NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rituximab for the 1st line treatment of Chronic Lymphocytic Leukaemia

Roche Products Limited

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Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand name: MabThera®

Approved name: Rituximab

Therapeutic class: Antineoplastic chimeric monoclonal antibody

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Rituximab does not currently have a UK marketing authorisation for the indication detailed in this submission.

Marketing authorisation (centralised process) has been applied for and a type II variation (90 day procedure) was started with the European Medicines Evaluation Agency (EMEA) on 27th July 2008. Assuming a clock-stop of one month to answer any questions raised by the EMEA, it is anticipated that opinion from the Committee on Medicinal Products for Human Use will follow on **18th December 2008**, with full European Union marketing authorisation following 42 days after this. Thus an estimated date for final authorisation is **Friday 30th January 2009.**

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

It is expected that the indication will be broader than detailed by NICE in the final scope, with a licence allowing the addition of MabThera to ***any*** chemotherapy combination deemed appropriate by the prescribing physician,

rather than only fludarabine based regimes. The following wording is anticipated in the summary of product characteristics (currently being evaluated by the regulatory authorities) :

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

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Currently there is one rituximab based CLL trial open and recruiting patients in the United Kingdom.

UK CLL208: Chief Investigator: Peter Hillmen. This is a single arm, open label Phase II study designed and running to test the safety and efficacy of rituximab in combination with chlorambucil for previously untreated patients with CLL who are unsuitable for fludarabine based treatments. It is a UK only study, with 12 recruiting centres. The sample size is 100, with 55 patients recruited to date. Final safety and efficacy results are anticipated in Q3 2010.

As noted in Section 1.2, it is anticipated that this indication will have an European Union marketing authorisation by Friday 30th January 2009.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Rituximab does not have regulatory approval in CLL in any country in the world currently.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Not currently. It is anticipated that Roche will submit this proposed indication to the Scottish Medicines Consortium for their own technology assessment within three months of marketing authorisation.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Two vials are available currently, and the same ones will be available for the new indication:

1: Single-use vial containing rituximab 100 mg/10 ml.
2: Single-use vial containing rituximab 500 mg/50 ml.

Each ml of solution contains 10 mg of rituximab.

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The proposed course of treatment is six cycles of rituximab to be given in combination with a chemotherapy regime of the physicians choice. Typically, courses are given four-weekly, thus a typical total treatment course would last 24 weeks.

The dosing is calculated according to body surface area, with a dose of 375 mg/m^2 given in course one, and $500mg/m^2$ for all subsequent courses. 6 cycles equates to a total rituximab dose of 2875 mg/m^2 over 24 weeks. For example, an adult with a body surface area of $1.8m^2$ would receive a total dose of 5175mg. The chosen regimen and doses used in the pivotal randomised Phase III study analysed (CLL-8) were based on Phase II studies (Keating et al 2005, Wierda et al 2005)

Repeat courses are not within the licensed indication and therefore will not be covered in this submission..

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The NHS cost of a 10 ml vial of rituximab (minus VAT) is £174.63.

The NHS cost of a 50 ml vial of rituximab (minus VAT) is £873.15.

1.10 What is the setting for the use of the technology?

Rituximab is administered by intravenous infusion typically in a hospital chemotherapy day-case unit or outpatient clinic.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No additional tests or investigations are required to select CLL patients for treatment with rituximab. Intravenous administration of rituximab does utilise healthcare resources.

When rituximab is added to chemotherapy as part of initial treatment, the antibody can be administered during hospital day-case visits for chemotherapy and no additional hospital visits should be required.

Whenever rituximab is administered, patients require routine nursing observation for the duration of rituximab infusion, in case of toxicity that may require intervention (usually in the form of interruption or slowing of the rituximab infusion). It has been reported that a patient's first rituximab infusion (a dose of 375mg/m^2) takes a mean of 5.2 hours, with subsequent infusions typically taking about 3.5 hours (McLaughlin et al. 1998) when the licensed infusion schedule is followed. As the dosing in CLL is higher, subsequent doses are likely to take nearer to 4 hours.

Roche is also aware that an accelerated infusion schedule has been increasingly adopted by UK treatment centres. This unlicensed schedule allows most patients to receive second and subsequent infusions of rituximab over much shorter times, with a total dose of 375mg/m^2 being given over 90 minutes (Sehn et al. 2007).

Since rituximab is already widely used for the treatment of diffuse large B-cell lymphoma and follicular lymphoma within the NHS, and there already appears to be some off-licence use in CLL (14% first line, 21% second and subsequent lines – Genactis CLL monitor Q2 2008), staff may be very familiar with the monitoring required during drug infusion and it is not anticipated that any additional training will be required.

For any centres using oral therapies for CLL, adding rituximab will add an intravenous drug to these combinations. The administration of rituximab will need adequate space and time in haematology clinics/day units together with appropriate staffing.

Even with the current regimes, patients attend outpatient clinics or day-unit treatment areas at least fortnightly for monitoring of their blood counts, clinical symptoms etc. This would continue when rituximab is added to these regimes, therefore the actual frequency of hospital visits may not increase.

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

The evidence submission, in line with the remit issued by NICE in the final scope, will evaluate the clinical and cost effectiveness of rituximab in combination with chemotherapy (the anticipated marketing authorisation) for use within the NHS for patients with previously untreated chronic lymphocytic leukaemia who require treatment for the first time.

Table 1. Overview of Decision Problem

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with previously untreated CLL	Approximately a third of patients with previously untreated CLL will never need treatment (Dighiero T, 2003) and die with, rather than of, their disease. Another third will need treatment immediately, and the remainder will need treatment eventually. Hence in this submission the population is limited to those untreated patients who require treatment, as defined by standard criteria published by The National Cancer Institute Working Group in 1996, updated earlier this year (Hallek et al 2008). It is anticipated that this equates to approximately 1200 patients per year in the United Kingdom. (Dores et al, 2007) The inclusion criteria in the pivotal Phase III study analysed in this submission (CLL-8) gives a study population that is consistent with the actual population that are treated in clinical practice.

Intervention	Rituximab (in combination with fludarabine therapies)	It is anticipated that the licence will be broader than the intervention noted in the final scope issued by NICE, and this submission will address a broader scope : Rituximab in combination with (any) chemotherapy. This is still entirely in line with the remit/appraisal objective as defined by NICE in the final scope: 'To appraise the clinical and cost-effectiveness of rituximab within its licensed indication for the first line treatment of chronic lymphocytic leukaemia'
Comparator(s)	Fludarabine combination therapies Chlorambucil	The submission will include both fludarabine combination therapies and chlorambucil as comparators. The pivotal, Phase III randomised study (CLL-8) 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. The comparison with chlorambucil will be informed by an indirect comparison study to be detailed in this submission.
Outcomes	The outcome measures to be considered include: -overall survival -progression free survival -tumour response rate -adverse effects of treatment -health-related quality of life	These outcomes are covered in the submission. 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. 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 CLL-8 data. An observational study estimating the health-related quality of life profiles of UK patients with CLL is underway and it is currently estimated that the results will be available in December 2008. These can be made available to NICE upon completion.
Economic	The reference case	A semi-Markov model with three health

Analysis	stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation should reflect the life expectancy of patients with CLL. Costs will be considered from an NHS and Personal Social Services perspective.	states: Progression Free Survival (PFS), Progressed or Death was developed over a lifetime time horizon. This required extrapolation of the primary endpoint, PFS, beyond the end of CLL-8 trial follow-up using the best parametric fit. Because median overall survival had not been reached in CLL-8, a Markov process was used to model the transition from the progressed health state to death. Drug administration, patient monitoring and pharmacy costs were taken from the NHS schedule of reference costs and the published literature. Both costs and outcomes were discounted by 3.5%. A supplementary validation of the base case clinical outcomes was performed utilising 6-year median follow-up data from the open label, phase II M.D. Anderson study (Tam et. al 2008). The observed treatment effect of R-FC may be a reasonable proxy for the community effectiveness obtained in the clinical setting.
Subgroups to be considered	Final scope noted that the subgroup of patients with p53 deletion/ mutation should be analysed if evidence and marketing authorisation allows	It is anticipated that the marketing authorisation will not exclude patients with p53 deletion/mutation. This subgroup of patients accounts for around 5% of previously untreated patients who require therapy for the first time. There are patients with p53 abnormalities included in the clinical trials appraised in this submission and data will be analysed accordingly.
Special considerations, including issues related to equity or equality	None noted	None apparent nor considered further in the submission.

Section B

3 Executive summary

Introduction

This submission concerns the use of rituximab (MabThera®) in the first-line treatment of chronic lymphocytic leukaemia. **Within this remit, a marketing authorisation is expected by the end of January 2009**. It is expected that the licence will read as follows:

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

It is not anticipated that there will be any restrictions within this licence, however as is consistent with current practice worldwide, treatment would only be initiated when patients were symptomatic and fulfilled standard accepted criteria. This submission will therefore present the clinical and economic evidence supporting the use of rituximab in this clinical situation.

Pharmacological Action of Rituximab

Rituximab is a chimeric murine/human monoclonal antibody that binds selectively to the CD20 cell antigen expressed on the surface of mature B lymphocytes and any tumour cell that expresses CD20 (i.e. all B-cell malignancies), including chronic lymphocytic leukaemia.

It causes depletion of normal and malignant B cells. Although its mechanism of action is not precisely defined, antibody-directed cytotoxicity, complement-dependent cytotoxicity, induction of apoptosis and sensitisation of cells to conventional cytotoxic drugs are all thought to be involved.

Rituximab Dosing, Frequency, Costs and Recommended Course of Treatment

Vials containing 100mg and 500mg rituximab solution for dilution to form an IV infusion are available. The 100mg vials come in packs of two while the 500mg vials come individually packed. It is anticipated that the marketing authorisation will endorse 6 cycles of rituximab (in combination with chemotherapy), with the dose of rituximab being 500mg/m^2 body surface area for cycles 2-6, and a dose reduction to 375mg/m^2 for cycle 1. The cost of a 10 ml (10mg/ml) vial of rituximab (minus VAT) is £174.63 and a 50 ml (50mg/ml) vial (minus VAT) is £873.15. Cycles of treatment are generally given every 28 days.

Comparators

As will be fully elaborated upon in the submission (sections 4 and 6), in the United Kingdom the commonest therapies for the initial treatment of chronic lymphocytic leukaemia are fludarabine combination therapy (primarily fludarabine and cyclophosphamide – FC) and chlorambucil. Results from recently published randomised

controlled studies (Section 4) have highlighted that the most efficacious non-antibody therapy for front-line treatment is FC. It is therefore appropriate to present specific data comparative to FC and chlorambucil. The key comparative randomised Phase III study (CLL-8) that forms the core of this submission is a direct comparison of rituximab combined with FC (R-FC) versus FC. With regards to chlorambucil, data is presented in the form of a mixed-treatment comparison (section 6.6). This analysis, through linking randomised trials through a network, enables a comparison to be made between R-FC and chlorambucil.

Table 2. Decision Problem Overview

Disease setting	Current standards of care in England	Relevant rituximab license indication	Questions for this appraisal
Patients with CLL who are symptomatic, and require treatment for the first time.	Fludarabine combination therapy and chlorambucil. Fludarabine and cyclophosphamide (FC) is increasingly becoming the standard of care following the publication of three randomised controlled trials highlighting the efficacy of FC over single agent fludarabine, and chlorambucil (sections 4,6). Chlorambucil still has a role in frailer patients with co-morbidities. Market research carried out on behalf of Roche suggests that around 15% of patients in the first-line setting have rituximab added to their cytotoxic chemotherapy (Section 4).	The anticipated licence is likely to read as follows: "MabThera is indicated for first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy."	Is rituximab, when given in combination with chemotherapy to patients with CLL needing treatment for the first time clinically and cost effective?

Clinical Effectiveness Evidence

CLL is an incurable disease, characterised by periods of active disease, during which patients are symptomatic, separated by remissions induced by chemotherapy. The main goal of therapy is to induce durable remissions during which patients are free of disease symptoms, the psychological burden of active life-threatening illness and the toxicity of chemotherapy. The evidence detailing the effectiveness of rituximab in combination with chemotherapy (R-chemotherapy) in the first-line treatment of CLL consists of a phase III trial, 4 supporting Phase II trials and a mixed treatment comparison.

In the Phase III trial CLL-8 (sections 6.1-6.4), patients with symptomatic CLL who needed treatment for the first time were randomised to induction therapy with 6 cycles of FC chemotherapy with or without rituximab. The main hypothesis being tested was that adding rituximab to the current standard of care (FC) would meaningfully improve progression-free survival (primary endpoint) for this group of patients. Further secondary endpoints, including response rates and overall survival have also been analysed. This is the only comparative, randomised Phase III trial available in the population of interest.

In the Phase II studies analysed (section 6.8), the hypotheses being tested were generally to assess the efficacy and tolerability of rituximab combination chemotherapy in patients with untreated CLL who needed treatment for the first time. As with follicular lymphoma, there has been some heterogeneity in the past about the optimal front-line treatment for CLL, therefore different research groups have combined rituximab with a variety of baseline regimes. The phase II data supports the pivotal Phase III study and gives extra evidence which supports the R-chemotherapy licence.

Key Clinical Results: CLL-8

CLL-8 randomised 407 patients to FC and 403 to R-FC. The efficacy results from the main analysis are summarised in Table 3 below.

Table 3: Summary of Overall Efficacy : CLL-8, Main Analysis.

Median Follow up 20.7 months

Parameter	**FC** **N = 407**	**R-FC** **N = 403**
Progression Free Survival		
Median (months)	32.2	39.8
p value (Log-Rank test)	**P <0.0001**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.56 (0.43; 0.72) **p < 0.0001**	
Stratified (not adjusted)	0.53 (0.41; 0.68) **p < 0.0001**	
Overall Survival		
Median (months)	Not reached	Not reached
p value (Log-Rank test)	**p = 0.0427**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.64 (0.41; 1.00) **p = 0.0487**	
Stratified (not adjusted)	0.60 (0.38; 0.94) **p = 0.0250**	
Event-Free Survival		
Median (months)	31.1	39.8
p value (Log-Rank test)	**p < 0.0001**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.55 (0.43; 0.70) **p < 0.0001**	
Disease-Free Survival		
Median (months)	Not Reached	Not Reached
p value (Log-Rank test)	**p = 0.7882**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.93 (0.44; 1.96) **p = 0.8566**	
Duration of Response		
Median (months)	34.7	40.2

	p = 0.0040	
	0.61 (0.43; 0.85) **p = 0.0036**	
Time to New Treatment		
Median (months)	Not Reached	Not Reached
p value (Log-Rank test)	**p = 0.0052**	
HR (95% CI) p value (Wald test) Unstratified (adjusted)	0.65 (0.47; 0.90) **p = 0.0082**	
End-of-Treatment Response Rate (Overall Response Rate)	72.7%	86.1%
Complete Response (CR)	17.2%	36.0%
Partial Response (PR)/ Nodular PR	55.5%	50.1%
Stable Disease (SD)	7.6%	4.7%
Progressive Disease (PD)	7.6%	3.5%
Missing	12.0%	5.7%

The results highlight a statistically significant and clinically very relevant improvement in progression-free survival (the primary-endpoint) in favour of R-FC over FC, with a 44% reduction in progression or death if rituximab was part of the combination treatment. With regards to the secondary efficacy endpoints noted, most showed significant and relevant improvements for the R-FC arm.

In total, three analyses from CLL-8 (with different lengths of follow-up) are available for clinical evaluation. With a median of 25.5 months of follow up, the statistically significant overall survival benefit seen in the R-FC arm at the main analysis (median of 20.7 months follow-up) was no longer present, but a trend towards overall survival remained. All other endpoint results were consistent with the main analysis of the study. Excess toxicity was limited in the R-FC arm, with a significant increase in grade 3/4 leukopenia and neutropenia not matched with an increase in infections in the rituximab containing arm. Out of the three clinical analyses available for discussion, two were carried out by Roche and one (with the longest follow-up), by the German CLL study group. Only the first two analyses (present in the clinical study report – median follow ups of 20.7 and 25.4 months) were presented in the regulatory submission to the EMEA for the marketing authorisation extension. It should also be noted that in the economic evaluation, a fourth cut of the data (median follow up of 26.4 months) has been used for modelling. This is presented in section 7.

Table 4. Summary of Data available for CLL-8

ANALYSIS	MEDIAN FOLLOW UP	DATE OF ANALYSIS	ANALYSED IN SUBMISSION
Main (as per protocol)	20.7 months	July 4th, 2007	section 6.4
Snapshot 1	25.4 months	February 8th, 2008	section 6.4
Snapshot 2	25.5 months	June 2008	section 6.4
Economic snapshot	26.4 months	July 2008	section 7 (economic analyses)

It should be noted that between the various data cuts, there is clear consistency in the results seen and this will be fully discussed subsequently. Snapshot 2 was not carried out by Roche, and the results for this data cut are taken from a published abstract which is due to be presented at the American Society of Haematology congress in December 2008. Even though there is 4 months between snapshots 1 and 2, there is only a minimal increase in the median follow up because very little additional data was accrued during this time and naturally median follow up in a cohort does not change linearly with time.

Key clinical results: Phase II studies

Results from four Phase II studies (section 6.8) looking at different combinations of chemotherapy in previously untreated patients with CLL gives extra efficacy and safety data in an additional 498 patients. Combinations used were R-FC (300 patients), R-F(rituximab and fludarabine -104 patients), R-PC (rituximab, pentostatin and cyclophosphamide – 65 patients) and R-FCM (R-FC and mitoxantrone – 30 patients).

The results of these studies consistently highlight high response rates and the good efficacy of R-chemotherapy.

In the study assessing R-FC in 300 patients (Tam et al.), at a median follow-up of six

years, the overall response rate was 95%, with complete response (CR) in 72%, and partial responses in 23%. Six-year overall survival (OS) and failure-free survival (FFS) were 77% and 51%, respectively. Median time to progression (TTP) was 80 months.

In the study assessing fludarabine and rituximab as a combination (with two different ways of applying rituximab – concurrent or sequential- Byrd et al.), the overall response rate with the concurrent regimen was 90% (47% CR, 43% PR; 95% confidence interval [CI], 0.82-0.98) compared with 77% (28% CR, 49% PR; 95% CI, 0.66-0.99) with the sequential regimen. With a median follow-up time of 23 months, the median response duration and survival had not been reached for either regimen.

