatment groups over a lifetime period (deterministic analysis) using REACH trial data

Outcome measure	R-FC	FC	Incremental
Mean Life Years (yrs)	**5.207**	**4.536**	**0.671**
Mean Life Years in PFS (yrs)	3.099	2.185	0.915
Mean life Years in Progression (yrs)	2.107	2.351	-0.244
Mean QALYs	**3.744**	**3.158**	**0.585**
Mean QALY in PFS	2.479	1.748	0.732
Mean QALY in Progression	1.264	1.411	-0.146

Figure 5: Cumulative time to progression and death for R-FC and FC using REACH trial data



Incremental Cost-Utility Ratio

Based on the assumptions used for the core model analysis, a cost per QALY of £15,593 for the RF-C combination therapy relative to FC therapy was calculated (table 21).

Table 21 Cost per life year/cost per QALY gained ratios for R-FC versus FC over a lifetime period (deterministic analysis) using REACH trial data

Cost-utility results	R-FC	FC	Incremental
Mean Life Years (yrs)	5.207	4.536	0.671
Mean QALYs	3.744	3.158	0.585
Mean Total Cost	£21,140	£12,012	£9,128
Cost per Life Year Gained (£)			£13,608
Cost per QALY Gained (£)			£15,593

Sensitivity analyses

Overview of one-way sensitivity analysis results

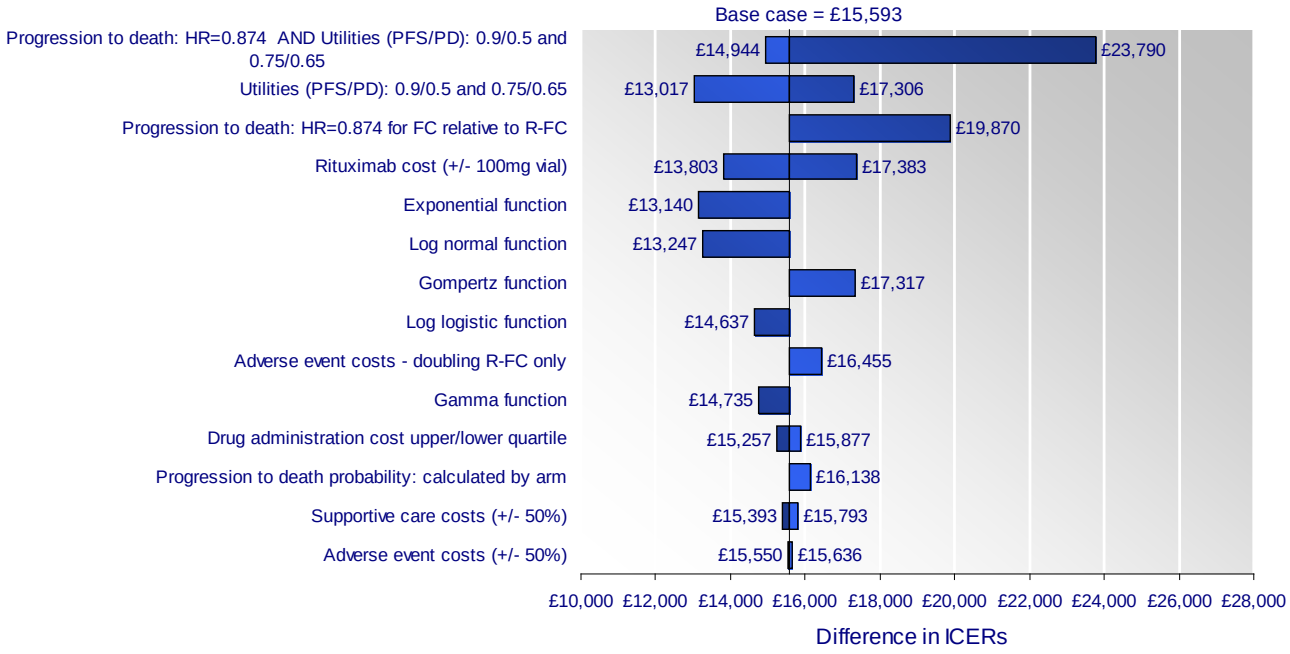
The following table provides the incremental cost-effectiveness results for a selection of one-way sensitivity analyses for the comparison of R-FC versus FC.

Table 24. One-way sensitivity analyses: R-FC versus FC

Sensitivity analyses	ICER
Base case (Weibull)	£15,593
Gamma function	£14,735
Exponential function	£13,140
Log logistic function	£14,637
Log normal function	£13,247
Gompertz function	£17,317
Utilities: PFS=0.9; Progressed = 0.5	£13,017
Utilities: PFS=0.75; Progressed = 0.65	£17,306
Adverse event costs increased by 50%	£15,550
Adverse event costs decreased by 50%	£15,636
Adverse event costs: doubling R-FC cost only	£16,455
Rituximab cost – less one 100mg vial per cycle for smaller patient	£13,803
Rituximab cost – one 100mg vial added per cycle for larger patient	£17,383
Monthly supportive care cost increase by 50%	£15,393
Monthly supportive care cost decrease by 50%	£15,793
Drug administration cost upper quartile	£15,877
Drug administration cost lower quartile	£15,257
Progression to death probability: calculated by arm*	£16,138
Progression to death probability: HR=0.874	£19,870
Progression to death probability: HR=0.874 & Utilities: PFS=0.9; Progressed = 0.5	£14,944
Progression to death probability: HR=0.874 & Utilities: PFS=0.75; Progressed = 0.65	£23,790

* PSA results are also based on this scenario

Tornado diagram of one-way sensitivity analyses: R-FC v. FC



The two one-way sensitivity analyses with the largest impact on the ICER (utilities and progression to death modeled via a Cox model) were also combined to illustrate the largest potential difference in ICERs using the most sensitive parameters test. The combination of using a small difference between PFS and progressed health state utilities (0.75 / 0.65) and the Cox model generated hazard ratio of 0.874 for the progression to death rate for FC versus R-FC, resulted in an ICER of £21,589. The tornado diagram ranks these scenarios in terms of impact on the ICER.

Scenario analysis: Considerations for R-chemo and Re-treatment

The assumed licensed indication within this submission is for rituximab in combination with any chemotherapy combination deemed appropriate by the prescribing physician (based upon draft SPC, awaiting CHMP approval). Due to data availability, the economic section has focused exclusively on rituximab in combination with fludarabine and cyclophosphamide.

The results from the Phase II trials (section 6.8) describe the assessment of efficacy and tolerability of other rituximab combination chemotherapy. This included R-CHOP (34 patients), R-PC (rituximab, pentostatin and cyclophosphamide – 17 patients) and R-FCM (R-FC and mitoxantrone – 52 patients). The results of these studies consistently highlight high response rates and the strong efficacy of R-chemotherapy.

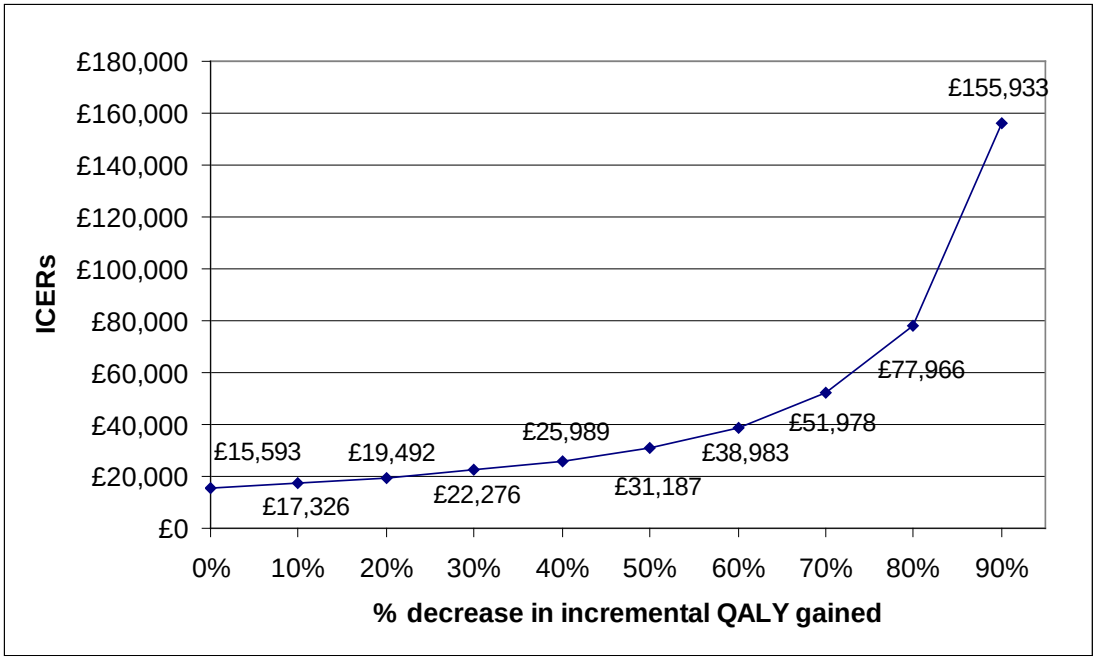
Without a comparator arm to represent baseline risk, it would not be possible to perform a reliable and comprehensive cost-effectiveness analysis of these alternative

rituximab based combinations. However, in order to assess the potential differences in cost-effectiveness when utilising alternative background chemotherapies with rituximab compared to FC, scenario and threshold analysis may be informative for the purposes of decision making.