In the study assessing R-FCM (Faderl et al.), Twenty-eight patients (97%) had responded at 3 months (41% CR, 17% nPR, 39% PR) and 10 patients (34%) had <1% detectable residual CLL cells in the bone marrow. Response rates at completion of therapy were: 77% CR, 10% nPR, 10% PR (overall response rate [ORR] = 97%). Seventeen patients (57%) had < 1% residual CLL cells in the marrow at the end of therapy.

In the study assessing R-PC (Kay et al.), responses occurred in 58 patients (91%), with 26 (41%) CRs, 14 (22%) nPRs, and 18 (28%) PRs. The median PFS was 32.6 months.

Toxicity in all of the Phase II studies was predictable and generally manageable, with no obvious added burden of additional toxicity compared to chemotherapy alone.

Demonstrating the Cost Effectiveness of Rituximab

The economic evaluation utilises the key outcomes of the ML17102 (CLL-8) clinical trial and is designed for the purposes of estimating lifetime NHS costs and QALYs for R-FC and two relevant comparators (FC and chlorambucil). The model conforms to the reference case as described in NICE's Guidance to the Methods of Technology Appraisal. The economic model developed was a three-state Markov model, where patients are assumed to be within one of three possible discrete health states at any given time; "progression-free survival", "progressed" or "death".

The health economic analysis also benefited from the unique opportunity to utilise longer term registry data relating to rituximab in CLL, despite the submission being made in advance of CHMP opinion. This provided the opportunity to validate the longer term predictions of the trial extrapolations and present an alternative estimate of the clinical benefits based upon alternative estimates of the treatment effect of rituximab within the existing model structure. The application of this registry data confirmed that the trial based estimates of the clinical benefit for rituximab appear reliable.

Lifetime progression free survival was estimated from an extrapolation of the PFS curves from the CLL-8 trial for the R-FC and FC arms. The comparison between R-FC and chlorambucil was informed by an indirect comparison and validated by a mixed-treatment comparison. Because median overall survival had not been reached, a Markov process was constructed to model the transition from the progressed health state to death. Remaining model inputs were taken from the published literature where possible and supplemented with UK expert medical opinion where necessary.

Six cycles of rituximab treatment cost an additional £10,128 per patient. Over an expected lifetime, R-FC is estimated to generate an additional £11,617 of total costs per

patient compared to FC alone and an additional £12,250 of total costs per patient compared to chlorambucil. R-FC is predicted to extend discounted progression free survival by 1.18 years and discounted overall survival by 1.07 years compared to FC. From the comparison against chlorambucil, R-FC is predicted to extend discounted progression free survival by 2.54 years and discounted overall survival by 2.33 years.

The cost per QALY has been demonstrated to be robust when subject to both one-way and probabilistic sensitivity analysis. R-FC can be regarded as a highly cost effective treatment for the first line treatment of CLL with a high degree of certainty.

The reference case cost per QALY for R-FC compared to FC is estimated to be £13,189. The reference case cost per QALY for R-FC compared to chlorambucil is estimated to be £6,422. Both ICERs are therefore below the lower NICE threshold of £20,000/QALY gained.

Summary

One large well-designed randomised controlled trial demonstrates that for patients with CLL who need treatment for the first time, R-FC is significantly more efficacious than FC alone. Adding rituximab dramatically improves the treatment outcomes traditionally targeted (time in remission), and reduces the risk of progression or death by 44%. In the main analysis, there was an overall survival benefit seen in favour of the R-FC arm, but with slightly longer follow up, this is no longer significant. It is therefore too early to speculate on this secondary endpoint, even though the survival benefit continues to looks highly encouraging. These important benefits are achieved with minimal extra burden of treatment being put upon patients, with very modest additional toxicity of adding rituximab to FC, which is entirely in keeping with the known safety profile of rituximab. The phase II data adds confidence that rituximab can be combined with other chemotherapy regimes, giving significant efficacy and predictable, mild and manageable toxicity. With regards to the comparison with chlorambucil, a mixed treatment comparison (section 6.6) provides a network meta-analysis which highlights the superiority of R-FC over chlorambucil. The MTC highlights that compared to chlorambucil, R-FC has the best chance of prolonging PFS, obtaining a CR and results of both fixed and random effects analyses suggest there was no significant heterogeneity across the network of studies analysed in the comparison. The quality of life of patients treated with rituximab will be enhanced by a prolonged first remission of their disease. The economic evaluation of R-FC versus two common UK chemotherapy treatments (FC and chlorambucil) illustrated that rituximab is a highly clinically and cost effective first-line treatment for CLL.

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

What is Chronic Lymphocytic Leukaemia (CLL)?

CLL is a B-cell lymphoproliferative disorder, characterised by the proliferation of genetically abnormal mature B-lymphocytes that accumulate in the blood, bone marrow and lymph nodes.

4.1.1 Epidemiology

CLL is the most common type of leukaemia in the western world, comprising approximately 30% of all adult leukaemias. The incidence is around 3/100,000 and this varies with age and sex. Incidence increases significantly with age, with a rate of almost 50/100,000 in patients over the age of 70. The median age of diagnosis is between 65 and 70, and men are twice as likely to be affected as women. CLL is generally rare in patients under the age of 50, however over the last few years , the incidence in this age group appears to be rising rapidly (Dighiero and Hamblin[1]).

The exact causes of CLL remain unknown, however a combination of genetic and environmental factors are thought to be involved. Recent research highlighting CLL arising in families and the phenomenon of monoclonal B-cell lymphocytosis (Rawstron et al.[2]) is helping to further characterise this complex malignancy.

4.1.2 Presentation, Diagnosis and Staging

The presentation of patients with CLL to healthcare providers can be very heterogeneous. Patients may present with lymphadenopathy, systemic symptoms such as tiredness, fever and weight loss and/or signs and symptoms of bone marrow infiltration/failure such as anaemia, bleeding or infection. However 70-80% of patients are now diagnosed as an incidental finding following a full blood count test for some other reason. Initial clinical assessment encompasses a detailed history and examination, looking specifically for family history of lymphoid malignancy, potential susceptibility to infection, documenting co-morbidity and examining for the presence of lymphadenopathy and hepatosplenomegaly.

A definitive diagnosis of CLL has a characteristic lymphocyte morphology on a blood film, together with a specific immunophenotype (as shown by flow cytometry) and requires an absolute B-cell lymphocytosis of at least 5 X 10^9/l.

Typically, CLL cells express weak monotypic surface immunoglobulin, CD5, CD19, CD23 and weak or absent CD79B, CD 22 and FMC7. A robust CLL scoring system was introduced in the mid 1990s to enable the differentiation of CLL from other B-cell lymphoproliferative disorders more easily, which can occasionally be mis-diagnosed as CLL (and vice-versa). For example, the leukaemic phase of mantle cell lymphoma and sometimes other traditionally CD5 negative diseases, such as hairy cell leukaemia and marginal zone lymphoma have caused diagnostic difficulty.

At diagnosis, prognostic biomarkers, including cytogenetics are being increasingly carried out and this is discussed further in section 4.1.4 below.

Additional investigations which are usually performed at diagnosis in order to be able to fully assess patients with CLL include a full panel of blood tests (renal and liver biochemistry, reticulocyte count, direct antiglobulin test, serum immunoglobulins), chest X-ray, lymph node biopsy (as required) and computed tomography (CT scan) of neck/chest/abdomen/pelvis to fully document and stage extent of disease (see below). Bone marrow aspirate and trephine are not mandatory at diagnosis, but are usually carried out at initiation of treatment.

Staging

Two methods have been devised to stage CLL – the Binet and Rai systems. The Rai system is more commonly used in the United States and Binet is used more in Europe.

Table 5: Staging Systems in Chronic Lymphocytic Leukaemia

	Features	**% of patients**
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**
Rai Stage		
0	**Lymphocytosis only**	**30**
I	**Lymphadenopathy**	**25**
II	**Hepato/splenomegaly +/-lymphadenopathy**	**25**
III	**Haemoglobin <11g/dL**	**10**
IV	**Platelets <100 X10^9/l**	**10**

4.1.3 Prognostic Factors

In the past decade, significant research has been carried out in this area. It is becoming increasingly apparent that specific expression patterns on CLL cells and cytogenetic abnormalities may predict a number of clinical variables such as initial response to treatment, potential aggressiveness of disease and prognosis. The majority of these are not currently used in routine therapy to guide decision making (except molecular genetics via fluorescence in situ hybridisation [FISH]).

4.1.4.1 Molecular Genetics

Using interphase FISH, cytogenetic abnormalities can be identified in more than 80% of all CLL cases (Dohner et al.[3]). The most common deletions are in the long arm of chromosome 13. Additional aberrations are often seen in chromosome 12 ,11, 6 and 17. There is increasing evidence that the type of cytogenetic abnormality has prognostic significance. Patients with leukaemia cells that have del(17p) – which frequently corresponds to a mutation in the p53 tumour suppressor gene generally have a poor prognosis and in many series appear to be resistant to standard chemotherapy regimes. It also appears that the frequency of del(17p) is low in newly diagnosed patients and increases as patients relapse (Thornton et al.[4]).

4.1.4.2 Mutational Status of IgV_H, ZAP-70/CD38

CLL cells express immunoglobulin that may or may not have acquired somatic mutations in the immunoglobulin heavy chain variable region genes (IgV_H genes). Patients with unmutated IgV_H have worse outcomes compared to those with mutated genes (Hamblin et al.[5]). It has also been found that leukaemia cell expression of ZAP-70 and CD38 correlates with the expression of unmutated IgV_H genes.

4.1.4.3 Summary

These additional tests are performed at diagnosis, and often repeated at relapse. Abnormalities in the short arm of chromosome 17 (especially del(17p)) are associated with poor prognosis and specific treatment strategies involving the anti-CD52 monoclonal antibody alemtuzumab (see 4.1.5) are often recommended (e.g. Kaufman and Rai[6]). The efficacy of rituximab combination chemotherapy in this sub-group of patients has not been analysed to date in a randomised Phase III study, but some data is now available from the pivotal study and is discussed subsequently in the efficacy section.

4.1.4 Treatment Principles

For the majority of patients, CLL is incurable, and the median life expectancy is between 5 and 10 years. Much disease is picked up incidentally and numerous patients remain asymptomatic for many years, and never require treatment. It is anticipated that approximately 1/3 of diagnosed patients (usually Binet A) will never need any form of treatment for their disease and that they will die with rather than of their disease (Dighiero G.[7]).

Standard criteria drawn up The National Cancer Institute Working Group in 1996 (Cheson et al.[8]), which have been updated this year (Hallek et al.[9]) are used to guide whether patients should start treatment. These criteria indicate that only patients with symptomatic disease, should start therapy; at least one of the following criteria should be met:

1. Evidence of progressive marrow failure as manifested by the development or worsening of, anaemia and/or thrombocytopenia.

2. Massive (i.e. >6cm below the left costal margin) or progressive or symptomatic splenomegaly.

3. Massive nodes (i.e. >10cm in longest diameter) or progressive or symptomatic lymphadenopathy.

4. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time of less than 6 months.

5. Autoimmune haemolytic anaemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy.

6. A minimum of any one of the following disease-related symptoms must be present:

- 10% weight loss within the last 6 months

- significant fatigue

- fevers of greater than 38.0^0C for 2 or more weeks without evidence of infection

- night sweats for more than one month without evidence of infection.

The question of whether treating asymptomatic early-stage disease offers any benefit to patients has been addressed by a meta-analysis of CLL treatment trials published in 1999 (CLL Trialists' Collaborative Group[10]). This analysis included 2048 early-stage patients who were randomly allocated to immediate or deferred treatment with chlorambucil with or without prednisolone. No benefit for either group was seen. This outcome has guided the modern management of asymptomatic, early-stage disease: It is now well established worldwide that patients with early-stage, asymptomatic disease (typically Binet A, but also some Binet B), should not be treated outside the remit of a clinical trial. This is re-endorsed in the updated guidelines published by Hallek et al. this year. There is a clinical parallel here with early stage, asymptomatic follicular lymphoma, which is also currently managed by a watch and wait strategy. There may well be a population of early-stage disease that does benefit from early intervention, but this group has not yet been defined by prospective clinical trials. It is important to note that all the trials analysed in this submission with reference to the decision problem only included patients who needed treatment as defined by the standard criteria discussed above.

4.1.5.1 Treatment Goals in CLL

Once the decision has been made to treat, the attending clinician initially needs to decide what the treatment goal is for each individual patient. CLL is generally incurable (a small proportion of patients may be cured by allogenic bone marrow transplantation) and treatment will alleviate signs and symptoms but relapse is expected and inevitable. As with other relapsing indolent diseases, progression-free survival is of key relevance to patients and their physicians. It is clinically intuitive that in a relapsing disease, aiming for the longest progression-free survival will give as much time free from the signs and symptoms of disease and also delay the psychological trauma of relapse and the requirement for further, potentially toxic treatment.

Historically, CLL has been managed with the aim of controlling the disease, minimising treatment-related toxicity and maximising quality of life. The meta-analysis discussed above in the context of early-stage disease (CLL trialists collaboration - 1999) also analysed available controlled studies of treatments for symptomatic patients. Its' analysis and conclusions supported the notion that different therapeutic approaches (e.g. aggressive treatment including an anthracycline) had no survival benefit to patients

compared to the less toxic, single agent oral chlorambucil. Following this publication, many UK clinicians decided that of all available treatments, chlorambucil allowed them acceptable efficacy, together with only mild toxicity and they felt reassured by the finding that aggressive, more toxic treatments did not seem to improve outcomes. Thus, at the start of the decade, chlorambucil was very much a popular treatment, and treatment goals were often aligned with minimising toxicity and maximising quality of life, without necessarily attempting to gain the best response/remission possible.

However, the need for treatments that provided better efficacy (and patients relapsing less quickly) with acceptable toxicity and the drive to improve relevant survival endpoints was naturally a desired outcome for clinicians and patients alike (as one would expect for a disease with significant unmet need). The CLL trialists collaborative meta-analysis reported before any of the encouraging data highlighting the use of the purine analogue fludarabine was published. As efficacy has improved with fludarabine combination regimes (see section 4.1.5.2) and the use of alemtuzumab (in sub-sets of patients), it has become increasingly clear that the depth of remission is relevant. The better the quality of remission and the ability to eradicate minimal residual disease (MRD), has been shown to strongly correlate with improved prognosis, (e.g. Bosch et. al[11], Rawstron et al[12], Provan et. al[13]). MRD assessment (which now is allowing the detection of low as ten CLL cells in a million leucocytes) is becoming a standard (secondary) endpoint of many new CLL studies, but is not currently routinely used in clinical practice. Assaying MRD only has relevance for treatments that have the ability to provide complete responses; less efficacious treatments (e.g. chlorambucil) will usually always leave some easily identifiable disease. So, in general the paradigm of treatment is shifting towards aiming to get a good a remission as possible – as measured by standard criteria. Of note, the eradication of MRD is currently not required in the revised criteria for the definition of a complete response and the role of eradicating MRD in this group of patients is being actively pursued in clinical trials.

It also must be noted that aiming for the deepest possible remission may not be possible for all patients. Older patients with co-morbidities make up a significant proportion of patients who require treatment, and their risk of treatment toxicity is higher, so adaptive treatment strategies are important, and in some cases a 'disease control' strategy that minimises toxicity may be appropriate. What has become apparent from recently published studies is that there are more patients than previously thought (older, frailer etc), that can tolerate therapy that aims for the best remission possible (e.g. Catovsky et al., as discussed below).

4.1.5.2 First-Line Treatments

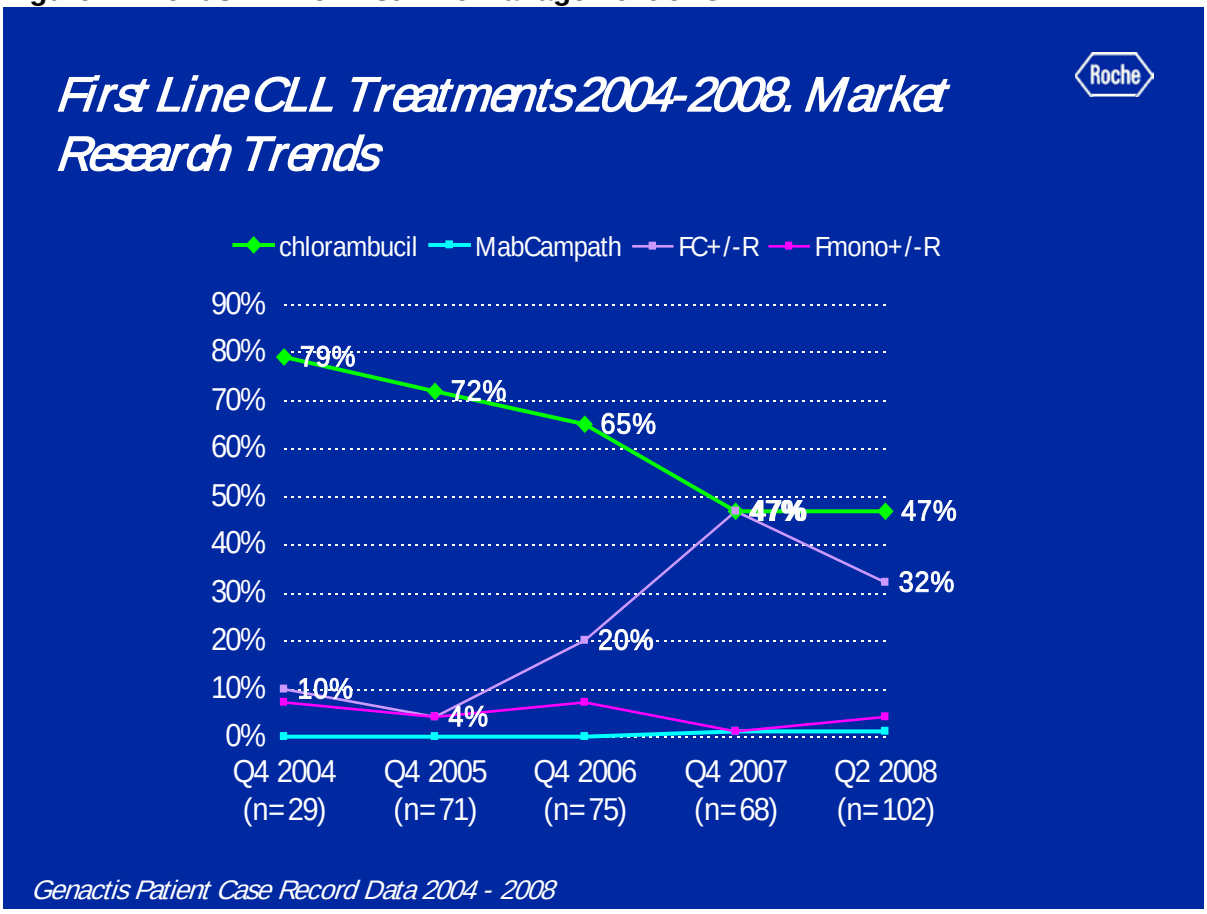
Since 1999, three major comparative randomised controlled studies that have analysed the use of fludarabine and fludarabine combination therapies (fludarabine and cyclophosphamide – FC) as front-line therapy for CLL (Eichhorst et al.[14], Catovsky et al.[15] and Flinn et al.[16]) have been published.

These studies have all highlighted that combination FC offers the best efficacy and tolerable toxicity for front-line treatment compared to single agent fludarabine and also compared to chlorambucil (chlorambucil was a comparator arm in Catovsky et al., single

agent fludarabine was a comparator in all three trials). These studies have guided clinicians towards using FC as the optimal first-line treatment, and various points relating to these studies will be analysed throughout the submission.

In the United Kingdom, the UK LRF CLL-4 study (Catovsky et al.), has informed practice significantly, and was the only study of the three that used chlorambucil as one of the comparator arms. The published results have led to a significant trend of treatment away from chlorambucil, towards FC as is highlighted by market research commissioned by Roche over the last five years (see figure 1 below).

Figure 1: Trends in The First-Line Management of CLL



In the UK, the initial management of patients with 17p deletions/ other p53 abnormalities is usually carried out in tertiary referral centres and often involves treatment with alemtuzumab or enrolment into a an ongoing 'high-risk' clinical trial (e.g. Campred study). As can be inferred from the data shown above, this group of patients appears to be very small. It should also be noted that even though it is currently off-label (and the subject of this submission), approximately 14% of patients receive rituximab combination therapies upfront. Chlorambucil monotherapy continues to be used, however it is anticipated that clinicians will continue to move towards more efficacious combination therapies, generally including fludarabine.

1.1.1.1 4.1.5.3 Second and Subsequent Line Treatments

When patients relapse after their initial treatment, there are a number of problems that need to be addressed that were often not present when treatment was planned and administered for the first time:

1. Nature of the disease: CLL can clonally evolve and relapses can often behave more aggressively and contain extra poor-risk cytogenetic abnormalities (e.g. 17p deletion)

2. Toxicities may have accumulated from initial treatment, adding to co-morbidities and making subsequent treatment more difficult to administer.

The management of relapsed disease is beyond the remit of this submission and is not relevant to the population in the final scope by NICE will not be discussed further, suffice to say that treatment is often more difficult, and allogenic transplantation (often now with reduced intensity conditioning) is considered in specific cases.

4.1.5.4 Supportive Care of Patients with CLL

Numerous other factors are critically important in the holistic treatment of patients with CLL. This includes:

1. Clear communication about diagnosis and treatments (it often being difficult to initially explain the concept of watchful waiting), and managing emotional and psychological needs appropriately.

2. Appropriate and swift treatment of infections and judicious use of prophylaxis during treatments as deemed appropriate. All CLL patients are at increased risk of infection because of compromised immune function and seemingly trivial infections can often become serious very quickly.

3. Management of autoimmune cytopenias: The increased risk of autoimmune haemolysis and thrombocytopenia are well established and require specific treatments as indicated. An extended discussion of this is beyond the scope of this summary.

4. Splenectomy for severe symptomatic splenomegaly, and the requirement of immunisations surrounding this procedure.

5. General management of patients with co-morbidities.

4.1.6 Considerations of comparators for current review

As noted in the final scope, fludarabine combination therapies and chlorambucil were considered as appropriate comparators for this submission. Roche considers this entirely appropriate as these two treatment groups make up approximately 95% of prescribed chemotherapy regimes for first-line treatment in The United Kingdom.

4.2 What was the rationale for the development of the new technology?

Early clinical trials demonstrated the efficacy of rituximab used alone in multiply relapsed CD20 positive, indolent B-cell malignancy. In the pivotal, registration study (Mclaughlin

et al.[17]), 30 patients with relapsed small lymphocytic lymphoma (SLL – the lymphomatous partner of CLL) were treated with rituximab monotherapy, as part of the total cohort of 166 patients. Subsequent studies have demonstrated the efficacy of rituximab in conjunction with cytotoxic chemotherapy in a variety of newly diagnosed and relapsed B-cell lymphomas. What also became apparent in initial studies was the excellent and predictable safety profile of rituximab, as a monotherapy or in combination with chemotherapy.

Against this background of efficacy and tolerability in B-cell NHL (and activity noted in SLL), and the fact that virtually all CLL is CD20 positive, it made clinical sense to aim to answer the questions of if and how rituximab should or could be used in CLL treatment strategies. There continues to be an unmet need in CLL with disease progression and relapse occurring after all current induction regimes.

Key questions that needed answering were as follows:

1. Is there activity and efficacy ?

2. What is the optimal dose ?

3. What is the safety profile ?

4. Is the risk/benefit profile improved when rituximab is used in combination with chemotherapy or as a monotherapy ?

O'Brien and colleagues[18] investigated the role of rituximab monotherapy in CLL (both in first-line and relapsed/ refractory patients). It was apparent from the results that monotherapy at escalating doses was increasingly efficacious, and that 375mg/m^2 (the standard lymphoma dose) would not necessarily be the ideal dose to use in CLL. From the results of published studies in aggressive and indolent B-cell lymphomas, it was also becoming apparent that combining rituximab with chemotherapy may actually be the best strategy for gaining an optimal safety/efficacy balance in CLL. On the basis of published combination studies in lymphoma and the dose-escalation work from the O'Brien study, it was mooted by Keating and his colleagues at MD Anderson Cancer Center in Texas, USA that rituximab combination chemotherapy with a higher dose of rituximab may be a highly efficacious approach in CLL. They therefore devised their Phase II chemoimmunotherapy study for the initial treatment of CLL (fludarabine and cyclophosphamide in combination with rituximab – R-FC), (Keating et al.[19], Tam et al.[20]). The dose of rituximab used was 500mg/m^2 (with a dose of 375mg/m^2 only for the first cycle). This study has reported its final results and will be analysed subsequently. The randomised Phase III study that compares FC to R-FC (CLL-8 analysed in detail in this submission) is the pivotal study that has been presented to the regulatory authorities for the extension to the marketing authorisation used the rituximab dose pioneered in the MD Anderson Phase II study.

4.3 What is the principal mechanism of action of the technology?

Rituximab is a chimeric murine/human monoclonal antibody that binds selectively to the CD20 cell antigen expressed on the surface of mature B lymphocytes and any tumour cell that expresses CD20 (i.e. all B-cell malignancies), including B-cell chronic lymphocytic leukaemia.

It causes depletion of normal and malignant B cells. Although its mechanism of action is not precisely defined, antibody-directed cytotoxicity, complement-dependent cytotoxicity, induction of apoptosis and sensitisation of cells to conventional cytotoxic drugs are all likely to be important (Reff et al. [21], Demiden et al. [22,] and Anderson et al.[23])

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

The goal of therapy in a generally incurable malignancy is to improve the time without signs and symptoms of the disease, which is best objectively measured by progression-free survival (PFS). The data presented in this submission highlights that for first-line treatment, rituximab in combination with chemotherapy offers the best opportunity for the longest PFS.

Therefore, it is suggested that the initial treatment of any patient receiving treatment for CLL for the first time receives a combination therapy including rituximab, irrespective of age, performance status or any genetic subgroup.

The data to be analysed infers that treatments currently used in this disease have evolved from older, less efficacious treatments and that adding rituximab to current regimes is the next stepwise addition to allowing the optimal initial treatment in this relentlessly relapsing, progressive malignancy.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Since the late 1990s and the publication of the CLL Trialists meta-analysis, a number of issues have come to light about the optimal initial therapy for chronic lymphocytic leukaemia:

1. The role of fludarabine based therapy (monotherapy or combination therapy) versus the role of chlorambucil monotherapy .

2. Disease ‘control’ versus aiming for best remission possible. What is the appropriate management strategy ?

3. Should minimal residual disease be eradicated after completing treatment ?

4. What is the role of rituximab and how should it be optimally used ?

5. What is the optimal management of patients with p53 mutations/deletions ?

6. How does one optimise outcomes for older patients with co-morbidites who require treatment ?

These issues (except 4 – which forms the core clinical discussion of this submission) have been extensively covered in Section 4.1.5.1, when treatment goals in CLL were discussed.

Best practice in the United Kingdom has been much more clearly defined by the results of the UK LRF CLL-4 study, and it is anticipated that the trend away from chlorambucil monotherapy towards the more efficacious fludarabine-based therapy will continue. The optimal management strategy for those in which fludarabine-based therapy is not deemed appropriate (e.g. because of co-morbidities/frailty) is less clear and improving on the generally poor efficacy of chlorambucil is being actively investigated, for example with the UK CLL201 study which combines chlorambucil and rituximab in an open label Phase II study. This study is based in the UK only, and open in 12 centres.

In terms of regional variations in practice, it appears that different clinicians have different 'tipping points' to decide who is fit enough for more aggressive fludarabine combination therapy versus milder chlorambucil therapy. Some clinicians will only reserve chlorambucil for the very, very frail and elderly and as a palliative measure, whereas some will consider it as their standard treatment, except for the very young and fit. Part of the reason why disease-control strategies are still fairly widely used may be because that no specific treatment in any randomised controlled trial to date has shown a statistically significant benefit in terms of improving overall survival, even though other increasingly relevant endpoints such as response rates, PFS, have been shown to be statistically different between arms. There are likely to be valid reasons for the lack of overall survival being seen for a specific treatment (e.g. the concept of cross-over in patients relapsing early on when randomised to a less efficacious treatment), and the difficulties of looking for overall survival in a disease with a long natural history.

4.6 Provide details of any relevant guidelines or protocols.

In the United Kingdom, the most up to date national practice guidelines on the diagnosis and treatment of CLL were published by The Guidelines Working Group of the UK CLL forum on behalf of The British Committee for Standards in Haematology in 2004 (Oscier et al.[24]).

These guidelines recommended that optimal initial treatment for most patients was entry into the MRC UK CLL-4 study, where the hypothesis testing the relative efficacy and tolerability of fludarabine alone, chlorambucil alone or fludarabine and cyclophosphamide combined (FC) were being analysed in a prospective randomised controlled study (Catovsky et al., as described earlier). At the time of publication of these guidelines, this was an entirely reasonable strategy as the superior efficacy and good tolerability of FC in this group patients had not been formally established, and the final analysis of this study reported last year. These guidelines also noted the role of rituximab in combination with fludarabine-based therapies and highlighted that further data needed to come to light before the group could offer meaningful guidance. Roche feel that this data is now available (as analysed in this submission) and we understand that these guidelines will be revised in the next 6 months. This will update UK clinicians on all changes in CLL management and within that give more guidance on how rituximab should be used in CLL.

More recent guidelines (2007) have also been published by the European Society of Medical Oncology (Hallek et. al.[25]). These take into account the published fludarabine randomised trials as discussed above and recommend fludarabine and cyclophosphamide as the first option for fit patients being treated for the first time, and either a dose-adjusted fludarabine regime or chlorambucil for the less fit. This again highlights the appropriateness of the choice of comparators for this submission. Regarding the role of rituximab, these guidelines noted that prospective Phase III trials were underway to assess chemoimmunotherapy rigorously. This data, now available, is presented in this submission.

American guidelines updated this year by The National Comprehensive Cancer Network (NCNN)[26] recommend the use of rituximab combination therapy for first line treatment with Category 2A evidence (by their definition Category 2A is " based on lower-level evidence in clinical experience and uniform consensus"). Specifically, their preferred noted options are purine analogue based treatment with or without rituximab (fludarabine +/- rituximab, fludarabine, cyclophosphamide +/-rituximab or pentostatin, cyclophosphamide and rituximab). These recommendations are based on American led Phase II studies, which will be analysed subsequently. It is relevant to highlight the uniform consensus that is highlighted by these American guidelines and the fact that rituximab is already a core recommendation of American treatment.

5 Equity and equality

5.1 Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No issues relating to equity or equalities have been identified.

How has the analysis addressed these issues?

Not applicable.

6 Clinical evidence

6.1 Identification of studies

There is significant published material in the literature concerning rituximab and chronic lymphocytic leukaemia. However, the decision problem at hand – ' rituximab *in combination* with chemotherapy for the *first-line* treatment of *previously untreated* patients with chronic lymphocytic leukaemia' narrows down the number of relevant studies. Trials with a mixture of first line/relapsed + refractory patients, rituximab monotherapy, other strategies involving consolidation and maintenance are not directly applicable to the decision problem and the filtering out of studies reflects this.

To date, there has not been a published Phase III, comparative randomised controlled trial that compares rituximab combination chemotherapy with chemotherapy. ML 17102 (The CLL-8 study, led by the German CLL Study Group –GCLLSG)[27] is the first study of this type available for analysis, and forms the key component of the marketing authorisation application for rituximab in CLL. The first data from this meeting is due to be published and presented at The 50th Meeting of The American Society of Haematology in December 2008. The clinical study report and conference abstract (Hallek et al.)[28] represent the only Phase III trial data available for inclusion and the results of the search reflects this.

Dialog Datastar was used to search Medline (MEYY), Medline in process (MEIP), Embase (EMYY), Embase alerts (EMBA) and Biosis (BIYY - for abstracts presented at The American Society of Haematology (ASH) annual meeting). The Cochrane Library controlled trials database was searched for clinical trials of rituximab in chronic lymphocytic leukaemia.

Additionally the Roche application for a Type II variation to the MabThera marketing authorisation was reviewed for the relevant study reports and any other information not obtained elsewhere.

The randomised and relevant non-randomised studies were filtered out using the same searches. Exact details and further information are provided in appendix 2, section 10.2, as requested.

6.2 Study selection

6.2.1 Complete list of RCTs

1. Roche. CLL-8 Final Clinical Study Report ML17102. 2008.[27]

2. Hallek M, Fingerle-Rowson G, Fink A-M, Busch R, Mayer J, Hensel M, et al. Chemoimmunotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (R-FC) versus Fludarabine and Cyclophosphamide (FC) improves response rates and progression-free survival (PFS) in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL).[28]

Blood (ASH Annual Meeting Abstracts) 2008

Both these sources relate to a single study, the German CLL-8 Trial.

6.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

As detailed in Section 6.1, there is only one available comparative randomised controlled study. There is only one study and it is directly relevant. None have been excluded.

6.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 5.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

As highlighted above, there is only one study for discussion, and none have been excluded. This is the German CLL-8 study.

At this point it should be noted that a randomised Phase II ***non-comparative*** study involving rituximab combined with fludarabine (rituximab given concurrently with fludarabine with rituximab monotherapy consolidation for responders, or fludarabine alone followed by rituximab monotherapy consolidation for responders) in first-line CLL has been published (Byrd et al.[29]). However this was not designed as a comparative study, and contained rituximab in both arms. It does however add important data about efficacy and safety in the relevant population at hand and is therefore put in the list in Section 6.2.4 and is discussed fully with non-randomised studies in Section 6.8.

6.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

Table 6: List of Relevant Non-Randomised Controlled Trials

Study	Title of Publication	Regimen	No and Type of Patients Included
Tam et al., 2008	Long term results of the fludarabine, cyclophosphamide and rituximab regimen as initial therapy of chronic lymphocytic leukemia	R-FC	300 patients aged 18 years or older with previously untreated CLL and symptomatic or progressive disease
Byrd et al., 2003	Randomized phase II study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with CLL: results from Cancer and Leukemia Group B 9712	R-F or F→R Patients with response ≥ S D were treated with an additional 4 cycles of R	Symptomatic, previously untreated patients with CLL
Byrd et al., 2005	Addition of rituximab to fludarabine may prolong PFS and OS in patients with previously untreated CLL; an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011	Historical cohort comparison	N=104 R-F (concurrent or sequential) N=178 F alone
Faderl et al., 2007	Update of experience with fludarabine, cyclophosphamide, mitoxantrone plus rituximab (FCM-R) in frontline therapy for CLL	R-FCM (+ pegfilgrastim)	30 symptomatic, previously untreated patients with CLL
Kay et al., 2007	Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia	R-PC	64 previously untreated patients with CLL

Justification For Inclusion

These studies have been included because they are 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. The comparative Phase III study looks at one combination regime only (fludarabine, cyclophosphamide and rituximab : R-FC) , whereas these trials add to this. These studies are the key supporting data in the application for the variation to the marketing authorisation that Roche hopes will allow a broad chemotherapy combination licence rather than a licence that restricts rituximab to be given only with fludarabine combination therapies (as mooted by NICE in the final scope). In addition the single-arm Phase II study by Tam et al. provides long term follow-up (6 years), of patients treated with the combination of R-FC, the same rituximab combination analysed in the comparative Phase III study. The Phase III study has a follow up of a maximum of 25.5 months to date, hence it is very appropriate to highlight some longer follow-up data from a single-arm Phase II study, with the same chemotherapy regime (R-FC) as one of the arms in the pivotal study.

6.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

It is expected that the first interim safety analysis of Roche study MO20927 (a single-arm Phase II study analysing the safety and efficacy of chlorambucil in combination with rituximab as initial treatment for CLL for patients ineligible for fludarabine-based treatments), will be published in abstract form at a major international congress in 2009.