Given the current economic model structure, it is likely that the incremental costs will be similar to adding rituximab to other chemotherapy regimens. Therefore only if the estimated incremental QALY was considered to be smaller those found in the R-FC v. FC analysis would the ICER be expected to increase compared to that observed in the R-FC based anlaysis.

The following describes a threshold analysis, considering alternative incremental gains in QALYs than those found in the base case analysis, to determine how much 'worse' the increment benefit of R in combination with other chemotherapies would need to be in order to no longer be considered cost-effective.

Figure 7: ICERs associated with decreased incremental QALYs gained from base case of R-FC versus FC



The above analysis indicates that the incremental benefit from rituximab in combination with other chemotherapy regimens would have to reduce by more than 50% of that observed when utilising R-FC for rituximab not to be considered cost effective. Consequently if this is considered an unlikely clinical assumption for alternative rituximab combinations, one may state with a high degree of certainty that ritxuimab in combination with other chemotherapies is likely to also be cost effective.

R-CHOP is a potential option for patients refractory to fludarabine. In Section 6.8.4.1 of the original submission, a simple comparison of the overall response rates among fludarabine-refractory patients from the phase II R-CHOP study was compared to CHOP patients from unpublished follow-up data from the phase III CLL-4 study. The comparison confirmed that the overall response rates (and subsequently the potential duration of progression-free and overall survival) may be improved for R-CHOP treated fludarabine-refractory patients. The absolute magnitude of the improvement of efficacy cannot be measured in a manner suitable for the economic evaluation, however from

the threshold analysis we can be certain that the incremental QALYs associated with this comparison could be half that observed for R-FC versus FC and still remain cost-effective.

By the time the NICE appraisal committee meet to discuss this technology appraisal, NICE will have already issued final guidance for the use of rituximab in 1st line CLL. Use of rituximab in this setting has been demonstrated to substantially prolong progression-free survival and therefore the need for subsequent lines of treatment in these patients may not be anticipated for several more years. However, our anticipated license will permit all relapsed CLL patients to be treatment with rituximab irrespective of previous (rituximab combination) treatments, and data presented in Section 6.8.4.3 of the original submission from Badoux et al demonstrates that the ORR, duration of PFS and duration of OS is not anticipated to differ between rituximab naïve and rituximab pre-treated patients in the relapsed setting. Whilst the threshold analysis confirms that the benefit associated with re-treatment could be as little as half that observed in REACH in order to remain cost-effective, the observational data from Badoux et al confirms that the incremental QALYs is likely identical for a rituximab re-treated relapsed CLL population, resulting in a highly cost-effective ICER.

Probabilistic Sensitivity Analyses (PSA)

When using a sufficiently high number of Monte Carlo simulations - as example 1,000 iterations - the model produces probabilistic health and economic outcomes that are comparable to that obtained from the deterministic analysis. The PSA is based on the scenario which allows for two separately progression to death probabilities for R-FC versus FC (and therefore also allows for the different levels of uncertainty across these two variables) which resulted in a deterministic ICER of £16,138 per QALY gained. Below are the mean cost and outcome results from 1,000 runs resulting in an ICER of £15,862 per QALY gained.

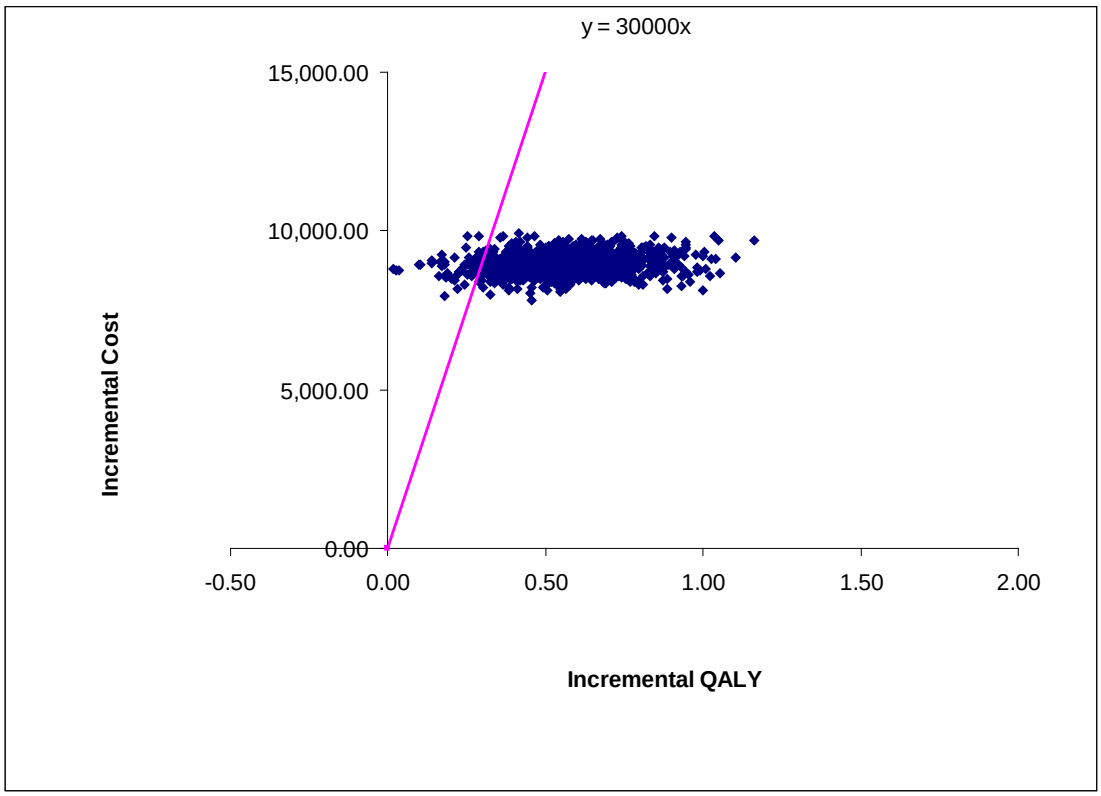
Table 23. Mean Cost Effectiveness results for R-FC versus FC (1000 runs)

Cost-utility results	**R-FC**	**FC**	**Incremental**
Mean Life Years (yrs)	5.085	4.452	0.633
Mean QALYs	3.672	3.106	0.566
Mean Total Cost	£21,006	£12,025	£8,981
Cost per Life Year Gained (£)			£14,191
Cost per QALY Gained (£)			**£15,862**

Scatter plots

The cost-effectiveness plane in the example presented below (assumption: 1,000 patients running individually through the model) shows the distribution of incremental cost per QALY ratios in relation to an assumed willingness to pay (WTP) ceiling ratio of £30,000 per QALY. This shows that Rituximab 's incremental cost per QALY values always with a few exceptions lies below the threshold. The results for chlorambucil are even more pronounced, with no points above the £30,000 per QALY threshold.

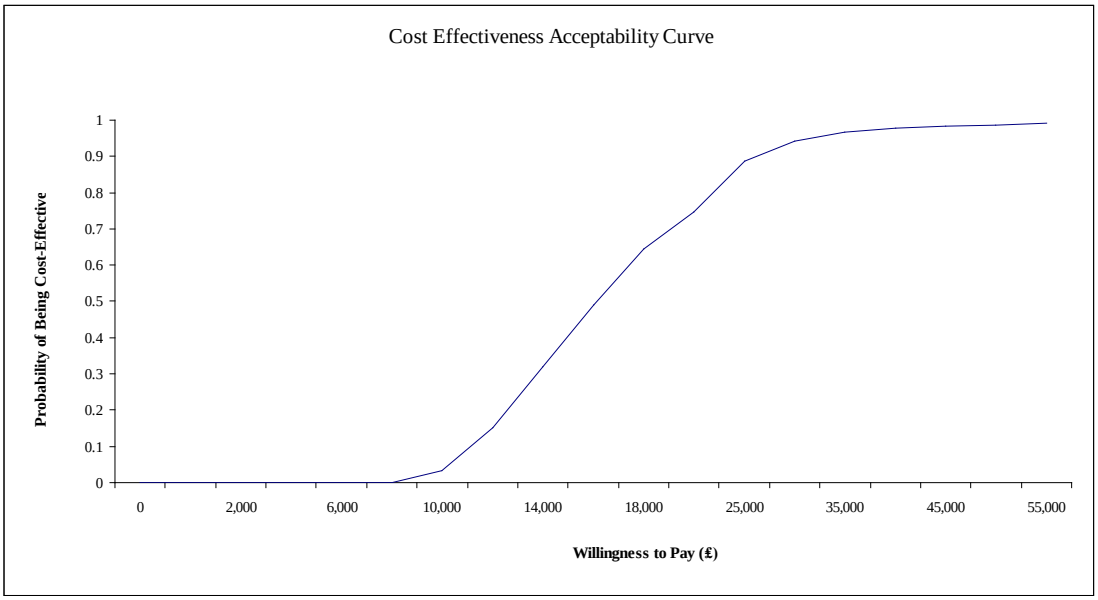
Scatter plot of cost per QALY for R-FC vs. FC (example:1,000 Monte Carlo simulations)



Cost-effectiveness acceptability curve (CEAC)

The CEAC graph shows the likelihood of the R-FC treatment being cost-effective at different WTP per QALY thresholds. The probability of R-FC not surpassing the commonly used threshold of £20,000 compared to FC is 74.7% and the probability of not surpassing the £30,000 threshold is 94.2%. Therefore, the PSA illustrates the robustness of the cost-effectiveness of R-FC compared to FC.