Figure 2: CONSORT Flow Chart for Randomised Study Selection Process for this Review

Publications identified	
Medline, EmBase,	94
ASH Abstracts via Biosis	42***
Medline in process EmBase Alerts	16 8
Cochrane Reviews	25
EMEA submission	1
Total	186

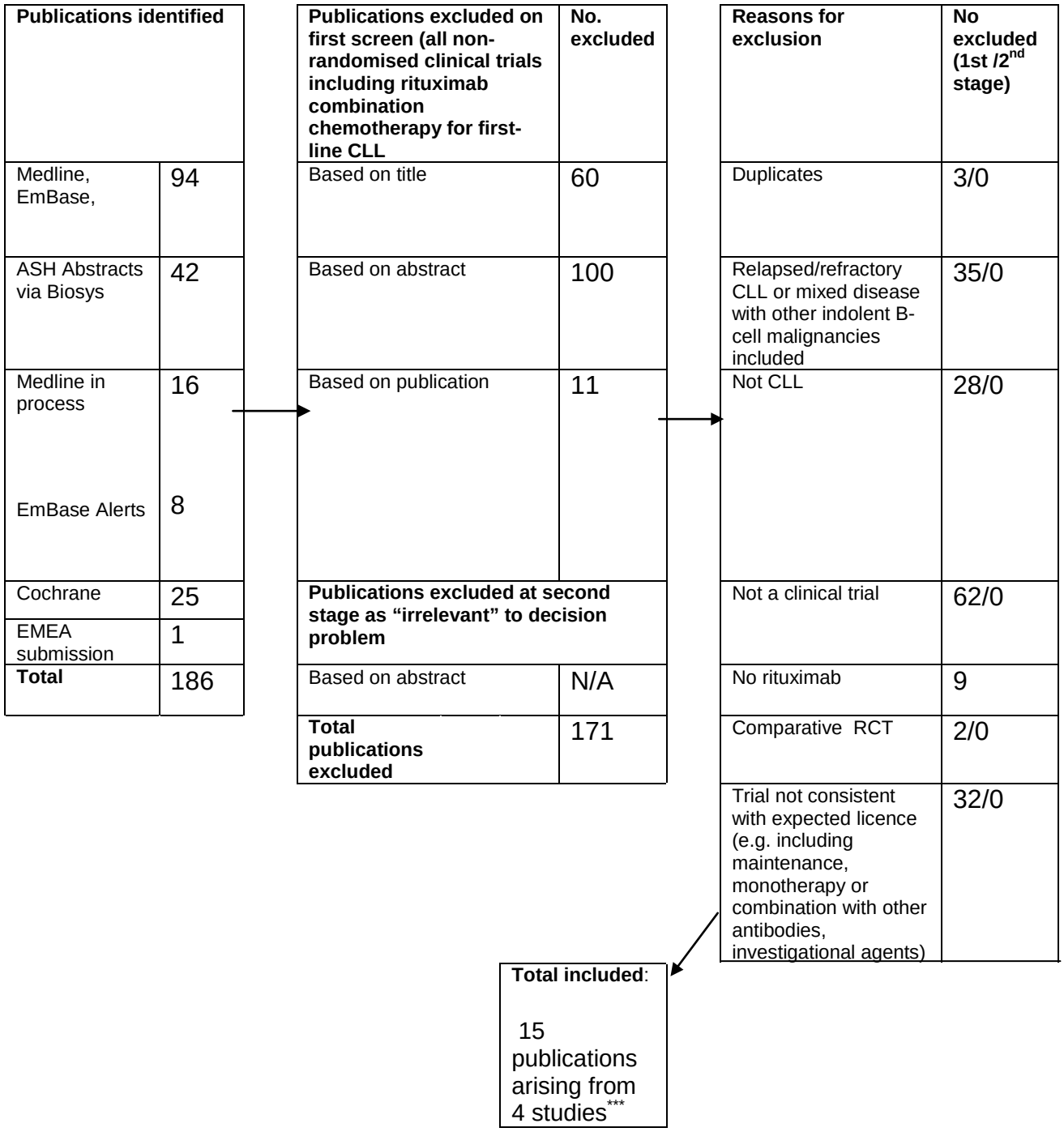
Publications excluded on first screening (all randomised clinical trials including rituximab combination therapy in untreated CLL aimed to be identified)	**No. excluded**
Based on title	149
Based on abstract	31
Based on publication	0
Publications excluded at second stage as "irrelevant" to decision problem	
Based on abstract	4
Total publications excluded	184

Reasons for exclusion	**No excluded (1st /2nd stage)**
Not a trial	56/0
Duplicates	3/0
Not CLL	12/0
Not a randomised trial including R-chemotherapy in first-line CLL	109/0
Not a comparative RCT	0/4

Total included:2 publications arising from 1 study (CLL-8) (clinical study report and one meeting abstract

***Please note, that when the Biosis was accessed for the literature review on 31 abstracts. Abstracts for the 50th Meeting of the American Society of Haematolog November 2008, therefore when the evidence review group perform their search abstract as detailed above. Therefore, in anticipation, 42 have been included rather than 41

Figure 3: CONSORT flow chart for non-randomised study selection process for this review



*** Please note out of the 4 studies, 3 have full peer reviewed journal publications (see sections 6.2.4 and 6.8), and one has a conference abstract only. For the fully published studies (R-FC: Keating et al. 2005[19], Tam et al. 2008[20]; R-F: Byrd et al. 2003[29], 2005[48] and R-PC Kay et al. 2007[46]), all data and analysis is taken from the full publications. For

Faderl et al. 2007[47], there is only a conference abstract available for analysis. So out of the 15 publications referring to the 4 studies, the 6 that provide the fullest, most up to date data are used).

6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

Rationale

Phase II studies in first-line and relapsed CLL have highlighted the efficacy and tolerability of adding rituximab to fludarabine based therapy. This study was designed to formally validate this concept for untreated patients in a Phase III setting.

Objectives Stated by The Investigators

The primary objective was to compare the clinical efficacy of rituximab in combination with fludarabine and cyclophosphamide (R-FC) to fludarabine and cyclophosphamide (FC) alone in patients with previously untreated chronic lymphocytic leukaemia who required therapy for the first time.

The primary efficacy endpoint was progression-free survival.

Secondary objectives were to evaluate numerous variables in patients treated with R-FC versus FC:

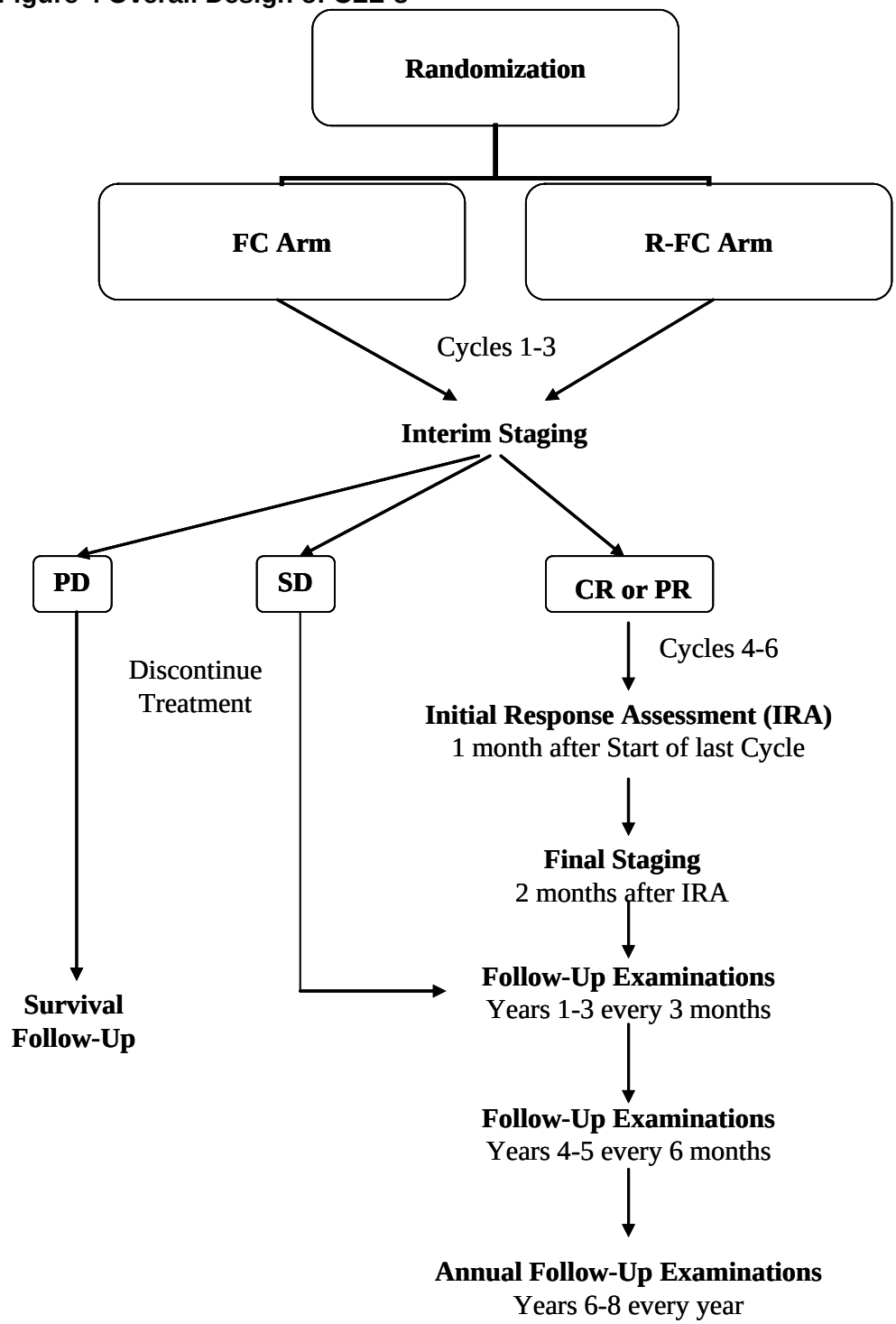
- Event-free survival
- Overall Survival
- Disease-free survival
- Duration of response
- Time to new CLL treatment or death
- Rates of molecular, complete and partial response
- Response rates and survival times in biological subgroups
- Rates of treatment-related adverse events
- Pharmacoeconomic impact
- Quality of life

Overall Design

CLL-8 was a randomised (1:1) multicentre, open-label, comparative, parallel group, two-arm Phase III study of R-FC versus FC in patients with previously untreated CD-20 positive CLL (according to National Cancer Institute [NCI] criteria).

Patients were randomised to induction with 6 cycles of FC+/-R and had an interim staging after 3 cycles. Patients with progressive or stable disease (as defined by standard NCI criteria), did not continue treatment but were eligible for alternative treatment and followed up for survival analyses. Patients with at least a partial response (PR) to therapy, continued through to 6 cycles**.** (See Figure 4 below).

Figure 4 Overall Design of CLL-8



Participating Research Groups

The study was a collaboration between Roche and the German CLL Study Group (GCLLSG).

Overall Patient Population Description

Untreated patients with CD-20 positive CLL.

Number of patients and Recruitment Period

A total of 817 patients were randomised at 190 centres in 11 countries (Australia 12, Austria 5, Belgium 6, Czech Republic 6, Denmark 3, France 13, Germany 121, Israel 6, Italy 11, New Zealand 3, Spain 4). Patients were recruited between July 21st 2003 and April 4th 2006.

Blinding

Open-label.

Randomisation Technique

A Block Randomisation procedure was used to separate the patients into the two groups. This was performed centrally at the data management centre of the GCLLSG in Munich. Randomisation was stratified by site up to 18th February 2005 and then stratified according to country and disease stage (Binet stage at pre-therapeutic staging).

Interventions

Patients were planned to receive 6 treatment cycles of FC chemotherapy (fludarabine [25 mg/m^2] and cyclophosphamide [250 mg/m^2] i.v. on days 1, 2 and 3 of each cycle) at intervals of 28 days. Patients randomised to the R-FC arm received FC in combination with rituximab (375 mg/m^2 i.v. on day 0 of cycle 1, 500 mg/m^2 i.v. on day 1 of cycles 2-6).

6.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

CLL-8: Inclusion and Exclusion Criteria

Inclusion Criteria

- Age ≥ 18 years
- Life expectancy > 6 months
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1

- Written informed consent
- B-CLL confirmed according to NCI Criteria
- Binet stage C
- Binet stage B (up to protocol amendment #1 also stage A)* requiring treatment, i.e. with the presence of at least one of the following signs or symptoms:
    - B symptoms (night sweats, weight loss ≥ 10% within the previous 6 months, fevers > 38°C [100.4°F] for ≥ 2 weeks without evidence of infection) or constitutional symptoms (fatigue).
    - Continuous progression (doubling of peripheral lymphocyte count < 6 months AND absolute lymphocyte count > 50 x 10^9/L).
    - Evidence of progressive marrow failure as manifested by the development/worsening of anemia and/or thrombocytopenia.
    - Massive, progressive or painful splenomegaly or hyperplenism
    - Massive lymph nodes or lymph node clusters (> 10 cm in longest diameter), danger of organ complications through large lymphomas (e.g. vascular compression, tracheal narrowing) or progressive lymphadenopathy.
    - Occurrence of symptomatic hyperviscosity problems at leukocyte counts > 200 x 10^9/L (symptomatic leucostasis).
- No previous treatment of the CLL by chemotherapy, radiotherapy or immunotherapy.
- Alkaline phosphatase and transaminases ≤ 2 x upper limit of normal (ULN).
- A negative serum pregnancy test one week prior to treatment had to be available both for pre-menopausal women and for women who were < 2 years after the onset of menopause.
- Willingness to use contraception for the entire duration of the treatment and 2 months thereafter.

Exclusion Criteria

- A patient with any of the following criteria was not allowed to enter the study:
- Binet stage A (from protocol amendment #1 onwards)
- Clinically significant auto-immune cytopenia, Coombs-positive haemolytic anaemia as judged by the treating physician.
- Active second malignancy currently requiring treatment (except basal cell carcinoma or tumour treated curatively by surgery).

- Pregnancy and/or nursing.
- Concomitant disease requiring prolonged use of glucocorticoids (> 1 month).
- Known hypersensitivity with anaphylactic reaction to humanized monoclonal antibodies or any of the study drugs.
- Cumulative Illness Rating Scale (CIRS) score > 6
- Cerebral dysfunction which made it impossible to perform chemotherapy.
- Transformation to aggressive B-cell malignancy (e.g. diffuse large cell lymphoma, Richter's syndrome, or pro-lymphocytic leukaemia).
- Active bacterial, viral or fungal infection. Although testing for hepatitis B was not mandatory, this was recommended to be considered for all patients at high risk of hepatitis B infection and in endemic areas. Patients with any serological evidence of current or past hepatitis B infection were excluded unless the serological findings were clearly due to vaccination.
- Total bilirubin > 2 x Upper limit of normal.
- Creatinine clearance < 70 mL/min. Patients with an estimated creatinine clearance just under 70 mL/min were eligible if a measured creatinine clearance (based on 24h urine collection or other reliable method) was ≥ 70 mL/min. Dehydrated patients with an estimated creatinine clearance less than 70 mL/min were eligible if a repeat estimate after adequate hydration was ≥ 70 mL/min.
- Treatment with any other investigational agent, or participating in another clinical trial within 30 days prior to entering this study.

* Protocol amendment #1 took place in July 2004. At this stage it was decided to remove patients with Binet Stage A as the benefits of treating this group of patients is not clear. This change reflects that there are small numbers of Binet Stage A in the patient population.

Demographics and Disease Characteristics at Baseline in CLL-8

The patient population in CLL-8 included mainly patients with symptomatic Binet stage B disease in need of therapy and Binet stage C disease (95%). Demographics (Table 7) and disease characteristics (Table 8) assessed at baseline were well balanced between the two treatment arms.

The overall study population comprised more males than females (74% versus 26%), with a median age of 61 years. The skew in sex was expected due to the established higher incidence of CLL in men. The majority of patients had a cumulative illness rating score (CIRS) of less than 4 (694/809 pts [86%]).

A total of 567 patients [70%] were below the age of 65 years (185 patients [23%] were ≥ 65- ≤ 70 years old) and 58 patients [7%] were older than 70 years).

Table 7: Summary of Demographic Data

	FC N=407	R-FC N=403	All N=810
Age (years) at Randomisation			
Mean	59.3	59.6	59.5
SD	8.55	8.70	8.62
Median	61.0	61.0	61.0
Min=Max	36–81	30–78	30–81
N	407	403	810
Sex			
Female	105 (26%)	105 (26%)	210 (26%)
Male	302 (74%)	298 (74%)	600 (74%)
N	407	403	810
CIRS Score at Baseline			
<4	341 (84%)	353 (88%)	694 (86%)
>=4	66 (16%)	49 (12%)	115 (14%)
N	407	402	809

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

Sixty-four percent of patients had Binet stage B disease at baseline, 31% had Binet stage C and 5% had Binet stage A disease (Binet stage A patients requiring treatment were excluded from the study in protocol amendment 1, as noted above).

Table 8: Summary of Disease Assessment

	FC N=407	R-FC N=403	All N=810
Binet Stage at First Diagnosis			
A	171 (42%)	202 (50%)	373 (46%)
B	175 (43%)	150 (37%)	325 (40%)
C	48 (12%)	37 (9%)	85 (11%)
Not Known	12 (3%)	12 (3%)	24 (3%)
N	406	401	807
Time from first diagnosis (months)			
Mean	28.15	31.31	29.73
SD	37.558	38.371	37.975
Median	13.14	16.72	15.15
Min-Max	0.0–331.4	0.0–208.7	0.0–331.4
N	405	402	807
Binet stage at baseline			
A	22 (5%)	18 (4%)	40 (5%)
B	257 (63%)	259 (64%)	516 (64%)
C	126 (31%)	125 (31%)	251 (31%)
N	405	402	807
B-Symptoms			
Yes	196 (48%)	165 (41%)	361 (45%)
No	208 (51%)	237 (59%)	445 (55%)
NK	1 (<1%)	–	1 (<1%)
N	405	402	807
ECOG performance status at baseline			
0	225 (58%)	221 (57%)	446 (57%)
1	161 (41%)	169 (43%)	330 (42%)
2	2 (<1%)	–	2 (<1%)
N	388	390	778

n represents number of patients contributing to summary statistics.

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

A total of 58% of patients had lymphocyte counts >50 x 10^9/L at study entry, splenomegaly was present in 70%, lactate dehydrogenase (LDH) was elevated in 41%, and the proportion of patients with B symptoms was around 45%.

Prognostic biomarkers (including cytogenetic abnormalities) were balanced between the arms (Tables 9 and 10)

Table 9: Prognostic Markers

	FC **N= 407**	**R-FC** **N=403**	**All** **N=810**
IgVH at Baseline			
Mutated	97 (36%)	87 (34%)	184 (35%)
Unmutated	169 (64%)	170 (66%)	339 (65%)
N	266	257	523
ZAP-70 at Baseline			
Positive	56 (38%)	60 (43%)	116 (41%)
Negative	91 (62%)	79 (57%)	170 (59%)
N	147	139	286
CD38+ at Baseline			
Positive	154 (44%)	166 (48%)	320 (46%)
Negative	193 (56%)	180 (52%)	373 (54%)
N	347	346	693

Table 10: Cytogenetic Abnormalities

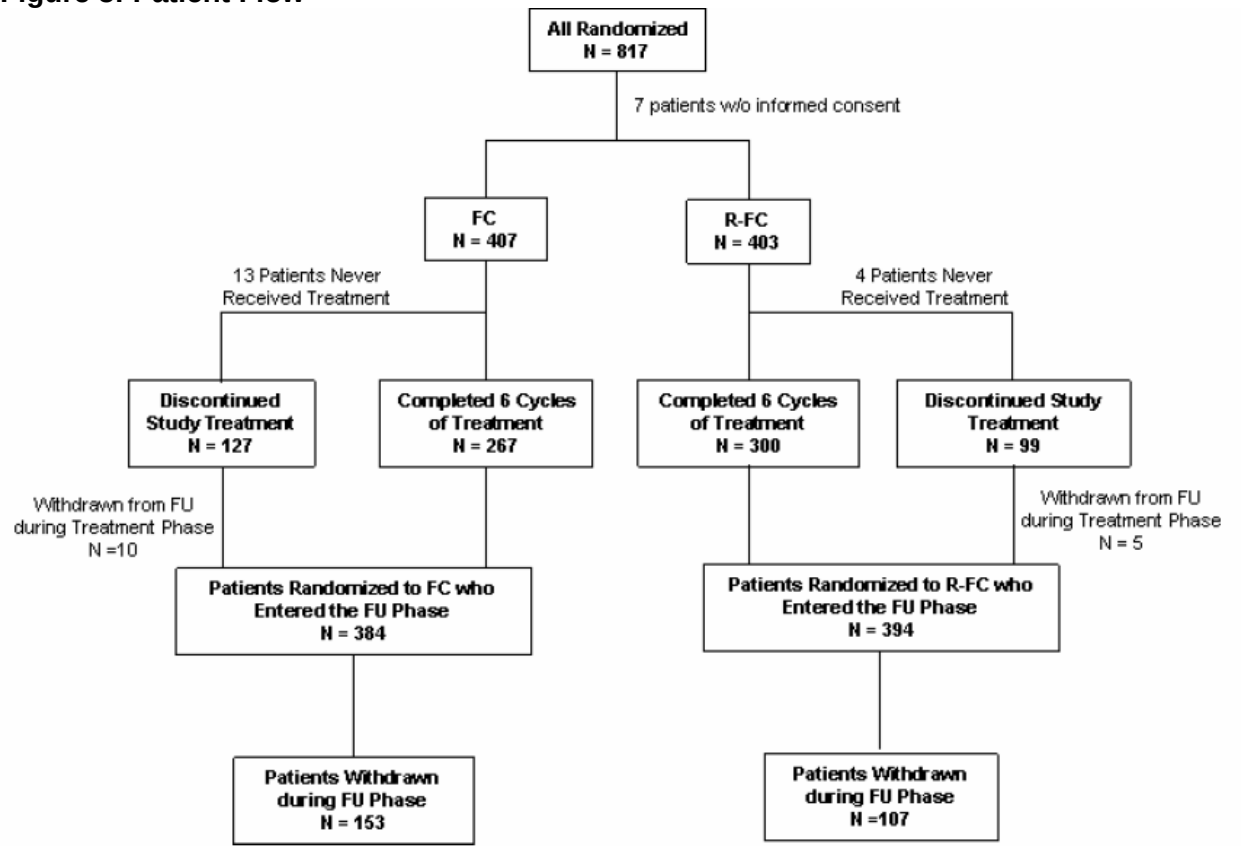
	FC N= 407	R-FC N= 403	All N=810
Del 11q at Baseline			
Yes	68 (23%)	80 (26%)	148 (25%)
No	232 (77%)	223 (74%)	455 (75%)
N	300	303	603
Del 13q at Baseline			
Yes	177 (59%)	165 (55%)	342 (57%)
No	121 (41%)	135 (45%)	256 (43%)
N	298	300	598
Del 17p at Baseline			
Yes	27 (9%)	19 (6%)	46 (8%)
No	271 (91%)	283 (94%)	554 (92%)
N	298	302	600
Trisomy 12 at Baseline			
Yes	42 (14%)	28 (9%)	70 (12%)
No	259 (86%)	273 (91%)	532 (88%)
N	301	301	602
Number of Cytogenetic Abnormalities			
0	60 (20%)	83 (27%)	143 (24%)
1	177 (59%)	153 (50%)	330 (54%)
2	58 (19%)	66 (22%)	124 (20%)
3	7 (2%)	1 (<1%)	8 (1%)
4	-	1 (<1%)	1 (<1%)
N	302	304	606

This distribution of prognostic biomarkers is representative of a population of previously untreated CLL patients in need of therapy.

6.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 5: Patient Flow



Patients who withdrew from the treatment phase (10 FC, 5 R-FC) did so primarily due to insufficient responses or administrative problems (i.e. processes, not issues related to drug administration).

During the follow up phase patients were prematurely withdrawn in both arms. A total of 47 patients (29 FC, 18 R-FC) were withdrawn due to safety concerns, including death, and 213 (89 FC, 124 R-FC) were withdrawn due to non-safety reasons, the primary reason being insufficient therapeutic response/ progressive disease (98 FC, 70 R-FC). All patients prematurely withdrawn from scheduled follow-up were followed for survival (except those that died).

6.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial

protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

Study CLL-8: Primary and Secondary Endpoints (as stated in Clinical Study Report)

Primary Endpoint

Progression-free survival (PFS): This was defined as the time between randomisation and the date of the first documented disease progression, relapse or death by any cause.

Secondary Endpoints

Event-Free Survival (EFS): This was defined as the time between randomisation and the date of progressive disease, relapse, start of new CLL treatment or death by any cause.

Overall Survival (OS): This was defined as the time between randomisation and the date of death from any cause.

Disease-Free Survival (DFS): This was defined for all patients with a confirmed complete response (CR). DFS was calculated from the time of first documented CR to the documented relapsed or death from any cause.

Duration of Response: This was defined for all patients who achieved any level of response (i.e. CR, nPR, PR). This was calculated from the time of first documented response to treatment to the documented disease progression or death by any cause.

Time to New CLL Treatment (TTNT): This was calculated from the date of randomisation to the date of starting a new CLL treatment.

Overall Response Rate: Calculated as the sum of complete and partial responses.

Further secondary ***objectives*** included analysing the molecular response rate and analysing health economic impacts and quality of life**.** Data on second line CLL therapies, the number of bone marrow transplants carried out subsequently and blood transfusions reported in the CLL-8 study were included in the economic analysis (see section 7).

Quality of life was measured by the attending physician at every visit using The Spitzer Quality of Life Index. This index documented the patient's activity level, independence/ dependence, general well-being, social support and mental state. In addition the EORTC-QLQC30 (European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30) was taken before therapy, after cycle 6 (initial staging), final staging and at months 6,12, 24, 36, 48, 60 and subsequent annual assessments in the follow-up period, regardless of progression or alternative therapy being initiated. None of the quality of life data is currently available for analysis and discussion, and is due to be presented in a separate, future publication.

Safety: All patients who received at least one dose of the study medication were followed for adverse events for at least 28 days after discontinuing study treatment. Events related to the study drug were followed up until resolution or deemed stable and irreversible, or for 1 year.

Response Assessments

The evaluation of the treatment outcome and disease progression was performed according to the standard criteria as defined by the National Cancer Institute (NCI) Sponsored Working Group on CLL.

Interim staging was performed after 3 cycles of therapy before starting the 4th cycle. All patients who showed at least a partial response (PR/CR) after the first 3 cycles, continued treatment according to the protocol for a total of 6 cycles of therapy. Patients who showed insufficient response (SD/PD) after the first 3 cycles of treatment were withdrawn from study treatment and were eligible to receive alternative treatment. However, all patients prematurely withdrawn from trial treatment were followed for disease progression (irrespective of new treatment), new treatment and survival.

A **first response assessment (IRA)** was performed 4 weeks after the beginning of the last cycle of therapy.

The **final staging** was performed at least 8 weeks after the IRA to confirm the response at IRA. For patients who achieved a CR at IRA, response confirmation at final staging included a bone marrow biopsy. If CT scans were clinically indicated and were performed pre-therapeutically, they were repeated at final staging.

Follow-up examinations were performed after completion of the final staging every 3 months during years 1-3 and every 6 months during years 4-5.

After a 5 year follow-up period, the patient's status was documented in **annual follow-up** reports up to 8 years after final staging.

In case of treatment discontinuation before completing 6 treatment cycles for reasons other than PD, a response assessment at 1 month after treatment discontinuation and a final staging 2 months after initial response assessment was performed.

Complete Response

Complete response (CR) required that a patient satisfied all of the following criteria for a period of at least 8 weeks:

- Absence of lymphadenopathy confirmed by physical examination and/or appropriate radiographic techniques (i.e. all lymph nodes $\leq$ 1 cm in diameter).

- No hepatomegaly or splenomegaly by physical examination and/or appropriate radiographic techniques.
- Absence of B-symptoms.
- Normal blood count with:
  - Lymphocytes < ULN
  - Polymorphonuclear leukocytes $\geq 1.5 \times 10^9$/L
  - Platelets > 100×10^9/L
  - Hemoglobin > 11 g/dL
- Bone marrow aspirate and biopsy had to be performed 8 weeks after the clinical and laboratory results demonstrated that a CR was achieved. The marrow sample had to be normocellular for age with less than 30% lymphocytes. Lymphoid nodules had to be absent. If the bone marrow was hypocellular, a repeat biopsy was taken 4 weeks later and samples were re-reviewed in conjunction with the prior pathology.

Nodular Partial Response

Some patients fulfilled all the above criteria but still had nodules of lymphocytes in the bone marrow histology despite a total lymphocyte proportion of < 30% . These cases were described as nodular partial response (nPR) and were listed separately in the evaluation.

Partial Response

Partial response (PR) was present if all of the following criteria were fulfilled for at least 8 weeks:

- Reduction in peripheral lymphocyte count by ≥ 50% from pre-treatment value.
- Reduction in lymph node enlargement by ≥ 50%
- Reduction of hepato- and/or splenomegaly by ≥ 50% if enlarged at baseline

Plus at least one of the following criteria:

- Polymorphonuclear leukocytes (granulocytes) $\geq 1.5 \times 10^9$/L or 50% improvement over baseline value.
- Platelets > 100×10^9/L or 50% improvement over baseline value.
- Hemoglobin > 11 g/dL or 50% improvement over baseline value without blood transfusions.

Progressive Disease

Progressive disease (PD) was present if at least one of the following criteria was fulfilled:

- ≥ 50% increase in the sum of the products of the diameters of at least two lymph nodes (at least one node had to be ≥ 2 cm) or appearance of new lymph nodes or any new extra-nodal lesion (regardless of size).
- ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the relevant costal margin or by ultrasound/CT scan; appearance of palpable hepatomegaly or splenomegaly that was not previously present.
- ≥ 50% increase in the absolute number of circulating lymphocytes to at least 5×10^9/L.

- Transformation to a more aggressive histology (e.g. Richter's syndrome or prolymphocytic leukemia [PLL] with > 55% of prolymphocytes).

In case of uncertain progression based on lymph node enlargement alone, measurements were repeated at least 2 weeks later since transient enlargement could occur and did not count as progressive disease.

Stable Disease

Stable disease (SD) was considered to be present if the criteria for CR, nPR, PR and PD were not fulfilled.

The outcomes measured are absolutely central and entirely relevant to the specification of the decision problem. The endpoints used and methods of measuring the outcomes are entirely in line with accepted CLL trial methodology.

Length of Follow-up

As noted in Table 3, there are 4 sets of data from this study with different lengths of follow-up.

In the clinical study report, two time points of follow up are provided:

1. The planned clinical interim analysis (cut-off July 3rd 2007), which became the main analysis as the study was halted at this time point (see 6.3.5). This gives a median follow-up of 20.7 months

2. A follow up analysis from February 2008, with a median follow-up of 25.4 months.

Both of these analyses were conducted by Roche.

The GCLLSG have performed a further, later follow up of the data (clinical cut-off June 2008), which gives a median follow up of 25.5 months.

All three of these different time-points will be analysed fully in section 6.4.

The economic analyses have been carried out using a fourth cut of the data (median follow-up 26.4 months), and this set is analysed in section 7.

The results seen across these sets of data are all very homogeneous and it is important to note, that even tough there are 4 cuts of data the median follow up only moves by a few months (from 20.7 to 26.4 months).

6.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and

assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

Primary Hypotheses of CLL-8

Null hypothesis: There is no difference in progression-free survival between patients treated with FC and R-FC.

H_0: PFS(FC) = PFS(R-FC)

Alternative Hypothesis: There is a significant difference between the progression-free survival in patients treated with R-FC compared to FC.

H_1: PFS(FC)≠ PFS(R-FC)

A two-sided (non-stratified) log-rank test was used to test the difference between the two treatment arms.

Sample Size

The primary endpoint PFS was used to determine the sample size of the study. Based on data from the German CLL-4 trial, (Eichhorst et al.[14] - a Phase III randomised comparative study which compared FC and fludarabine in a similar population at identical doses), the median PFS was assumed to be 40 months in the FC arm (corresponding to a 66% PFS rate at 2 years) and 54 months in the R-FC arm.

For the calculation of the number of events, the following assumptions were made:
• A two-sided Log-Rank test at the 5%-level was used for the comparison, the power was 80%.
• One planned interim analysis was performed after two-thirds of the number of events.
• Exponential distribution.

Table 11 provides an overview of the required number of events depending on the hazard ratio.

Table 11: Required Number of Events

Hazard Ratio	Treatment Effect	Median PFS (months)		Two-year PFS Rate (%)		Number of Events
		FC	R-FC	FC	R-FC	
0.769	30%	40.0 45.0	52.0 58.5	66.0 69.1	72.6 75.2	465
0.741	**35%**	**40.0** **45.0**	**54.0** **60.75**	**66.0** **69.1**	**73.5** **76.0**	**357**
0.714	40%	40.0 45.0	56 63	66.0 69.1	74.3 76.8	285

A median benefit of 35% corresponding to a hazard ratio of 0.741, was judged as both realistic and clinically relevant. Thus, the main analysis was triggered once 357 events (disease progression or death) were reached. With this number of events, it could also be possible to detect a median PFS benefit of 45% with a power of 80% at the overall alpha level of 1%.
Assuming a linear recruitment over 38 months resulting in 760 patients, a study duration of approximately 62 months was expected to reach the required 357 events which triggered the main analysis. An interim analysis was planned after 238 events occurred (66.7% of 357). If the median in the FC arm was in truth 45 months (the benefit was still at 35% and the exponential assumption held), the study lasted approximately 5 months longer.

The efficacy analyses on PFS, OS, EFS, DFS, DR and TTNT were based on a non-stratified, two-sided log-rank test. Response rates were compared applying a two-sided Chi-square test. For the primary endpoint PFS, the significance level's alpha was 0.012 at the interim analysis (after 2/3 of the events) to maintain an overall two-sided type I error of 5%. All tests on secondary endpoints were performed at a nominal significance level α = 0.05 (2-sided). No adjustment for the multiplicity of testing was performed for the secondary parameters. No formal testing of safety endpoints was performed.

At the interim analysis (clinical cut-off July 4th 2007) there were 254 PFS events available.

An intention-to-treat population including all patients randomised in the study was carried out. Patients were analysed according to the therapy they were randomised to, *regardless of whether they received any treatment or not*. **All efficacy results have been analysed based on the ITT population**. Efficacy analyses were also carried out on a 'Full Analysis Set (FAS)' which contained all patients who received at least one course of treatment. **All efficacy results will be presented for the ITT population.**

Subgroup Analyses

The following sub-group analyses were planned:

Table 12: Details of Sub-Groups

Subgroups	Details of subgroups
Gender	male, female
Age categories	<60, 60-70, ≥70 years, <65, 65-74, ≥75 years
Binet stage at screening	A, B, C
ECOG performance status	0, >1
IgVH status (if possible)	mutated, unmutated
ZAP-70 at baseline (if possible)	≥ 20%, <20%
Chromosomal aberrations	Yes, No (two categories for each chromosomal aberration: del(13q), trisomy 12, del(11q), del(17p))
B-symptoms	Yes, No
CD38+	Yes, No
Time from first diagnosis	< 6 months, 6-12 months, 12-24 months, >24 months

Following protocol amendment 2, two further subgroups for analysis were defined: Binet B+C patients together, and Binet A. It was also highlighted that if subgroups contained less than 20 patients at time of analysis they would not be reviewed.

6.3.6 Critical Appraisal of Relevant RCTs

Table 13: Critical Appraisal

Criterion	CLL-8
How was allocation concealed ?	CLL-8 was an open-label study. Placebo control for a study involving IV rituximab administration and pre-medication would 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.
What randomisation technique was used ?	A block randomisation was used, which is an appropriate method for randomising a Phase III study
Was the sample size justified adequately?	Yes. See section 6.3.5
Has there been adequate follow-up ?	Yes Unblinding of the data and full analyses of all endpoints was mandated by the independent DSMB at the interim analysis given highly statistically significant differences between the two arms (R-FC and FC), making further follow-up very unlikely to change the magnitude of difference seen between the two arms. However the median PFS values in both arms may increase with time. It is appreciated that the median survival of CLL is between 5-

	10 years, and further results with a longer follow-up will become available.
Assessors aware of treatment allocation?	It is likely that assessors were aware of treatment allocation and outcomes in this study were assessed by the investigators. An independent assessment of the data was not performed. However the assessment of CLL post treatment is very objective and it is very unlikely that this will have biased results.
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 treatment post randomisation was not considered an event or a reason for censoring.
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**	CLL-8 was an international study not including the UK. However 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. Certainly the generally caucasian population in Germany (over 500 of the 817 patients were recruited were from there) would compare very favourably with a British population. Other countries involved in recruitment (Australia, Austria, Belgium, Czech Republic, Denmark, France, Italy, Spain, New Zealand and Israel), 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 82.
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), 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 CLL-8 was based on the MDAAC Phase II studies. A dose reduction of 375mg/m^2 in cycle 1 was decided on to minimise any potential cytokine release/ tumour lysis that may have been triggered by the known large circulating tumour burden in CLL. 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 and based upon dosing that has been independently used in Phase II and III studies in CLL (e.g. Eichhorst et al) and represent the best current clinical experience of these drugs combination use in CLL. 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.
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.
Were appropriate statistical tests used?	Yes, fully detailed in section 6.3.5.
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.
Are there any confounding factors that may attenuate the interpretation of the study ?	There are not thought to be any confounding factors that attenuate the interpretation of the primary endpoint and most of the secondary endpoints. For the analysis of overall survival, it is likely that cross-over limits 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.