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



5.4 Comment on validity of results presented with reference to methodology used

In general the results have been well explained in relation to the assumptions made. However, the spreadsheet model supplied included a number of sheets that were hidden not merely from immediate view but from the "Format / Sheet / Unhide" command within Excel. There seems to be no good reason for this. Accordingly, we were not able to examine these sheets.

There appear to be some errors of logic within the model. One of these was found on initial examination and the manufacturer's revised results have adjusted for this. The effect of others was explored as additional work undertaken by the ERG and is reported in Section 6 below.

5.5 Summary of uncertainties and issues

The main limitations of the analysis are as follows:

- The analysis is heavily based on the results of a single study (REACH).
- The quality of life scores used, while apparently the best available, are not drawn from a source that meets the requirements of the NICE reference case.
- While a range of different parametric curves have been applied to the data for progression free survival, none of them is a particularly good fit to the data, and there are doubts about the long term extrapolation of these curves.
- The overall survival has been modelled by applying death rates to the PFS and progressed states in each arm of the model separately. The cumulative deaths modelled show a divergence between the two arms of the model from the start: this does not accord with the observed pattern of deaths in the trial.

Figure 5 from new cost-effectiveness results (clarification document)

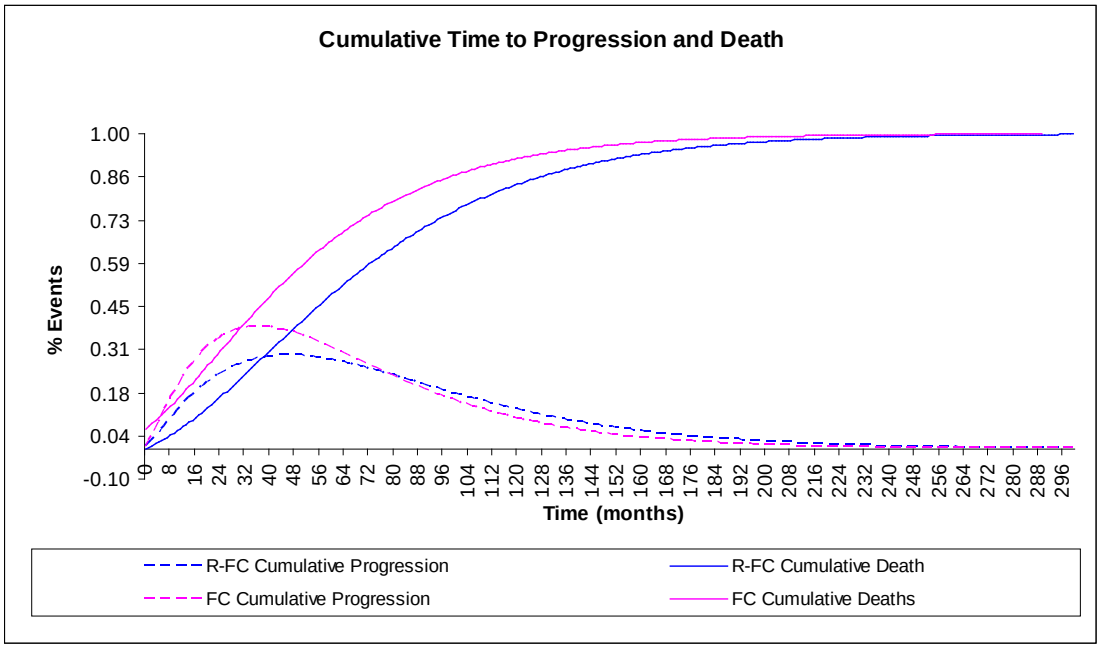
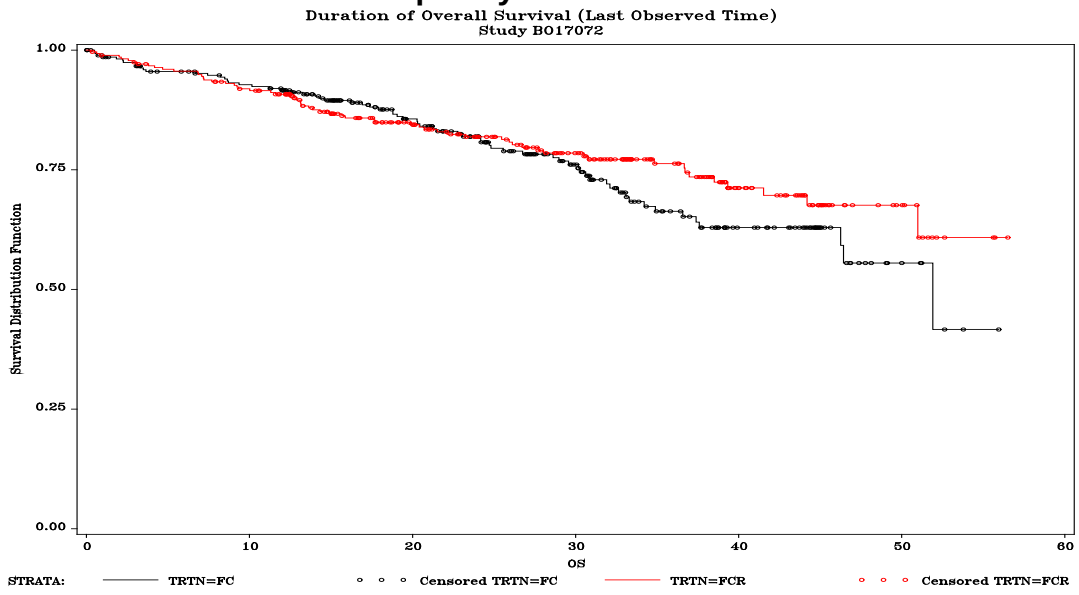


Figure 21 from company submission (page 177). Overall Survival of R-FC versus FC: median follow-up 2.1 years



Source: SAS v8.2 aultmanr $HOME/cd11899a.pbe/117072u.pbe/modldth.sas 20MAR2009 09:05

6 Additional work undertaken by the ERG

A number of alternative analyses based on the model have been carried out. The aim of these is to test the effect of changes to the various assumptions contained within the manufacturer's submission. It is important to note that the results here do not in any way represent the ERG's view of the "correct" ICER.

6.1 Correction of minor errors of logic in transitions

There appear to be two errors in the logic of the model. First, the proportion of the population moving from PFS to death within the first cycle is only a tiny fraction of the numbers making such a transition in the second cycle. The overall logic of the model is that the proportions in each of its three health states are mid-month proportions. One would therefore expect that the proportion dying within the first cycle of the model would be about half that in the second cycle.

The second issue to be discussed here relates to the transition from "progressed" to death. The fraction of the original population making this transition in any cycle is a product of the fraction of the original population in the "progressed" state and the probability of death from that state. It appears that the first of these factors has been measured one month earlier than it should have been.

Correcting for these two apparent errors changes the base case ICER from £15,593/QALY to £15,584/QALY. In view of the very small size of this effect, exploration of other assumptions within the model has been made on the basis of the model as supplied without incorporating this correction.

6.2 Costing of rituximab

The modelled costs of rituximab are spread through the first six monthly cycles of the model. This appears to assume that the costs are incurred throughout the cycle, and so a patient progressing in the middle of the month incurs only half a month's costs of rituximab. Given that rituximab is

administered as a single treatment at the start of each cycle, this seems inappropriate. An attempt has been made to adjust for this by remodelling the total costs of rituximab as follows:

Table 3. Assumptions about retiming of rituximab costs

Cycle	Treated population	Dose	Timing of treatment
1	All	375 mg/m^2	In 1st month
2	PFS after 1 month	500 mg/m^2	In 1st month
3	PFS after 2 months	500 mg/m^2	In 2nd month
4	PFS after 3 months	500 mg/m^2	In 3rd month
5	PFS after 4 months	500 mg/m^2	In 4th month
6	PFS after 5 months	500 mg/m^2	In 5th month

Note that the timing of the treatment allows for 28 day cycles but full (30.4 day) months in the model.

This has been done for each of the different functional forms for the PFS curve. For consistency with the manufacturer's results, the amended results are shown to the nearest pound per QALY in the following table. There is a non-negligible increase in ICERs from this reanalysis.

Table 4. Effect of retiming rituximab costs

Case considered	**ICER**	
	"Original"	**Amended**
Base case (Weibull)	£15,593	£18,129
Gamma function	£14,735	£17,140
Exponential function	£13,140	£15,277
Log logistic function	£14,637	£17,050
Log normal function	£13,247	£15,443
Gompertz function	£17,317	£20,110

Legend: "Original" results are those supplied by the manufacturer in response to initial clarification questions from the ERG. "Amended" results derive from retiming the rituximab costs as explained in the text.

6.3 Removal of overall survival advantage

The purpose of this analysis is to explore what might happen if there is no overall survival advantage for the option including rituximab compared to the option without rituximab. In the manufacturer's model, the overall survival in each arm of the model is calculated by applying mortality rates to the PFS and progressed states within the model. The simplest way of removing the survival advantage is to transfer the cumulative death probabilities from one arm of the model to the other. To maintain the PFS advantage, the PFS curves have been left unchanged, and therefore the proportion in the "progressed" state in

the amended model has been found by subtraction. Since there is no obvious reason to choose one direction of transfer to the other, both ways have been tried. In the analysis referred to as "Amended 1", the cumulative probability of death calculated in the comparator arm of the model was applied also to the rituximab arm, while in the analysis referred to as "Amended 2", the cumulative probability of death calculated for the rituximab arm was applied also to the comparator arm.

This has been done for each of the different functional forms for the PFS curve.

As was noted by PenTAG for first line treatment, the results with no overall survival benefit are far more sensitive to the assumptions about quality of life scores than the "original" results, as shown also in the last two lines of the table below.

Table 5. Effect of removing overall survival advantage

Case considered	ICER		
	"Original"	Amended 1	Amended 2
Base case (Weibull)	£15,593	£40,568	£42,444
Gamma function	£14,735	£37,533	£39,595
Exponential function	£13,140	£32,158	£34,498
Log logistic function	£14,637	£35,852	£38,381
Log normal function	£13,247	£31,009	£33,927
Gompertz function	£17,317	£46,320	£47,963
Utilities: PFS=0.9; Progressed = 0.5	£13,017	£20,284	£21,222
Utilities: PFS=0.75; Progressed = 0.65	£17,306	£81,135	£84,889

Legend: "Original" results are those supplied by the manufacturer in response to initial clarification questions from the ERG. "Amended 1" and "Amended 2" results derive from two methods of removing overall survival advantage as explained in the text.

Intermediate results can be obtained by taking a weighted average of the two survival curves. This makes it possible to consider any desired fraction of the modelled advantage in overall survival from rituximab. The following table shows the effect of such changes, using a Weibull curve for PFS. Similar patterns could be expected for other options.

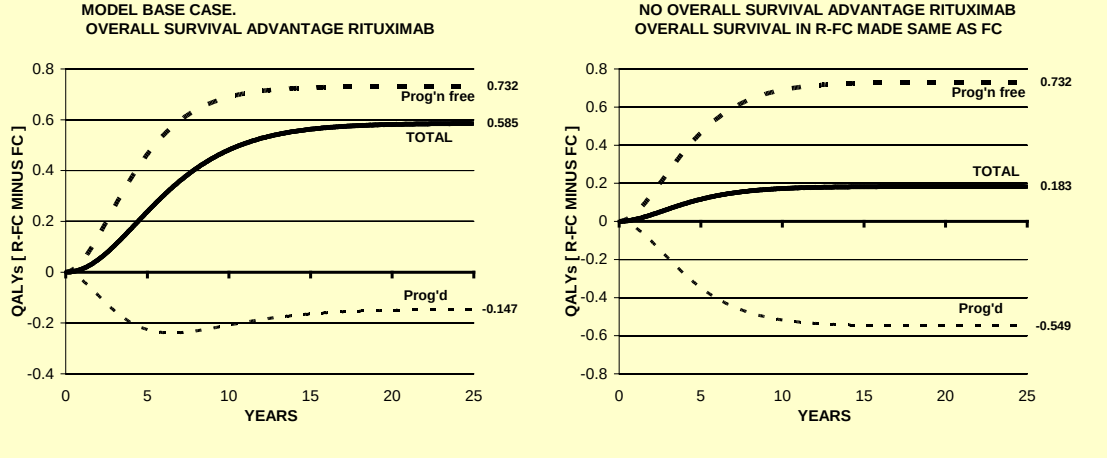
Table 6. Effect of reducing overall survival advantage

Case considered	ICER	
Percentage reduction in overall survival advantage for rituximab	**Amended 1**	**Amended 2**
0 (as base case)	£15,593	£15,593
10	£16,457	£16,478
20	£17,453	£17,508
30	£18,615	£18,721
40	£19,991	£20,169
50	£21,647	£21,925
60	£23,681	£24,098
70	£26,242	£26,852
80	£29,573	£30,455
90	£34,088	£35,365
100 (no overall survival advantage)	£40,568	£42,444

Legend: "Amended 1" and "Amended 2" results derive from two methods of removing overall survival advantage as explained in the text.

The effect on mean health gain (QALYs) of adopting the “Amended 2” version with Weibull function for PFS is contrasted below with the manufacturer’s original base case.

Figure 2 Difference between R-FC and FC arms in QALY gain from non-progressed and progressed patients



6.4 Using independent assessment of progression

All results supplied by the manufacturer were based on progression free survival assessed by the investigator. Data were also available for progression independently assessed. We have fitted selected parametric curves to these data and replaced the parameters in the model by those derived from the newly fitted curves. The results are shown in the following

table. There are small differences in the resulting ICERs, and the direction of change is not consistent.

Table 7. Effect of changing from investigator assessment to independent assessment

Case considered	ICER	
	Investigator	Independent
Base case (Weibull)	£15,593	£17,507
Log normal function	£13,247	£17,467
Gompertz function	£17,317	£16,911

Combining the effect of using the "independent assessment" curves with the removal of survival advantage gives the following results.

Table 8. Effect of changing from investigator assessment to independent assessment combined with no overall survival

Case considered	ICER	
	Amended 1	Amended 2
Base case (Weibull)	£46,700	£48,385
Log normal function	£45,426	£47,397
Gompertz function	£44,669	£46,428

6.5 Removal of bone marrow transplant costs

As noted earlier, it is not clear why bone marrow transplant costs were included in the model. Removal of these costs changes the ICER from its base case value of £15,593/QALY to £15,920/QALY, so their effect in the model is not great.

7 Discussion

7.1 Summary of clinical effectiveness issues

Only one RCT was included in the submission and there was also some non-randomised evidence submitted. No additional relevant RCTs were found from independent searches. The quality of the submission was reasonable. The REACH trial is unpublished and was open-label and patients in the trial were relatively young and none were refractory to fludarabine. It gave investigator and independent panel results which differed for progression-free survival. There was insufficient information available on overall survival to

determine median survival times. Euroqol was not measured. There was a quality of life measure used (FACT-G) but only for one year maximum, or progression or adverse event. There were no differences between the two groups at this early stage of the trial.

The submission claimed that Phase II studies (briefly summarised in Appendix 5) provide evidence for effectiveness of rituximab in various combination therapies additional to R-FC. The evidence presented is consistent with this claim, but, as mentioned in the submission this is impossible to quantify accurately through lack of appropriate control groups.

7.2 Summary of cost effectiveness issues

The submission included a de novo model similar to the one used for the appraisal of rituximab for first line treatment of chronic lymphocytic leukaemia. The intervention in the model was rituximab combined with fludarabine and cyclophosphamide compared to the same combination without rituximab. Quality adjusted life years were estimated based on utility scores from a report by Hancock et al (2002)(Hancock et al.). The perspective was NHS, a 25 year time horizon was used and the discount rate was 3.5% per year for costs and utilities. Scenario and some probabilistic sensitivity analyses were undertaken. The model was constructed within MS Excel, using macros to change scenarios and for the probabilistic sensitivity analysis.

The following table summarises the effects of various changes to the base case result of the model:

Table 9. Summary of cost effectiveness issues

General issue	Details for this submission	Effect on ICER (£)
(Roche base case following clarification questions)		15,593
Model structure	Alternative choice of curves for PFS	13,140 to 17,317
	Correction of minor errors of logic	15,584
Measurement of effectiveness	Removal of overall survival benefit from rituximab	31,009 to 47,963
	Use of PFS curves based on independent assessment of progression	16,911 to 17,467
Measurement of utility	Halving and doubling difference between utilities for PFS and Progressed states	13,017 to 17,306
Adverse events	Doubling costs for rituximab arm only	16,455
Rituximab costs	One fewer or one more 100mg vial per cycle	13,803 to 17,383
	Retiming of rituximab costs	15,277 to 20,110
Combination	Independent assessment of progression combined with no overall survival benefit	44,669 to 48,385

7.3 Implications for research

The main implication for research is the need to know whether rituximab affects overall survival or not in CLL. Establishing the optimum chemotherapy for patients is important for future treatment decisions. It would also be useful to know if rituximab improved quality of life so a utility measure such as Euroqol could be incorporated as an outcome measure in any future trials.

Appendices

Appendix 1: List of those involved with developing the ERG scope.

Please refer to NICE.

Appendix 2 Independent assessment of progression-free survival (PFS)

The REACH trial included both investigator and independent assessments of PFS. There were differences between the assessments. The investigator assessment was used in manufacturer's economic modelling. In order to explore the impact that the differences between assessments might have on the results of economic modelling the ERG used the available Kaplan-Meier traces for independent assessment to derive parametric fits that could be used in modelling. Individual patient data was not available so this was the only approach possible.

The Kaplan-Meier graphs submitted were over-layered with a grid (see figure below), enlarged to A3 size and the proportion progression-free at each 45.5 day intercept was extracted.