6.3.6.1 Summary

The critical appraisal reveals that CLL-8 was a rigorously run, very well designed comparative Phase III study which asked a very pertinent question in the correct population against the appropriate comparator. Roche feels that its limitations are very limited and the analysis of its results represent a fair and objective view on the differences between R-FC and FC for the initial treatment of CLL.

6.4 Results of the relevant comparative RCTs

6.4.1 Introduction: CLL-8 Results

One pre-planned interim analysis was conducted according to the protocol using a clinical cut-off of July 4th, 2007. The analysis was performed by an independent statistical centre (the Bremen Institute for Prevention Research and Social Medicine [BIPS]) and presented to the Drug and Safety Monitoring Board (DSMB) members for their review in January 2008. Following their review of the interim data, the DSMB indicated that the results demonstrated a significant difference in PFS in favour of the R-FC arm. The statistical significance crossed the threshold for early stopping of the study (critical p-value for the two-sided Log-Rank test: $p = 0.012$). On the basis of these results, the DSMB concluded that:

The primary endpoint PFS of the study had been met with a significantly better progression-free survival for the R-FC arm compared to the FC arm ($p < 0.0001$).

They also concluded that the results of the secondary endpoints were in keeping with the primary endpoint and were internally consistent and robust.

Hence the DSMB recommended that the study should be formally stopped and fully evaluated with all secondary endpoints analysed. As a result, the interim analysis has become the main analysis of CLL-8. However, all patients will be followed for progression and survival for a maximum of 8 years.

At the time of the clinical cut-off for the interim analysis (July 4th 2007), patients had been followed for a median of 20.7 months. Two further clinical analyses with longer follow up have also been carried out*:

1. A snapshot analysis with a cut off of February 8, 2008. This second data set corresponds to a median follow up of 25.4 months. This snapshot data will be presented after the main analysis, and is sourced from the clinical study report.

2. A further snapshot with a cut off of June 2008. This corresponds to a median follow-up of 25.5 months. This analysis with the longest follow up is presented by Hallek et al. in their forthcoming oral presentation and abstract at The 2008 ASH conference. This data set is also covered in due course.

It should be noted that only the first two analyses are in the dossier that form the regulatory submission for the marketing authorisation extension. Of note, even though there is 4 months between snapshots 1 and 2, there is only a minimal increase in the median follow up because very little additional data was accrued during this time and naturally median follow up in a cohort does not change linearly with time.

* The snapshot with 26.4 months of follow up (fourth data cut) carried out for the economic analyses is discussed in section 7.

6.4.2: Efficacy Results

The overall efficacy results are summarised for the intention to treat (ITT) population below in Table 14.

The addition of rituximab to fludarabine plus cyclophosphamide resulted in a clinically relevant and statistically significant improvement in the primary endpoint of progression-free survival. Under a nominal significance level $\alpha = 0.05$ (2-sided), significant improvements were observed in most of the secondary endpoints including overall survival, event-free survival, duration of response, time to new CLL treatment or death and response rates.

Table 14. Summary of Overall Efficacy (Clinical Cut-Off July 4, 2007; ITT)

Parameter	FC N = 407	R-FC N = 403
PFS		
Median (months)	32.2	39.8
p value (Log-Rank test)	**p <0.0001**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.56 (0.43; 0.72) **p < 0.0001**	
Stratified (not adjusted)	0.53 (0.41; 0.68) **p < 0.0001**	
Overall Survival		
Median (months)	Not reached	Not reached
p value (Log-Rank test)	**p = 0.0427**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.64 (0.41; 1.00) **p = 0.0487**	
Stratified (not adjusted)	0.60 (0.38; 0.94) **p = 0.0250**	
Event-Free Survival		
Median (months)	31.1	39.8
p value (Log-Rank test)	**p < 0.0001**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.55 (0.43; 0.70) **p < 0.0001**	
Disease-Free Survival		
Median (months)	Not Reached	Not Reached
p value (Log-Rank test)	**p = 0.7882**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.93 (0.44; 1.96) **p = 0.8566**	
Duration of Response		
Median (months)	34.7	40.2
p value (Log-Rank test)	**p = 0.0040**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.61 (0.43; 0.85) **p = 0.0036**	
Time to New Treatment		
Median (months)	Not Reached	Not Reached

p value (Log-Rank test)	**p = 0.0052**	
HR (95% CI) p value (Wald test)		
Unstratified (adjusted)	0.65 (0.47; 0.90) **p = 0.0082**	
End-of-Treatment Response Rate	72.7%	86.1%
Complete Response	17.2%	36.0%
Partial Response/nPR	55.5%	50.1%
Stable Disease	7.6%	4.7%
Progressive Disease	7.6%	3.5%
Missing	12.0%	5.7%

Primary Efficacy Parameter – Progression-Free Survival (ITT)

The primary efficacy analysis was based on a non-stratified, two-sided log-rank test of PFS. At the time of the interim (i.e. main) analysis (clinical cut-off July 4, 2007), a total of 254 patients (31%: 152 pts in FC, 102 pts in R-FC) had progressed (127 pts in FC, 85 pts in R-FC) or died (25 pts in FC, 17 pts in R-FC). In the FC arm, 37% (152/407 pts) of the patients had experienced an event compared to 25% (102/403 pts) in the R-FC arm.

R-FC significantly prolonged the median PFS when compared to the FC regimen alone ($p < 0.0001$, log-rank test). The Kaplan-Meier estimated median PFS was 39.8 months with R-FC and 32.2 months with FC. The risk of having a PFS event (progression or death, whichever occurred first) was statistically significantly decreased by 44% (adjusted Hazard Ratio [HR] 0.56; 95% CI [0.43; 0.72]; $p < 0001$, Wald test) for patients in the rituximab arm compared to the FC arm (Table 15). Seventy-seven percent of the patients in the R-FC arm, and 60% of those in the FC arm, were progression-free at two years.

Table 15. Summary of Progression-Free Survival (ITT)

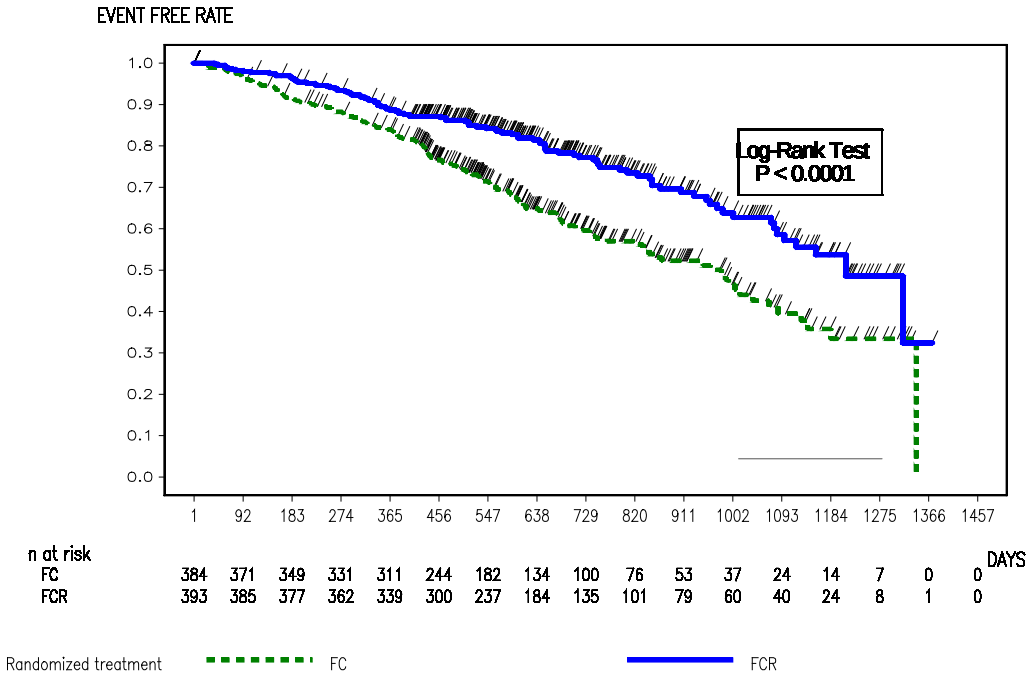
	FC (N=407)	R-FC (N=403)
Patients with event	152 (37.3%)	102 (25.3%)
Patients without events	255 (62.7%)	302 (74.7%)
Time to event (days)		
Median	981.0	1212.0
95% CI for Median	[935;1069]	[1098;1400]
p-Value (Log-Rank Test)	**p<.0001**	
Hazard Ratio (adjusted)	0.56	
95% CI	[0.43;0.72]	
p-Value (Wald Test)	**P<0.001**	
2 year duration		
Patients remaining at risk	100	135
Event Free Rate	0.60	0.77
95% CI for Rate	[0.54;0.65]	[0.72;0.82]

The Kaplan-Meier curves for duration of PFS show a separation of the curves starting approximately 3 months after study entry (Figure 6).

Figure 6 Kaplan-Meier Curve of Progression-Free Survival (ITT)

eg_pfskm_I Kaplan-Meier Plot Of Progression-Free Survival (Censored Observations Shown)

Protocol(s): ML17102 (I17102G)
Analysis Population: Intent-To-Treat Population (N=810)
Snapshot Date: 08FEB2008 Cutoff Date: 04JUL2007



Program: $PROD/cd11899a/i17102a/eg_pfskm.sas / Output : $PROD/cd11899a/i17102g/reports/eg_pfskm_I.cgm
18MAR2008 20:41

In addition, the results of the stratified (country/disease stage [Binet stage at pre-therapeutic staging]) analysis of PFS were similar to the non-stratified analysis, as shown in Table 14.

Comparability of Results from the FC arm of CLL-8 with Those in Other Studies Using the Same Regimen

Three comparative randomised controlled studies (Flinn et al., Eichhorst et al. and Catovsky et al.) in patients treated for the first time for CLL have been published in the last three years. All used FC as one of the comparative arms. It is important to compare and analyse the results across these studies.

The median PFS of 32 months seen in the FC arm of CLL-8 is in line with PFS results from the US Intergroup study E2997 (Flinn et al[30]), in which a median PFS of 31.6 months was reported in the FC arm. The proportion of patients with Binet stage A disease in this study was low (3%) making this study population comparable to that in study CLL-8.

In the German CLL-4 study (Eichhorst et al[14]) and the UK CLL-4 study (Catovsky et al[15]) –*both studies are called CLL-4 but are different*, the median PFS values are not grossly comparable.

The German Study CLL-4 included slightly more patients with Binet stage A disease (7.4% versus 5% in the study CLL-8) .In addition, in the German study only 'eligible' patients (339/375 randomised patients [90.4%]) were analysed for PFS, whereas in study CLL-8 all patients randomised (i.e. intention to treat) were analysed. This difference in analysis is likely to explain why the median PFS seen (48 months) in the FC arm is longer compared to CLL-8.

In the UK study, the median PFS with the FC regimen was 43 months which also appears longer than the results achieved with the FC arm in CLL-8 but shorter compared to the CLL-4 study by the GCLLSG. However, in this study the proportion of patients with Binet stage A disease (25%) was significantly higher than in study CLL-8 (5%). In addition, the definition of PFS in this study was different (time from randomisation to relapse *needing further treatment*, progression or death.

It should be noted however, that qualitative explanations of the differences seen between the same treatment regime in different randomised Phase III studies has inherent limitations but it is useful to discuss up to a point, knowing that every trial population in itself is unique.

Secondary Efficacy Parameters

Overall Survival

At the time of the main analysis (clinical cut-off July 4, 2007), a total of 81 randomised patients had died: 48 patients (11.8%) in the FC arm and 33 patients (8.2%) in the R-FC arm.

At the time of the analysis, overall survival was significantly improved in the R-FC arm compared to the FC arm (p = 0.0427, log-rank test). The median survival time could not be estimated for both arms. Treatment with R-FC reduced the risk of death by 36% when compared to FC alone (adjusted HR 0.64; 95% CI [0.41; 1.00], p = 0.0487, Wald test).

Table 16. Summary of Overall Survival (ITT)

	FC (N=407)	R-FC (N=403)
Patients included in analysis	406 (100.0%)	403 (100.0%)
Patients with event	48 (11.8%)	33 (8.2%)
Patients without events	358 (88.2%)	370 (91.8%)
p-Value (Log-Rank Test)	**0.0427**	
Hazard Ratio (adjusted)	0.64	
95% CI	[0.41;1.00]	
p-Value (Wald Test)	**0.0487**	
2 year duration		
Patients remaining at risk	135	161
Event Free Rate	0.87	0.92

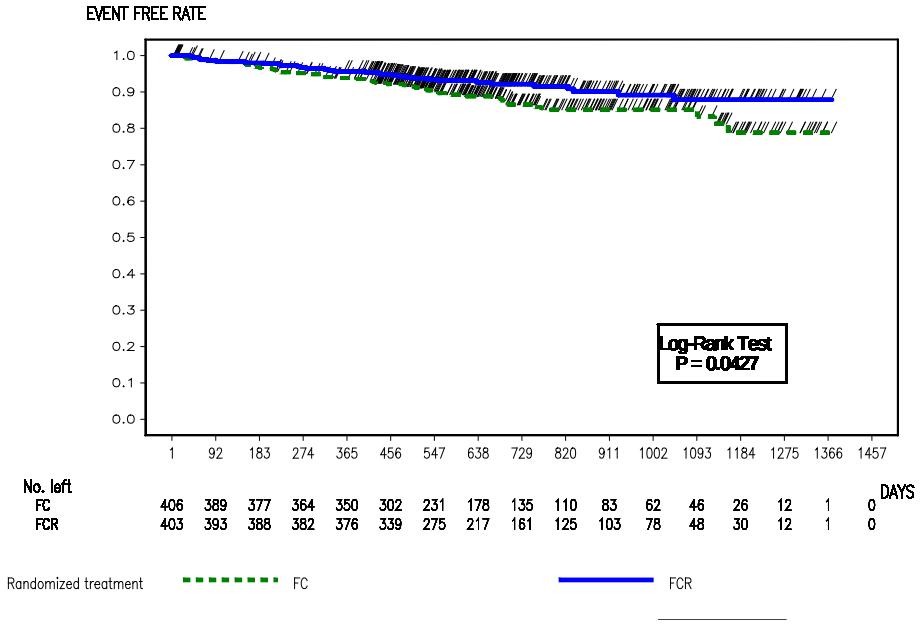
95% CI for Rate	[0.83;0.90)	[0.89;0.95]

The Kaplan-Meier curves for duration of survival are shown in Figure 7.

Figure 7: Kaplan Meier Curve of Overall Survival (ITT)

eg_oskm_I Kaplan-Meier Plot Of Overall Survival (Censored Observations Shown)

Protocol(s): ML17102 (I17102G)
Analysis Population: Intent-To-Treat Population (N=810)
Snapshot Date: 08FEB2008 Cutoff Date: 04JUL2007



Censoring date based incl. central laboratory and tumor data.

Program : $PROD/cd11899a/i17102a/eg_oskm.sas / Output : $PROD/cd11899a/i17102g/reports/eg_oskm_I.cgm
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The Kaplan-Meier estimated 24-month survival rates were 87% in the FC arm and 92% in the R-FC arm in the ITT population.

The results of the stratified analysis factoring in relevant risk factors (country/disease stage [Binet stage at pre-therapeutic staging]) of OS confirmed the non-stratified analysis.

Event-Free Survival

In the FC arm, 39.3% (160/407 pts) of the patients experienced an EFS event (disease progression, relapse, death or start of a new CLL treatment) compared to 26.3% (106/403 pts) in the R-FC arm. Most of the events reported were disease progressions (116 events in FC, 77 events in R-FC). A total of 24 patients (5.9%) on the FC arm and 14 patients (3.5%) on the R-FC arm received a new treatment for CLL before reporting PD or death. The difference between arms was probably due to the higher proportion of patients with an insufficient response (stable disease: SD) and thus, requiring alternative therapy in the FC group compared to the R-FC group.

The median EFS was significantly increased by 8.7 months from 31.1 months in the FC arm to 39.8 months in the R-FC arm ($p < 0.0001$, log-rank test). There was a clinically meaningful and statistically significant decrease of the risk of having an EFS event for

patients in the R-FC arm compared to the FC arm. The reduction in risk of an event was 45% (adjusted HR 0.55; 95% CI [0.43; 0.70]; p < 0.0001, Wald test) in the R-FC arm compared to the FC arm. At 2 years, 75% of the patients in the R-FC arm, and 57% of those in the FC arm, were event-free.

End-of-Treatment Response Rate

The proportion of patients with an objective response (CR/PR) was significantly higher in the R-FC arm (86.1%; 347/403) compared to the FC arm (72.7%; 296/407) (p < 0.0001, Chi-square test). The complete response rate was doubled in the R-FC arm (145/403; 36.0%) compared to the FC arm (70/407; 17.2%) (p < 0.0001, Chi-square test).

There were more patients with stable disease (31/407; 7.6% in FC vs. 19/403; 4.7% in R-FC) or progressive disease (31/407; 7.6% in FC vs. 14/403; 3.5% in R-FC) in the FC arm compared to the R-FC arm. This is presented in Table 17.

Table 17: Summary of End-of-Treatment Response Rate (ITT)

	FC (N=407)	R-FC (N=403)
Responders	296 (72.7%)	347 (86.1%)
Non-Responders	111 (27.3%)	56 (13.9%)
95% CI for Response Rates	[68.1;77.0]	[82.3;89.3]
Difference in Response Rates	13.38	
95% CI for Difference in Response Rates	[7.8;19.0]	
p-Value (Chi-squared Test)	**<.0001**	
Odds Ratio	2.32	
95% CI for Odds Ratio	[1.63;3.32]	
Complete Resonse (CR)	70 (17.2%)	145 (36.0%)
95% CI for CR Rates	[13.7;21.2]	[31.3;40.9]
Difference in CR Rates	18.78	
95% CI for Difference in CR Rates	[12.7;24.9]	
p-Value (Chi-squared Test)	**<.0001**	
Odds Ratio	2.71	
95% CI for Odds Ratio	[1.95;3.76]	
Partial Response (PR)	226 (55.5%)	202 (50.1%)
95% CI for PR Rates	[50.6; 60.4]	[45.1;55.1]
Difference in PR Rates	-5.40	
95% CI for Difference in PR Rates	[-12.4;1.6]	
p-Value (Chi-Squared Test)	0.1234	
Odds Ratio	0.80	
95% CI for Odds Ratio	[0.61;1.06]	
Stable Disease (SD)	31 (7.6%)	19 (4.7%)
95% CI for SD Rates	[5.2;10.6]	[2.9;7.3]
Progressive Disease (PD)	31 (7.6%)	14 (3.5%)
95% CI for PD Rates	[5.2;10.6]	[1.9;5.8]

Missing (No Response Assessment)	49 (12.0%)	23 (5.7%)

Information on molecular response in blood was available for a limited number of responding patients (FC 110/296 responders [37%]; R-FC 74/347 responders [21%]), therefore interpretation of the results are limited. Of patients with available information on minimal residual disease (MRD) status, the percentage of patients who achieved an MRD negative CR in the blood was higher in patients who received R-FC compared with patients who received FC (7% FC; 25% R-FC). As one would expect, in patients achieving a nPR or PR there was no difference in molecular response rates. It is anticipated that a more detailed analysis of MRD will be available in future publications arising from this study. As discussed in section 4, MRD negativity is directly linked to prognosis and it is highly encouraging that adding rituximab to FC markedly improved (by 18%), the number of patients who obtained an MRD-negative CR.

Duration of Response

The duration of response was assessed in patients who had a confirmed response (CR, nPR or PR). The median duration of response was significantly longer in the R-FC arm (40.2 months) than in the FC arm (34.7 months) (p = 0.004, log-rank test) and the adjusted HR was 0.61 (95% CI: 0.43; 0.85; p = 0.0036 Wald test) in the R-FC arm. Eighty percent (80%) of the patients in the R-FC arm, and 69% of those in the FC arm, were event-free at two years.

Disease-Free Survival

Disease-free survival was defined for patients with a confirmed complete response only. Ninety-one patients in the FC arm (91/407 pts; 22%) and 186 patients (186/403 pts; 46%) in the R-FC arm were included in this analysis. This analysis also included patients with a 'late response' of CR (after end of treatment response assignment and more than 12 months after study start), potentially explaining the less pronounced treatment benefit in this group (adjusted HR 0.93), since the follow-up for some of these patients may be too short to allow for meaningful conclusions.

The phenomenon of 'late CR' should be expanded further: The investigators found that a number of patients who only fulfilled criteria of a PR at end of treatment response, subsequently became CRs over time. This is commonly seen in CLL, and other indolent malignancies – certainly rituximab can continue to exert an anti-tumour effect for numerous months following a dose, with serum levels being present for up to 3-4 months post dose.

At the time of the analysis (clinical cut-off July 4, 2007), 12.1% (11/91 pts) of the patients in the FC arm experienced an event compared to 12.4% (23/186 pts) in the R-FC arm. The median was not reached in either arm and the number of events in both arms was very small (reflecting the generally favourable outlook for patients who achieved a CR).

Time to New CLL Treatment

At the time of the analysis, a total of 157 patients (22.1% [90/407 pts] in FC; 16.6% [67/403 pts] in R-FC) had started a new treatment for CLL (59 pts in FC, 44 pts in R-FC) or died (31 pts in FC, 23 pts in R-FC).

The median time to new CLL treatment or death could not be estimated for both arms, however, the difference between arms was statistically significant (p = 0.0052). The risk of receiving a new CLL therapy or of death was reduced by 35% with the addition of rituximab to the FC regimen compared to FC alone: the adjusted HR was 0.65 (95% CI: 0.47; 0.90) with a p-value of 0.0082 (Wald-Test). At 2 years, 74% of patients in the FC arm had not received a new anti-CLL therapy or died compared to 85% of patients in the

R-FC arm.

Subsequent Therapies for CLL

A total of 103 patients (12.7%; 103/810) received at least one subsequent CLL treatment (14% [59/407] in FC, 11% [44/403] in R-FC). The majority of new treatments consisted of combined cytotoxic regimens including alkylating agents, nucleoside analogues and doxorubicin. In the FC arm, 35/59 (59%) patients received rituximab either in combination with a chemotherapy regimen or as single agent compared to 19/44 (43%) patients in the R-FC arm.

Subgroup Analyses

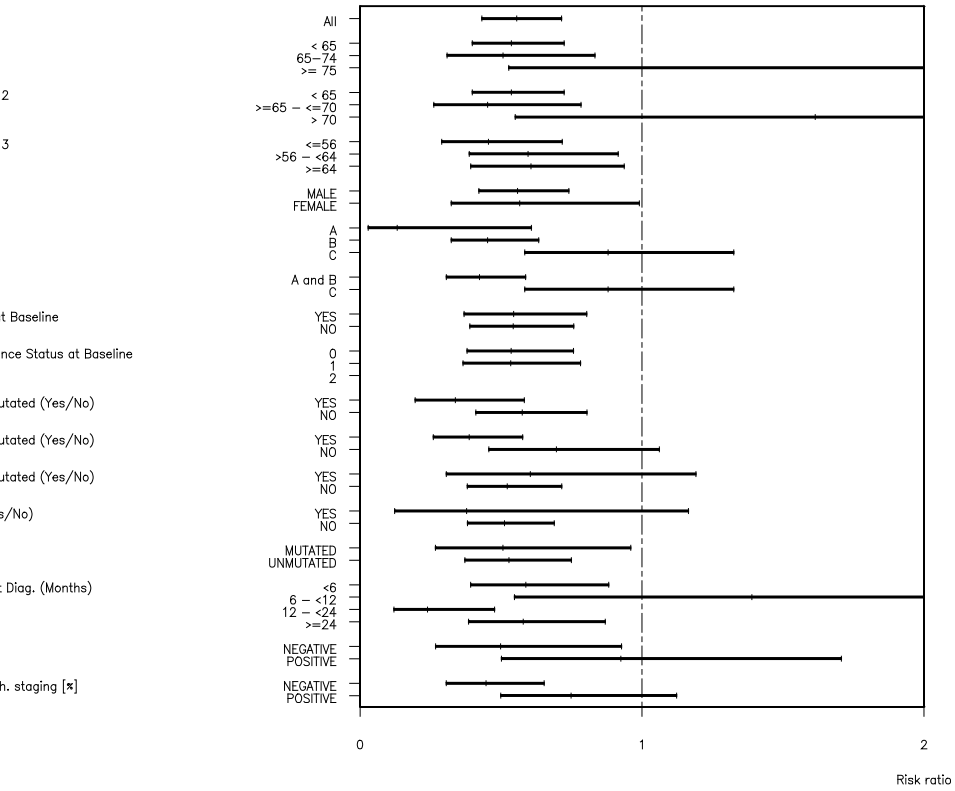
Progression-Free Survival

In order to assess the impact of potential prognostic factors on the treatment effect, baseline characteristics were analysed. Risk ratios with 95% CI (R-FC vs. FC) for patient subgroups based on baseline factors are shown for progression-free survival in the forest plot, figure 7, below. Overall, the results of the PFS subgroup analyses were consistent with the results seen in the overall ITT population. The risk of disease progression or death was reduced in the R-FC arm compared to the FC arm in most of the subgroups analysed, except for patients older than 70 years and those who were diagnosed 6-< 12 months before study entry. In these two subgroups, however, the number of patients was relatively small (58 pts > 70 years old; 73 pts diagnosed 6-< 12 months before study entry) and the number of PFS events observed was too small (15 events [5 FC, 10 R-FC] in pts > 70 years; 18 events [8 FC, 10 R-FC] in pts diagnosed 6-< 12 months] before study entry) to draw meaningful conclusions. In all other subgroups, the risk of disease progression or death was reduced with a risk reduction ranging between 7% (ZAP-70+) and 87% (Binet Stage A). In most of the subgroups analysed, the risk reduction ranged between 40 and 60%, and point estimates of the HR (not adjusted) were below 1 (see forest plot, Figure 8 below) with an upper limit of the 95% CI being less than 1, indicating the significance of these findings based on a nominal significant level $\alpha = 0.05$ (2-sided). Some of the confidence levels in the sub-group analyses were reasonably wide (often because of small numbers in the groups) and it is therefore difficult to make meaningful conclusions about certain sub-groups, and this is explored further below. It must however be noted that the study was NOT powered to look at any of these sub-groups so any conclusions in either direction must be tempered.

Figure 8. Forest Plot of Hazard Ratios for Progression-free Survival by Subgroups (ITT)

eg_pfscox_hr1_all_I Hazard Ratios And 95%-Confidence Intervals For PFS

Protocol(s): ML17102 (I17102G)
Analysis Population: Intent-To-Treat Population (N=810)
Snapshot Date: 08FEB2008 Cutoff Date: 04JUL2007



Category	Subgroup	N	Lower confidence limit	Estimate	Upper confidence limit
All	All	810	0.43	0.56	0.71
Age Categories	< 65	567	0.40	0.54	0.72
	65−74	225	0.31	0.51	0.83
	>= 75	18	0.53	3.00	17.04
Age Categories 2	< 65	567	0.40	0.54	0.72
	>=65 − <=70	185	0.26	0.45	0.78
	> 70	58	0.55	1.61	4.74
Age Categories 3	<=56	271	0.29	0.46	0.72
	>56 − <64	254	0.39	0.60	0.92
	>=64	285	0.39	0.61	0.94
Sex	MALE	600	0.42	0.56	0.74
	FEMALE	210	0.32	0.57	0.99
Binet stage	A	40	0.03	0.13	0.61
	B	516	0.32	0.45	0.63
	C	251	0.58	0.88	1.33
Binet Stage 3	A and B	556	0.31	0.42	0.59
	C	251	0.58	0.88	1.33
B−Symptoms at Baseline	YES	361	0.37	0.55	0.80
	NO	445	0.39	0.54	0.76
ECOG Performance Status at Baseline	0	446	0.38	0.54	0.76
	1	330	0.37	0.53	0.78
	2	2	.	.	.
Del11q At BL Mutated (Yes/No)	YES	148	0.20	0.34	0.58
	NO	455	0.41	0.58	0.81
Del13q At BL Mutated (Yes/No)	YES	342	0.26	0.39	0.58
	NO	256	0.46	0.70	1.06
Del17p At BL Mutated (Yes/No)	YES	46	0.31	0.60	1.19
	NO	554	0.38	0.52	0.72
Trisomy 12 (Yes/No)	YES	70	0.12	0.38	1.17
	NO	532	0.38	0.51	0.69
IgVH At BL	MUTATED	184	0.27	0.51	0.96
	UNMUTATED	339	0.37	0.53	0.75
Time From First Diag. (Months)	<6	295	0.39	0.59	0.88
	6 − <12	73	0.55	1.39	3.52
	12 − <24	107	0.12	0.24	0.48
	>=24	332	0.39	0.58	0.87
ZAP−70 At BL	NEGATIVE	170	0.27	0.50	0.93
	POSITIVE	116	0.50	0.93	1.71
CD 38+ at preth. staging [%]	NEGATIVE	373	0.31	0.45	0.65
	POSITIVE	320	0.50	0.75	1.12

Subgroup Analyses Based on Binet Stage at Study Entry

Of particular interest are subgroups of patients based on Binet stage at baseline (stratification factor) and more detailed analyses on these groups are warranted and discussed further.

In all subgroups analysed according to Binet stage, the risk of disease progression or death was decreased by the addition of rituximab to FC when compared to FC alone. The effect was most pronounced in the group of patients with stage A disease (not adjusted HR 0.13, 95% CI [0.03; 0.61]; p = 0.0093) and stage B disease (HR 0.46, 95% CI [0.32; 0.63]; p < 0.0001). The risk reduction in patients in stage C disease was less pronounced (not adjusted HR 0.88, 95% CI [0.58; 1.33]; p = 0.5406), and the p value and upper-confidence interval crossing 1 leaves a certain amount of uncertainty on the reality of any extra benefit rituximab may have added in this group.

A potential explanation for the lower treatment effect observed in the subgroup of Binet stage C patients when compared to the Binet stage A or B patients may be the observation that certain prognostic biomarkers, mainly IgVH mutational status and ZAP-70 expression were imbalanced between treatment arms in the Binet C subgroup. More patients in the R-FC arm expressed these adverse prognostic factors, whereas most of the biomarkers were relatively balanced in subgroups of patients with Binet stage A or B disease. In Binet stage C patients, more patients in the R-FC group had unmutated IgVH (46% FC, 59% R-FC) or were ZAP-70+ (33% FC, 41% R-FC) compared to the FC arm (i.e. had worse prognostic features than patients in the FC arm). This is further supported by additional exploratory analyses of outcome of Binet C patients according to these prognostic factors, which demonstrated that in the overall group of Binet C patients the risk for disease progression or death with either IgVH unmutated or ZAP-70+ disease was higher when compared to patients with mutated IgVH or ZAP-negative disease.

Of note, an analysis of PFS in Binet C patients who were included in the group defined as the ‘per-protocol set: PPS’ (these received at least three cycles of treatment or died/progressed before three cycles) demonstrated a risk reduction of 27% for disease progression or death when rituximab was added to FC compared to FC alone. For patients excluded from the PPS, the majority (45/80, 56%) had not received at least 3 cycles of therapy. Moreover, an analysis of response rates in the Binet C patient group demonstrated that R-FC significantly increased end-of-treatment response (77.6% R-FC, 65.1% FC; p = 0.0283) and CR rates (26.4% R-FC; 10.3% FC; p = 0.0010) highlighting the superior efficacy of R-FC over FC.

Subgroup Analysis based on Cytogenetics at Baseline (specifically 17p deletion)

The management of patients with 17p deletions is particularly challenging, and as noted in Section 4, this abnormality is seen more in relapsing patients, and management strategies often include the monoclonal antibody alemtuzumab. In CLL-8 there were 46 patients with del 17p noted at the start of treatment. The 95% confidence level for PFS in this sub-group is wide, with an estimate of 0.6, but a range of 0.31 to 1.19. It is therefore difficult to make firm conclusions about the efficacy of R-FC over FC on PFS in this group of patients, but again it must be noted that the study was not powered to specifically look for any difference in this, or any other subgroup.

Efficacy Results with Longer Follow-up Data (1)

At the time of the clinical cut-off for the interim (i.e. main) analysis, patients had been

followed for a median of 20.7 months, which is relatively short in the light of the long disease course of CLL, which has a median survival of 5-10 years. Therefore, a follow up analysis (snapshot analysis) was performed with an additional observation time of 4.8 months (median observation time of 25.4 months; 23.9 months in the FC arm and 26.6 months in the R-FC arm). Overall, results of the primary endpoint PFS confirm those generated using the July 2007 cut-off date.

Progression-Free Survival

As of February 8, 2008, a total 296 patients (171 patients on FC, 125 patients on R-FC) had died or progressed, an approximate 5% increase in progressions or deaths compared to the original analysis. Kaplan-Meier estimates of the median PFS of the main analysis were confirmed by the follow-up analysis. The median PFS was significantly longer for patients in the R-FC arm (42.8 months [1303 days]) than for those in the FC arm (32.5 months [988 days]), $p < 0.0001$, log-rank test) (Table 18)

The risk of death or progression was significantly reduced by 40% for patients in the R-FC arm compared to those in the FC arm (adjusted HR 0.60; 95% CI [0.48; 0.76], $p < 0.0001$, Wald test). Fifteen percent more patients in the R-FC arm than in the FC arm (77% on R-FC versus 62% on FC) had not progressed or died 2 years after the start of therapy.

Table 18: Summary of Progression-Free Survival (February 8, 2008 Cut-off, ITT)

	FC (N=407)	R-FC (N=403)
Patients with event	171 (42.0%)	125 (31.0%)
Patients without events	236 (58.0%)	278 (69.0%)
Time to event (days)		
Median	988.0 [846;1086]	1303.0 [1156;1400]
p-Value (Log-Rank Test)	**<.0001**	
Hazard Ratio (adjusted)	0.60	
95% CI	[0.48;0.76]	
p-Value (Wald Test)	**<.0001**	
2 year duration		
Patients remaining at risk	150	205
Event Free Rate	0.62	0.77
95% CI for Rate	[0.57;0.67]	[0.72;0.81]

Overall Survival

With an additional 4.8 months of observation time, the difference in OS between treatment arms was not significant (adjusted HR 0.72: 95% CI [0.48;1.09], $p = 0.1252$, Wald test). However, survival difference still remained positive with a 28% reduction in the risk death and a trend in favour of the R-FC arm (adjusted HR 0.72: 95% CI [0.48;1.09], $p = 0.1252$, Wald test). Two years after the start of the study, 88% of

patients in the FC arm (95% CI [85%, 92%]) and 91% of patients in the R-FC arm (95% CI [89%; 94%] were still alive.

Table 19: Summary of Overall Survival (February 8, 2008 Cut-off, ITT)

	FC (N=407)	R-FC (N=403)
Patients included in analysis	406 (100.0%)	403 (100.0%)
Patients with event	52 (12.8%)	42 (10.4%)
Patients without events	354 (87.2%)	361 (89.6%)
p-value (Log-Rank Test)	**0.1208**	
Hazard Ratio (adjusted)[$]	0.72	
95% CI	[0.48;1.09]	
p-Value (Wald Test)	**0.1252**	
2 year duration		
Patients remaining at risk	202	244
Event Free Rate	0.88	0.91
95% CI for Rate	[0.85;0.92]	[0.89;0.94]

Efficacy Results with Longer Follow-up Data (2)

For presentation at The ASH conference 2008, Hallek and colleagues will present the data with the longest follow-up to date. The results are entirely in keeping with the first two data sets, but are presented differently from the results in the clinical study report. For completeness, these results are presented in tabular form below (Table 20). The values in the table below have been taken from the printed abstract which will become available on The American Society of Haematology website in the middle of November and the lead investigator (Professor Hallek) will present these results on Monday 8th December 2008.