Figure 3. Reading of PFS from graph

The data was then plotted and over-layered on the Kaplan-Meier plots to test the visual match between extracted and original data (see figure below)

Figure 5. Testing of visual match to data

Figure 7 Visual test of fit to data; upper independent, lower investigator assessments.

Weibull, lognormal and Gompertz parametric fits were derived for the extracted data under the same proportional hazards assumption used by the manufacturer. The parameters are summarised in the table below.

Table 10 Parametric parameters fit to extracted data & model parameters

		Independent	Investigator	Investigator model value
Gompertz				
	gamma	0.0001838784	0.00938157	0.009632453
R-FC	*lambda*	*0.0229389969*	*0.017726973*	*0.018423665*
FC	lambda	0.0319852829	0.028249608	0.028526053
	mean sqrs	0.0834997212	0.084678338	
Weibull				
	gamma	1.0504745584	1.190181507	1.168851232
R-FC	*lambda*	*0.0192863396*	*0.010828097*	*0.012247453*
FC	lambda	0.0271386083	0.017432034	0.019089139
	mean sqrs	0.0793714107	0.085278899	
log normal				
	sigma shape	1.1307029248	0.997942215	1.26999224
R-FC	*mu scale*	*3.3617795267*	*3.4533826*	*3.43910477*
FC	mu scale	3.0404267985	3.046656508	3.03372945
	mean sqrs	0.067509132	0.051713273	

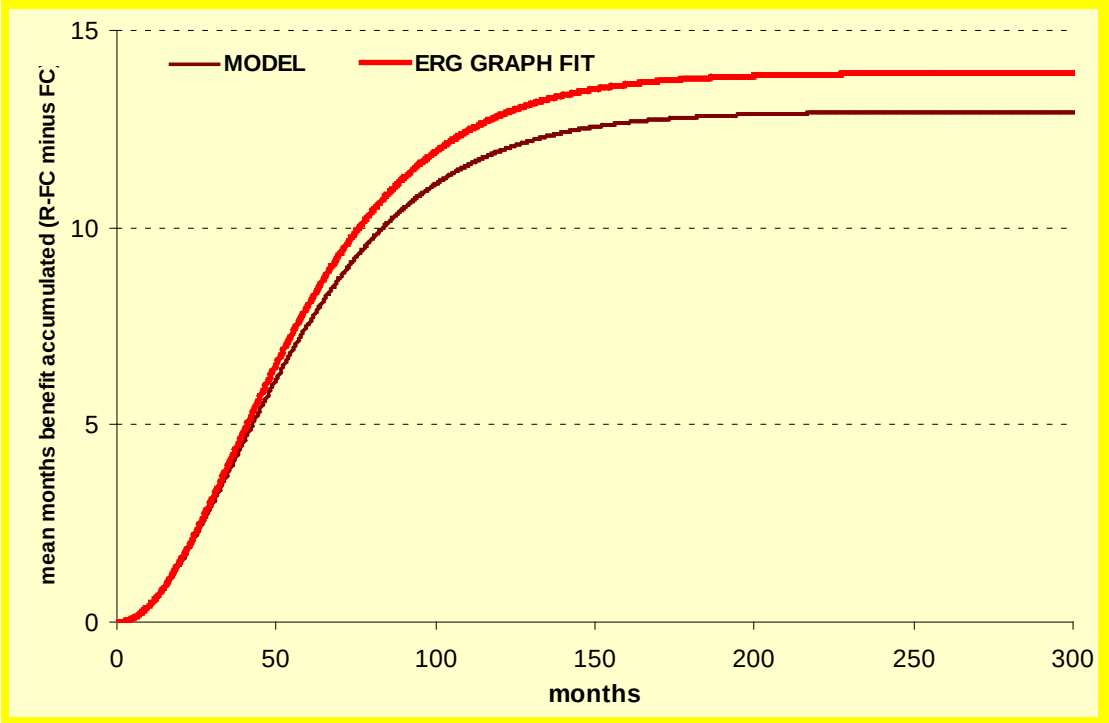
The correspondence between the manufacturer's and the ERG derived parametric Weibull fits (base case) for investigator assessment are shown below.

Figure 9. Correspondence of parametric fits to investigator assessment of PFS

The fits are similar, that for the R-FC arm indicates rather better performance for this arm in the derived relative to the manufacturer's modelled fit.

The benefit from R-FC relative to FC in terms of months gained in the non-progressed state depends on the difference in the areas under the R-FC and the FC curves. When the curves are extrapolated to the 25 year model time horizon the derived fits generate slightly more mean months benefit than do the manufacturer's fits (see figure below).

Figure 11. Mean PF months benefit derived from R-FC v. FC (undiscounted)



Appendix 3: Quality Assessment using ScHARR-TAG economic modelling checklist

Factor	Appraisal
Title	Rituximab for the treatment of relapsed / refractory chronic lymphocytic leukaemia (CLL)
A statement of the problem	What is the incremental cost-effectiveness of Rituximab in combination with Fludarabine and Cyclophosphamide (R-FC) compared to a combination of Fludarabine and Cyclophosphamide (FC) for treating CLL patients?
A discussion of the need for modelling	Modelling is required for the following reasons: • To extrapolate long-term changes in outcomes beyond the follow-up period of the clinical trials. • To obtain comparable outcomes of the effect of different CLL therapies, in terms of generic quality of life (QALYs) measures. • To test the robustness of conclusions to changes in key parameters and assumptions. **Assessment by ERG:** The decision to use modelling was appropriate given the data constraints.
A description of the relevant factors and outcomes	Relevant factors and outcomes are the following: • Predicted time in each of the three health states (Progression Free Survival -PFS, Progressed or Death) measured in terms of months. • Overall, Event Free and disease Free Survival (measured in months). • Response (duration of response, response rates, BOR and ETR) • Time to new treatment • Quality of life assessments at the end of cycles 3, 6 and at 1 year (measured in terms of FACT-G scores). • Generic health-related quality of life (QALYs). **Assessment by ERG:** The factors and outcomes used in the model appear to be appropriate.
A description	A Markov model with three health states: PFS, Progressed or Death.

of model including: type of model; time frame; perspective; and setting	Patient lifetime time horizon. NHS perspective. UK secondary care setting. **Assessment by ERG:** The general modelling framework chosen was appropriate to the decision problem and consistent with the NICE reference case.
A description of data sources, with description of respective strengths and weaknesses	Data sources used to model the effectiveness of different forms of treatment were the following: • Transition probabilities were obtained from the REACH trial and UK national sources. • Costs of care and drugs were taken largely from standard databases of health care costs. • Data on utilities were obtained from Hancock et al (2002)(Hancock et al.). These data are described in the manufacturer's submissions to NICE. However, a shortcoming in the data is the use of non-preference based utility scores from the previous appraisal and based on Hancock et al (2002)(Hancock et al.). **Assessment by ERG:** Though the utility scores based on Hancock et al (2002)(Hancock et al.) are apparently the best available, they are not drawn from a source that meets the requirements of the NICE reference case.
Key assumptions relating to model structure and data stated	• Rituximab is assumed to delay progression of disease (based on observations from the REACH trial) but is not assumed to impact on time to death once progression (treatment failure) occurs. • Following treatment failure, all patients are assumed to have the same sequence of further health care resource use. • Orally administered FC has the same safety and efficacy profile as IV administered FC. • There is an overall survival advantage for the R-FC compared to the FC arm. **Assessment by ERG:** The broad structural assumptions used in modelling were appropriate. However the results obtained are based on the assumption of overall survival advantage for the option

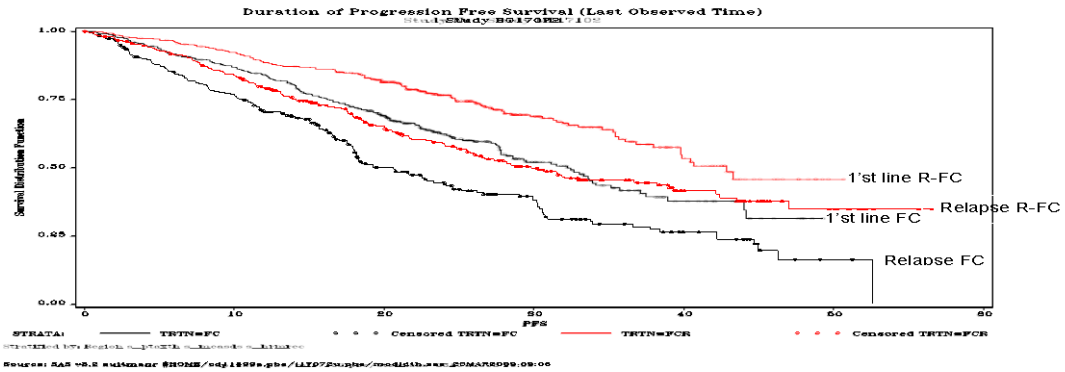
	including rituximab compared to the option without rituximab. When this advantage is removed, the results with no overall survival benefit are far more sensitive to the assumptions about quality of life scores than the "original" results.
Disease specific factors included within modelling (Items to be specified in conjunction with expert clinical input)	• Progression free survival. • One visit with a clinical oncologist during each cycle of chemotherapy. • Pharmacist time required to prepare different chemotherapy regimens. • No differences in treatment-related adverse events are assumed between the R-FC and FC arms. **Assessment by ERG:** These seem appropriate.
Validation	Outcomes International, an independent consultant company specialized in the development and validation of decision analytic models used for health economic analyses, conducted the internal validation and debugging of the model. **Assessment by ERG:** The reviewer was independent from the whole process and there thus does not seem to be any conflicts of interest. However, an initial examination of the model revealed an error in the way in which the background death rate was calculated.
Results	The reference case cost per QALY for R-FC compared to FC was estimated to be £14,240 which is below the lower NICE threshold of £20,000/QALY gained. **Assessment by ERG:** Removing the overall survival gain from the use of rituximab caused the ICER to exceed the higher ICER threshold level of £30,000 per QALY gained to be exceeded.
Sensitivity analysis	In sensitivity analyses, the incremental cost-effectiveness ratio (ICER) of R-FC versus FC for CLL patients ranged from £11,886 -

results	£21, 589 for CLL patients. A number of variables were subjected to sensitivity analysis. **Assessment by ERG:** Both deterministic and probabilistic sensitivity analyses were conducted. However, changing the assumption of overall survival advantage for the option including rituximab compared to the option without Rituximab resulted in ICERs of between £20,284 and £84,889, with the latter being beyond the higher NICE threshold of £30,000/QALY gained.

Appendix 4 Progression free survival in first line and relapse therapies

The economic model has the same structure as that submitted for the assessment of R-FC versus FC in first line therapy. The submitted ICERs for first line and relapsed treatments were similar in the base case, being £13,319 and £15,593/QALY respectively. In both models the important health benefit inputs were the gain in PFS and overall survival for R-RC versus FC, and the utility differential between progression-free and progressed states (base case = 0.8 – 0.6 = 0.2 in both models).

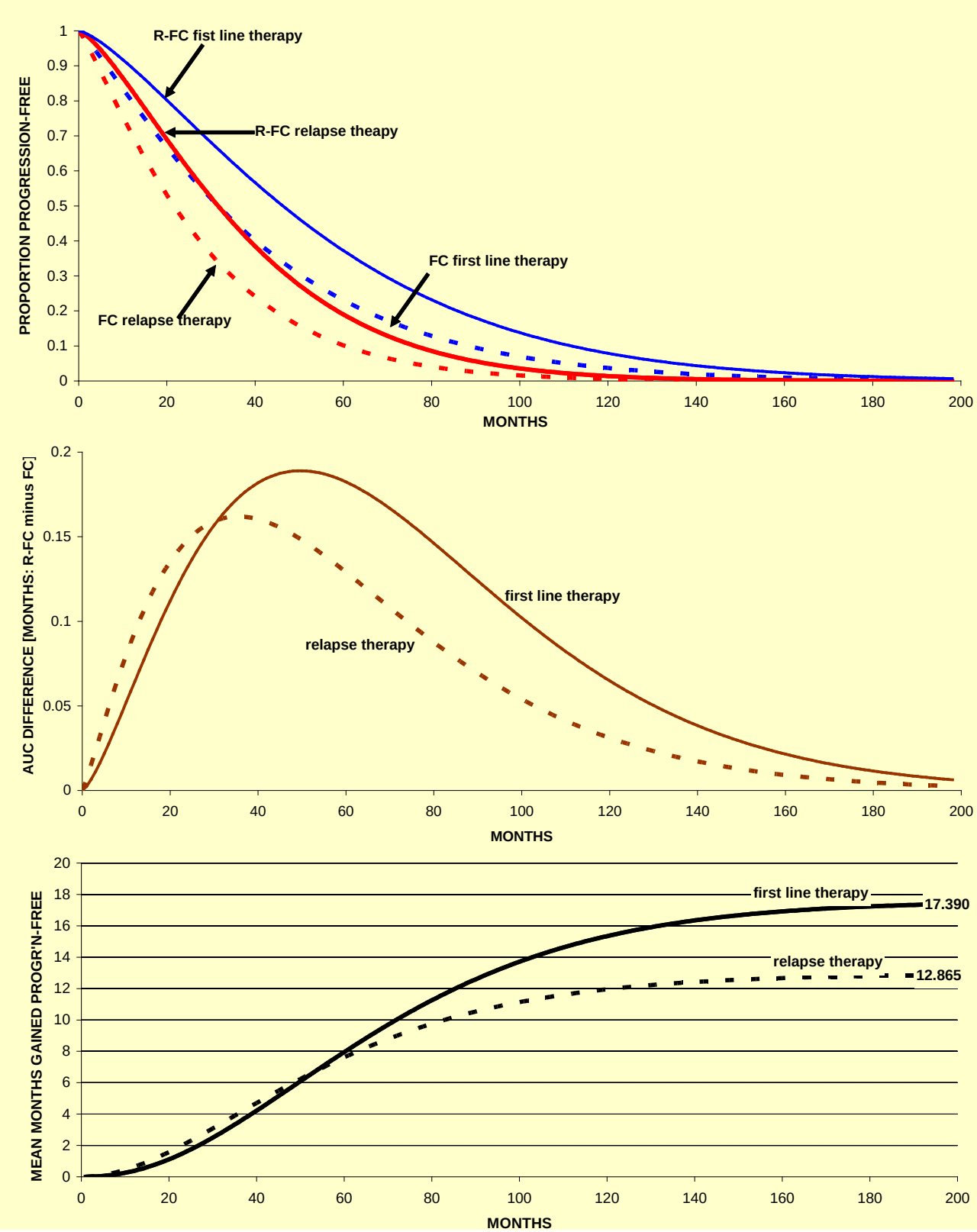
It is informative to compare the health gain from rituximab in the two scenarios. For both R-FC and FC arms PFS was superior in first line therapy than in relapse. In the figure below the PFS Kaplan-Meier plots from both submissions are superimposed on the same time axis.



The area between R-FC and FC curves in each case represents the observed mean gain from rituximab treatment and appears approximately the same in each comparison. Median time to event was 39.8 (R-FC) and 32.2 (FC) months (difference 7.6 months) for first line treatment, and 30.6 (R-FC) and

20.6 (FC) months for relapse treatment (difference 10.02 months). For the base case economic modelling both submissions used Weibull parametric fits to extrapolate beyond the observed PFS data (As shown in).

PFS in first line and relapse therapy showing mean years gained (not discounted) from R-FC fv. FC



The mean months gained over the full time horizon of the model is larger for first line therapy than that for relapse therapy (lower graph. no discounting).

Appendix 5 Results from Phase II studies presented in the submission.

Wierda 2005(Wierda et al. 4070-78)

This was an uncontrolled study in 177 patients with previously treated Rai stage III to IV CLL. Patients were given up to six courses of FC-R. Thirty-seven patients (21%) were refractory to fludarabine, 22 (12%) had previously received rituximab. Complete remission was achieved in 25% (n=45), nodular partial remission (nPR) in 16% (n=28) and partial remission in 32% (n=57). The overall response rate was 73%. CR was significantly associated with remission on a previous fludarabine-based regimen and was lower in fludarabine refractory patients (59%). It was also significantly associated with younger age, earlier Rai stage and fewer pre-treatments. At the time of the 2005 publication median follow-up time for all patients was 28 months, and 35 months for surviving patients. Time to progression was significantly shorter for patients not achieving remission versus those that did not.

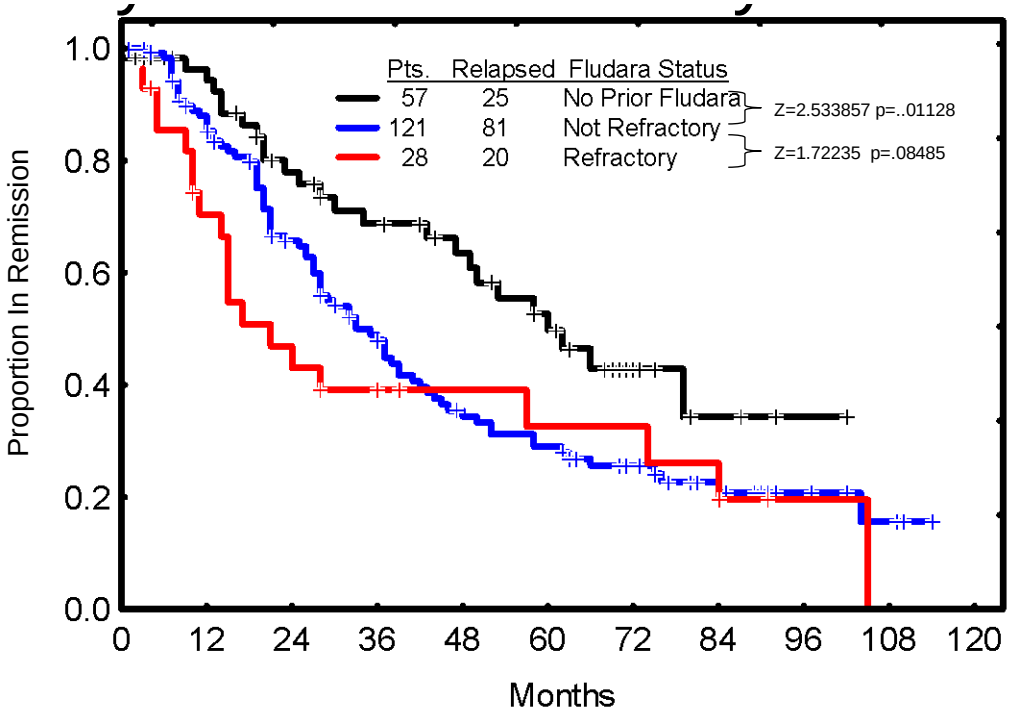
This study is ongoing and additional unpublished data for this study was provided in the submission and in the response to clarification questions. CICData was available for 284 patients, 35% had prior rituximab exposure and 19% were fludarabine refractory. Median age of patients was 60 (range 31-84). The overall response was 74%, 56% for fludarabine refractory patients. Eighty-six patients (30%) achieved complete remission, 41 (14%) achieved nodular partial remission and 84 (30%) achieved partial remission. With 42 months follow-up, the median overall survival was 46.3 months (95% CI 41.3-53.6). Among the 211 patients achieving a response, median time to progression was 31.8 months (95% CI 27.5-38.7). Overall response rates (72% and 76%) and complete remission rates (31% and 30%) were similar in patients with and without prior rituximab exposure respectively.

A KM curve of time to progression was also presented for the following patient sub-groups: no prior fludarabine (n=57, 25 relapsed), fludarabine sensitive (n=121, 81 relapsed) and fludarabine refractory (n=28, 20 relapsed). The figure shows that patients without prior fludarabine exposure stay in remission

for longer, which would be expected. Fludarabine sensitive and fludarabine refractory patients progress more quickly, with median survival times of approximately 22 and 35 months for refractory and sensitive sub-groups respectively (read off graph by ERG). This is based on a small number of patients only for the fludarabine refractory sub-group so should be interpreted cautiously. A KM curve of overall survival showed median survival times of approximately 39 and 44 months for refractory and sensitive sub-groups respectively (read off graph by ERG, based on n=163, 110 died for fludarabine sensitive and n=46, 36 died for refractory). Further KM curves were presented for time to progression and overall survival in sub-groups with and without prior rituximab therapy. Median time to progression was approximately 31 and 41 months for groups with and without prior rituximab (read off graph by ERG). Median overall survival was similar at approximately 46 and 48 months for groups with and without prior rituximab (read off graph by ERG).

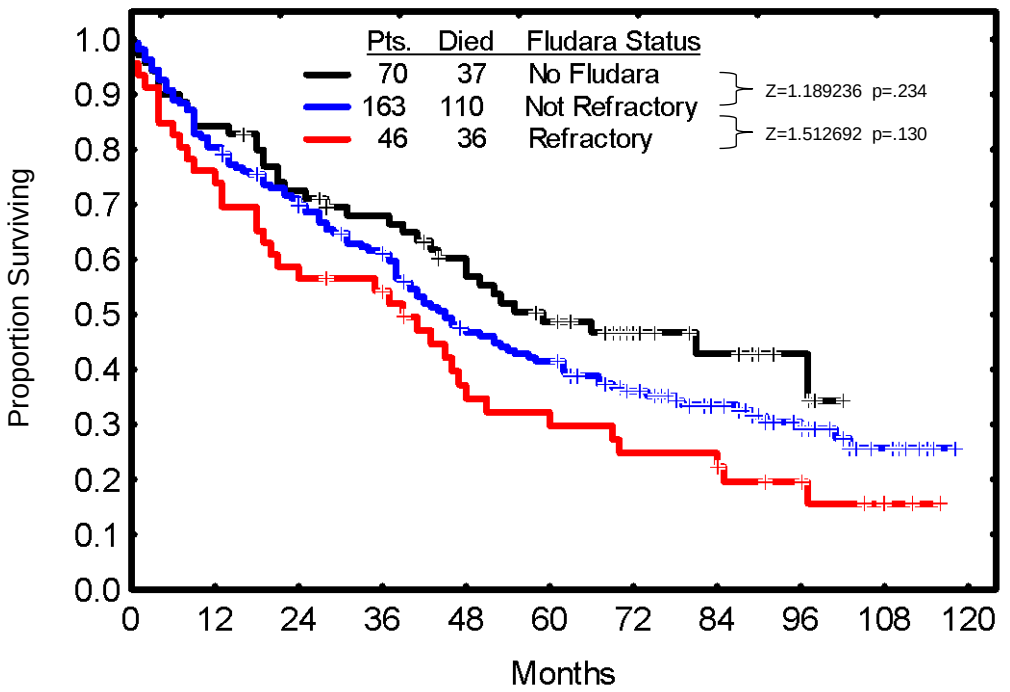
The graphs are reproduced below:

CIC Time to Progression for Patients salvaged with R-FC by Fludarabine Refractory Status



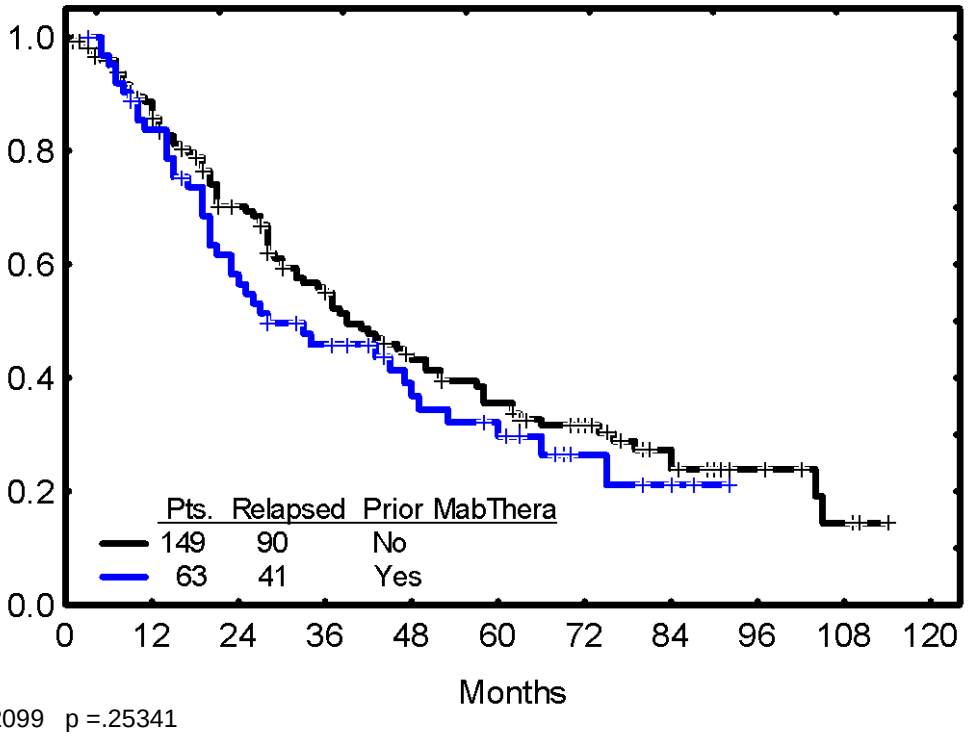
Chi-square =10.90965 df = 2 p=.00428

CIC **Overall Survival for Patients salvaged with R-FC by Fludarabine Refractory Status**



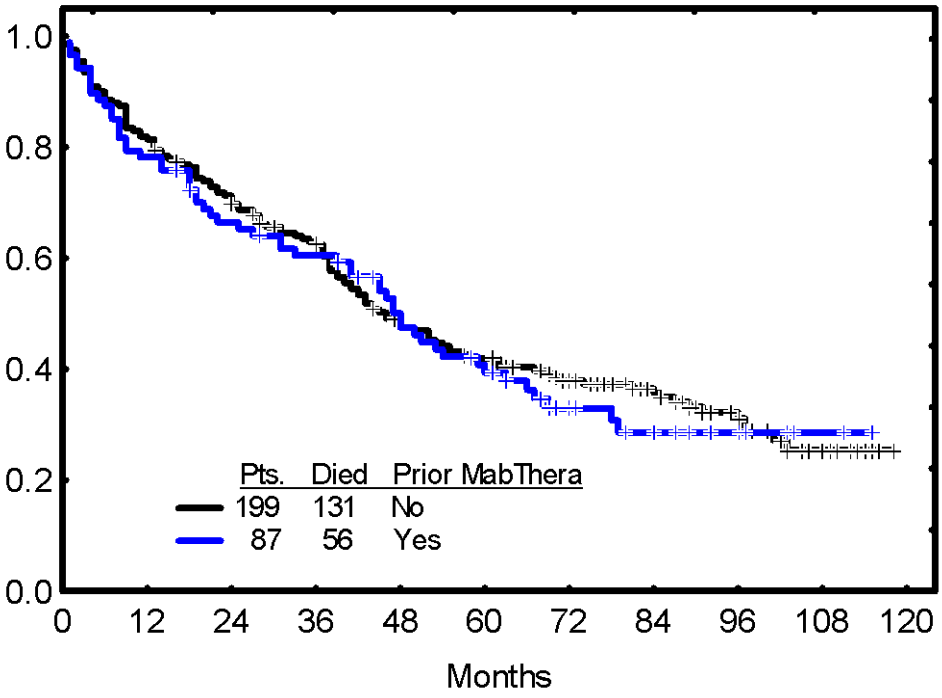
Chi-square =4.873594 df = 2 p=.08746

CIC Time to Progression for Patients salvaged with R-FC by Rituximab (MabThera) Status



Z = 1.142099 p =.25341

CIC Overall survival for Patients salvaged with R-FC by Rituximab (MabThera) Status



Z = .4152997 p =.67792

Wierda 2006(Wierda et al. 337-45)

Three non-overlapping, chronologically sequential groups of patients with recurring or refractory CLL were analysed retrospectively. One is the group from the Wierda 2005 study (n=143 of the original n=177 patients). These patients received FC-R and are the most recently treated group. The other groups received fludarabine with or without prednisone (F±P, n=251) or FC (n=111). The F±P group was the one treated first. Patients treated with FCR had higher complete remission and overall response rates compared to the other groups. There was a statistically significant difference between KM curves with an estimated median survival of 19, 31 and >42 months (F±P, FC and FC-R respectively). Prior treatment differed substantially between the three groups, and the F±P group was more heavily pre-treated and had slightly more patients with Rai stages III and IV compared to the other two groups. This is likely to have a confounding effect on the results.

Eichhorst 2005(Eichhorst et al. Abstract 2126)

This was an uncontrolled study in 34 patients with advanced stage Binet C(72%) and B. Patients were given a CHOP-rituximab combination for up to six cycles (eight cycles in Richter's transformation patients). Seventeen patients were evaluable for response, and the overall response rate was 70%. There was no complete remission in any patients. Of six reported deaths, four were due to progressive disease and two were due to infectious complications.

Winkler 1999(Winkler et al. 2217-24)

This was an uncontrolled study in eleven relapsed fludarabine refractory patients (ten with CLL), who received rituximab monotherapy. One patient achieved PR (partial remission), seven achieved stable disease and one progressed (of nine evaluable patients). After the first patient experienced a severe cytokine release syndrome during the first infusion, a fractionated dosing schedule was subsequently used. Despite this, patients with lymphocyte counts exceeding 50 x 10^9/L experienced severe side effects during application of rituximab on day 1, resulting in a temporary interruption of the infusion in five patients.

Appendix 6. Details of drug cost estimates in submission and clarification documents

Two sets of costs are provided in the clarification response from the manufacturer regarding costs used in the economic model. Only the costs listed under "model parameters" included wastage, which is relevant as there is likely to be wastage given the way the drugs are provided in vials or tablet packs. The manufacturer states that the costs including wastage are used in the base case, which would be appropriate. All calculations are based on an average patient surface area of 1.8636 m^2.

Recommended doses are as follows:

- Rituximab (infusion only): 375mg/m^2 in cycle 1 and 500 mg/m^2 in cycles 2-6
- Fludarabine (oral): 24 mg/m^2 for 5 days in each cycle (for 6 cycles)
- Fludarabine (infusion): 25 mg/m^2 for 3 days in each cycle (for 6 cycles)
- Cyclophosphamide (oral): 150 mg/m^2 for 5 days in each cycle (for 6 cycles)
- Cyclophosphamide (infusion): 250 mg/m^2 for 3 days in each cycle (for 6 cycles)

NB FC together is not licensed for treatment therefore we do not know the recommended dose. The recommended dose for F alone (BNF, SPC) is 40 mg/m^2 for 5 days in each cycle (for 6 cycles).

Standard costs are:

- Rituximab: 100mg vial £174.63; 500mg vial £873.15
- Fludarabine: unit price per mg (oral): £1.86 (15 x 10mg pack=£279, 20 x 10mg pack=£372)
- Fludarabine: 50mg vial £156
- Cyclophosphamide: unit price per mg (oral): £ 0.0024
- Cyclophosphamide infusion: 500mg vial £3.54

Different variations in cost calculations for rituximab and fludarabine are explored in the tables below. The impact on cost effectiveness is in the next sections.

Table 11 Doses and costs for Rituximab

Rituximab dose and cost	Calculation/comment
From original submission Average dose (per person, 1 cycle):not stated Average cost (per person, 6 cycles): **£9871**	The manufacturer states that this figure is incorrect as it is based on monthly cost rather than cycle cost. Using a multiplier of 1.08705 to convert cycles of 28 days into months, the cycle cost is therefore £9080.54, which does not correspond to any of the other new figures provided. We will therefore disregard this original estimate.
From clarification response ***Planned licensed dose:*** Average dose (per person, 1 cycle): **892.98mg** Average cost (per person, 6 cycles): **£9356.20**	The licensed dose specifies 375mg/m^2 in cycle 1 and 500 mg/m^2 in cycles 2-6, which is a total of 2875 mg/m^2. Assuming m^2=1.8636, this is a total dose of 5357.85mg (698.85mg in cycle 1 and 931.8mg in cycles 2-6) or an average of 892.98mg per cycle. Cost: 500mg = £873.15, 5357.85mg = £9356.20. This does not take into account wastage.
From clarification response ***Based on REACH:*** Average dose (per person, 1 cycle): **864.20mg** Average cost (per person, 6 cycles): **£9054.66**	In REACH, the licensed doses were used, but summary statistics indicated that the actual average dose per person was 864.20mg (likely due to variations in m^2 and/or the fact that not all patients completed all six cycles). Cost: 500mg = £873.15, 5185.2mg = £9054.91 This does not take into account wastage.
From clarification response ***In economic model:*** Average dose (per person, 1 cycle): **866.39mg** Average cost (per person, 6 cycle): **£9077.89**	The average dose used in the economic model is estimated 866.39 mg per cycle. The calculations for this estimate have not been provided, but may reflect the fact that some patients will die or not respond prior to completing the full six cycles. The cost is calculated as above and does not take into account wastage.
From clarification response ***Including vial wastage:*** With wastage, the dose is estimated as 700 mg/m^2 (cycle 1) and 1000 mg/m^2 (cycles 2-6). This is reflected in the new base case analysis. Total cost was not provided and was	R is provided in vials containing 100mg or 500mg. Assuming an average use of 698.85mg in cycle 1 and 931.8mg in cycles 2-6, this equates to 1* 500mg and 2 * 100mg vials in cycle 1 and 2* 500mg vials in cycles 2-6.

calculated by the ERG (see right hand column).	At a cost of £174.63 for the 100mg and £873.15 for the 500mg vial, this results in a total cost of **£9953.91** or an average per cycle of £1659.00.
From list of model parameters provided: Cost of rituximab in month 1: £1326.60-£1328.81 depending on excluding/including wastage status (base case: £1328.81 includes wastage) Cost of rituximab in months 2-6: £1640.52-£1898.32 depending on excluding/including wastage status (base case: £1898.32 includes wastage) The total cost for the base case is thus **£10820**	It appears that this total cost of £10820.41 is a monthly cost, as a cycle cost would equate to **£9953.91,** as calculated above. This cost does not appear to include any adjustment for not all patients completing 6 cycles.

Table 12 Doses and costs for Fludarabine

Fludarabine dose and cost	Calculation/comment
From original submission Average dose (per person, 1 cycle):not stated Average cost (per person, 6 cycles): **£2343.6 (oral)**	It is unclear how this cost was derived. It does not correspond to any of the new costs provided and will be disregarded.
From clarification response ***Planned licensed dose:*** Average dose (per person, 1 cycle): **140mg infusion; 224mg oral** Average cost (per person, 6 cycles): **£2620.80 infusion; £2499.84 oral**	Dose: IV: 25mg * 1.8636 * 3 (days)=139.77 mg Oral: 24mg * 1.8636 * 5 (days) =223.63 mg Cost: IV: 139.77 mg * 6 (cycles)=838.62mg 50mg=£156, 838.62mg=£2616.49 Oral: 223.63 mg* 6 (cycles)=1341.792mg 1341.792mg * £1.86 = £2495.73
From clarification response ***Based on REACH:*** **Infusion only**	Cost: 130mg * 6 (cycles) = 780mg 50mg=£156, 780mg=£2433.60

Average dose (per person, 1 cycle): **130 or 131mg depending on treatment arm** Average cost (per person, 6 cycles): **£2433.60 or £2452.32 depending on treatment arm**	(Equivalent calculation for 131mg)
From clarification response ***In economic model:*** Average dose (per person, 1 cycle): **230mg or 225mg depending on treatment arm (oral)** Average cost (per person, 1 cycle): **£2568.79 or £2510.37 depending on treatment arm**	Oral only Dose: Average daily dose estimated at 46.06mg (R-FC arm) and 44.99mg (FC arm). It is unclear how these doses were calculated. This equates to 230mg or 225mg over 5 days. Cost: 230 * 6 (cycles) * £1.86 =£2566.8 225 * 6 (cycles) * £1.86 =£2511.0
From clarification response ***Including vial wastage:***	No details were provided on likely wastage.
From list of model parameters provided: Cost per month in FC arm £422.57 to £485.26 depending on scenario; **£485.26** used in base case Cost per month in R-FC arm: £420.83 to £485.26 depending on scenario; **£485.26** used in base case It is stated that the base case includes wastage.	ERG calculation: £485.26 * 6 months=£2911.56, if use adjustment factor for cycles, total cost is **£2678.40** These costs are slightly higher than those provided above, so this seems to concur with the fact that wastage is included (packs of tablets with leftover tablets).

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