Table 20. Summary of Overall Efficacy (Clinical Cut-Off June 2008, median FU 25.5 months).

	FC	R-FC	p-value/ Hazard Ratio
Response Rates (761 evaluable)			
Overall Response Rate	88% (328/371)	95% (370/390)	p=0.001
Complete Response Rate	27%	52%	p<0.0001
Progression-Free Survival at 2 years (787 evaluable)	62.3%	76.6%	p<0.0001 HR= 0.59
Overall Survival at 2 years (all evaluable)	88%	91%	p=0.18 HR=0.76

From the printed abstract data, it is important to make one point – the response rate data is different to what has been presented above. This is because of the concept of 'late CRs' as discussed above, where patients who actually did not technically have a CR at the time of final response assessment, did so at a follow-up appointment a couple of months later. It is well accepted that the time of best response may not always be at the time of formal assessment, and an actual CR may only become apparent in the months

following the last treatment. Also with the stringency of the criteria, a patient at final response assessment with no identifiable malignant CLL cells would still not be defined as a CR if they had a haemoglobin of less than 11g/dL or platelets less than $100X10^9$/L. After 6 courses of immuno-chemotherapy, marrow recovery could be delayed enough that even though no disease was present, blood counts would have not fully recovered. Mildly delayed marrow recovery is often seen following treatment, especially in older patients with more 'fragile' bone marrows.

Summary and Conclusions

The results of CLL-8 demonstrate a meaningful clinical benefit when rituximab is added to FC for the first-line treatment of patients with symptomatic CLL. The primary endpoint of PFS was significantly prolonged by a median of 8 months at the main analysis, and this had increased to 10.8 months by the analysis in February 2008. This equates to reducing the risk of progression or death by 40% if rituximab is part of the induction regime. The clinical relevance of these numbers should not be under-estimated – to provide nearly an extra year of time without progression, and to produce a risk reduction of such a magnitude is of core clinical relevance in managing this inevitably relapsing malignancy. This is significant extra time free from the psychological trauma of relapse, the necessary second-line treatments and more importantly, PFS is very likely to be a good surrogate marker for overall survival in this context.

Subgroup analyses, as discussed above demonstrated a consistent treatment effect across most treatment groups, but naturally in small groups results should not be over-interpreted. The lack of significant benefit in Binet C patients is interesting, but readily explained in terms of the excess of poor prognostic biomarkers in the R-FC Binet C patients. It is difficult to comment on the relative benefit of adding rituximab to FC in patients with deletion 17(p).

The improved clinical and statistical benefit of rituximab added to FC was seen for all secondary endpoints except overall survival and disease-free survival. The lack of difference between the arms for disease-free survival is readily explainable as this was a parameter measured for patients who achieved a complete response, and this results reflects the generally good outlook for patients if they achieve a complete response, irrespective of treatment. It is relevant to note that adding rituximab to induction therapy doubled the chance of obtaining a CR, and as discussed in section 4 the quality of remission obtained is undoubtedly linked to prognosis. The data on MRD negativity is potentially even more impressive – even though this data was not available for all patients who obtained a CR, adding rituximab increased the chance of obtaining an MRD negative CR by 18%. It is well accepted that as a group of patients, those that are MRD negative after treatment (irrespective of treatment strategy), have the most favourable prognosis. Further data surrounding MRD negativity is anticipated from this study in future publications, and will be of great clinical interest.

The results for overall survival are at first glance confusing and require further explanation. At the time of the main analysis it was apparent that treatment with R-FC significantly improved the overall survival of patients with CLL when compared to FC ($p=0.047$, log-rank test) and reduced the relative risk of death by 36%. This finding was unexpected as it was remarkable: to date no Phase III randomised CLL study has found an overall survival (OS) benefit in favour of any particular treatment arm. Studies have shown trends towards overall survival and it is well accepted that the phenomenon of cross-over is a major reason why showing an OS benefit is very difficult: patients given a

less efficacious treatment in an arm will relapse earlier and often be given the treatment that patients in the other arm received. For example, this happened in the UK CLL-4 study where a number of patients who relapsed after chlorambucil were given FC therapy. Therefore at the time of the main analysis the power of seeing an OS benefit for R-FC in CLL-8 was remarkable. With further follow up (25.4 and 25.5 month follow-ups), the significance of the OS benefit in CLL has not been maintained, however a trend for OS in the R-FC arm remains, with a 24% risk reduction in death for R-FC. This is despite 87% of the FC patients and 89% of the R-FC patients still being censored for overall survival. It is possible that as further mature results from this trial become available, a statistically significant OS benefit will again become apparent in favour of the R-FC arm (as has been seen in R-chemotherapy follicular lymphoma trials), but further cross-over may also confound the likely benefit that R-FC offers. Substantial cross-over is already known to have occurred in CLL-8 at the time of the main analysis. At this time-point (July 4th 2007, 20.7 months median follow-up), in the FC arm, 35/59 (59%) patients who received subsequent therapy for CLL are known to have received rituximab, either in combination with a chemotherapy regimen or as a single agent. This compares with 19/44 (43%) of patients in the R-FC arm.

Also with regards to further follow up, the absolute median values for PFS may change, but because of the very large absolute differences between the arms, the magnitude of risk reduction in terms of progression/death are unlikely to change.

6.5 Meta-analysis

There is only one comparative randomised controlled study presented, thus meta-analysis is not possible or relevant.

6.6 Indirect/mixed treatment comparisons

Background
A mixed treatment comparison (MTC) was performed in order to identify all relevant evidence to assess the relative efficacy of R-FC in comparison to chlorambucil, alemtuzumab, fludarabine and bendamustine in the first-line management of CLL.

Methods
A systematic review was performed to identify randomised controlled trials, meta-analyses and reviews published in English by searching Medline, Embase and Biosis databases. In addition, one trial from the clinical development program of R-FC for CLL (CLL-8) was included in the analysis.

The identified studies were included according to the following predetermined conditions:

- **Study design** – randomised controlled trials (RCT) that may either be blinded or non-blinded and published or unpublished.

- **Study population** – De novo CLL patients, age > 18 years, male or female, requiring treatment, not been previously treated and having a good ECOG performance status (0 to 2).

- **Outcome measures** – the primary outcome was PFS, defined as the time between randomisation and the date of first documented disease progression, relapse or death by any cause whichever came first. Other endpoints of interest were event-free survival, overall survival, disease-free survival, duration of remission, time to new CLL treatment or death and rates of molecular complete and partial remission.

Study quality was assessed by the Jadad checklist for randomised controlled studies. The Jadad checklist (Jadad et al. 1996[31]) has been used to test for internal consistency, reliability, and validity and is relatively easy to use.

For the time to event outcomes (i.e. PFS, event-free survival, overall survival, disease-free survival, duration of response, time to new CLL treatment), the cox regression model was assumed, which implied that the hazard ratio (relative efficacy with respect to instantaneous risk of an event) is constant over time. The log hazards were summarised across studies and interpreted in terms of medians, based on the PFS curve for R-FC presented in the CLL-8 trial report.

For the CLL treatments of interest, the results of individual studies were combined with both a Bayesian fixed and random effects model. The goodness of fit of the model to the data was checked. Whether the fit of the random effects model was better than the fit of the fixed effects model was assessed based on the overlap of the credibility intervals for the residual deviance and was used as an indication of heterogeneity.

The results of the MTC were analysed using a Bayesian approach. In contrast to a frequentist approach, a Bayesian analysis allows for ranking and calculation of the probability that a treatment is better with respect to each comparator. The probabilities were calculated based on the posterior uncertainty distributions of the treatment effect relative to each of the treatments compared.

Analyses were performed using WinBUGS version 1.4 statistical software.

Results of the Literature Search

Figure 9 presents the flow chart of the search strategy. The search strategy identified 683 abstracts. Of these abstracts, 671 papers were excluded for several reasons, some papers only reported overviews of CLL management and some provided clinical descriptions, without providing efficacy estimates. Five additional papers were excluded for the following reasons:

- The percentages within the Binet stages differed significantly across the arms. This implied that the estimated treatment effect would also be influenced by the difference in severity (Jaksic et al. 1997[32]).
- High-dose chlorambucil is not seen as relevant and does not indirectly link main comparators (Karlsson et al. 2004[33],Jaksic et al. 2000[34]).
- Definition of PFS was not defined as the time between randomisation and first time point of progression. The treatment scheme seemed to imply downwards bias: persons obtaining fludarabine at the start of the research period and not responding to the treatment at 3 months of treatment switch to cyclophosphamide, doxorubicin plus prednisone (CAP), where the CAP group

was closed during the study because of toxicity. For the cyclophosphamide, vincristine, prednisone plus doxorubicin (CHOP) arm, a switch was only possible after 6 months of treatment. The fludarabine group therefore has a larger chance to obtain a less effective treatment (CAP) than the CHOP group, so that the results for the fludarabine group from time of randomisation seems to be biased downwards (Leporrier et al. 2001[35]).

- Links chlorambucil with CHOP and CAP, which are both not relevant comparators, and no two-step path from chlorambucil to another relevant comparator goes via CHOP or CAP (CLL Trialists' Collaborative Group 1999[10]).

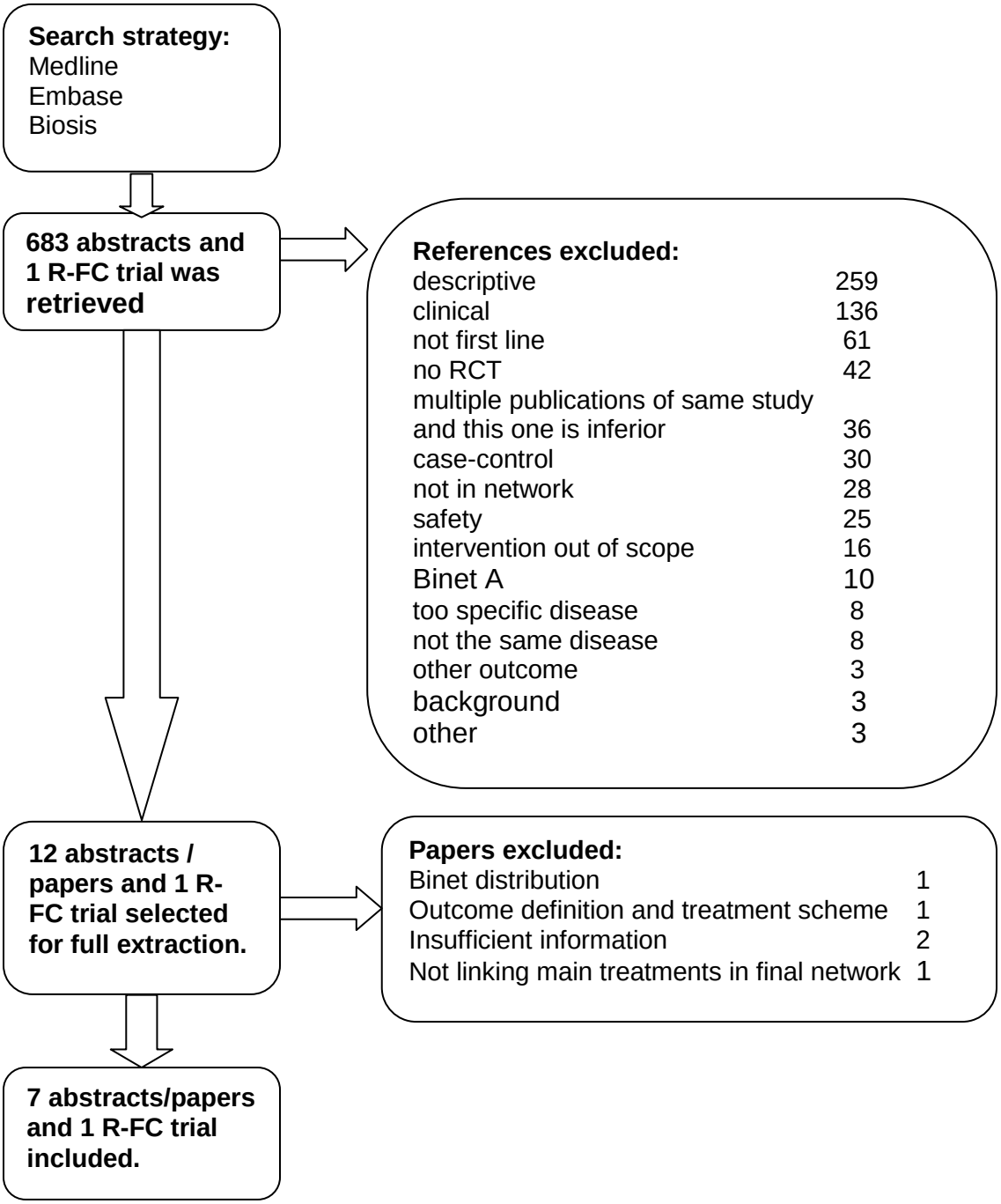
In addition to the CLL-8 R-FC trial, seven eligible studies were identified by the systematic review. The studies were sufficiently similar in design, inclusion criteria and patient characteristics to perform a MTC. It was possible to compare R-FC with FC, fludarabine, chlorambucil and alemtuzumab.

Since few studies were identified, an additional search of the Cochrane library was performed by selecting those record titles that were related to drug treatment and chronic + lymphocytic + leukaemia in the record titles. Only the papers and abstracts not previously found were selected for further investigation.

Five additional trials were found in the Cochrane library. Robak et al. 2000[36] considered Cladribine, which is neither a main comparator in the current study nor a comparator used in the network concerning indirect links. Abdelhamid et al. 2006[37] is an abstract and only presented median PFS and not the percentage of patients without progression at a certain point in time or a hazard ratio. The median could not be used. The results with respect to complete remission and overall response may be used but since it is only an abstract, which even was not found by the previous search, we assessed the quality to be not high enough to incorporate the abstract in the analyses. Gregory et al. 1998 [38] was regarded as outdated supplement and no corresponding full paper was found. Further, the population was very broadly defined, for example including low-grade non-Hodgkin's lymphoma. Johnson et al. 1994[39], is also a supplement, and outdated (1994) and a corresponding paper was not found. Plosker et al. 2003[40] is a review of Rituximab, so therefore excluded.

Overall, no additional relevant papers or abstracts were found to add to the search of Medline, Embase and Biosis. This means that the current search results in a similar number of papers identified in the Cochrane library.

Figure 9. Flow-chart of included studies



Overview of Individual Studies selected for the MTC

Table 21 provides an overview of the characteristics and quality of the included studies. All studies were randomised studies. Only Hillmen et al.[41] (2007) mentioned that the study was blinded. Catovsky et al.[15] (2007) mentioned that the clinicians treating the patients assessed the response. Blinding was therefore not reached, because the number of cycles differed per treatment. All other papers did not mention blinding at all.

All studies considered similar populations with respect to age (median was about 60 years), gender (about 70% men) and the line of treatment (first line). The CLL-8 study[27], together with Catovsky et al. 2007, Eichhorst et al. 2006, Eichhorst et al. 2007 and Knauf et al. 2007 presented the disease stage in terms of Binet stages, while Flinn et al. 2007, Hillmen et al. 2007, Eichhorst et al. 2006 and Rai et al. 2000 presented it in Rai stages. The stages were compared based on the expected length of overall survival for the different Binet and Rai stages. The percentage of patients with Binet A stage reported by Catovsky et al. 2007 is equal to 25%, which is relatively high with respect to the percentages found in the CLL-8 trial (5%), and in Eichhorst et al. 2006 (10%), Knauf et al. 2007 (0%) and Eichhorst et al. 2007 (15%). Moreover, the chlorambucil dose administered in Catovsky et al. 2007 is 70 mg/m^2, while the minimum dose is equal to 20-40 mg/m^2 given by Eichhorst et al. 2007. Dosing seemed to depend on the severity and other patient characteristics. The influence of Catovsky et al. 2007 and Eichhorst et al. 2007 on the results is evaluated by a scenario analysis.

Only Hillmen et al. 2007 obtained a Jadad score of 5, because of blinding. All other papers have therefore a Jadad score of 2 or 3.

Table 21. Evidence table

Ref	*Intervention*	*Country*	*Endpoints*	*Inclusion criteria*
ML17102 (CLL-8)[27]	**FC** **R-FC**	Australia, Austria, Belgium, Czech Republic, Denmark, France, Germany, Israel, Italy, New Zealand, Spain	Primary: PFS Secondary: event free survival, overall survival, disease free survival, duration of response, time to new CLL treatment, overall response rate, molecular response rate, health economic impacts and quality of life	Age >= 18 years Binet C and (Binet B (up to protocol amendment 1 also stage A) requiring treatment) No previous treatment ECOG 0, 1
Catovsky (2007)[15]	**F** **FC** **Chlorambucil**	UK (most), Argentina, Croatia, Greece, Ireland, Italy, New Zealand, Russia	Primary: overall survival Secondary: response rates, progression-free survival, toxic effects, quality of life.	Binet B, C and A-progressive who needed treatment No previous treatment
Hillmen (2007)[41]	**Chlorambucil** **Alemtuzumab**	USA and Europe	Primary: PFS Secondary: overall response, complete response rate, time to alternative treatment, safety, overall survival, CMV infection	Age >= 18 years old Rai stage I through IV with evidence of progression No previous treatment WHO performance status of 0 to 2
Flinn (2007)[14]	**F** **FC**	USA	Primary: complete response rate Secondary: overall response, PFS, toxicity	Age >= 18 year Rai stage 0 to IV with symptomatic/progressive CLL No previous treatment
Rai (2000)[42]	**F** **Chlorambucil**	USA and Canada	Primary: PFS Secondary: response rate, complete response, median duration of remission, overall survival	Age >= 18 Rai stage III or IV (40%) or Rai stage I or II (60%) having at least any disease-related symptom No previous treatment ECOG 0 to 2
Eichhorst (2006)[14]	**FC** **F**	Germany	Complete response, overall response, PFS, treatment-free survival, overall survival, response to second-line treatment	Age 18 - 65 Binet stage C and stage B having rapid disease progression or symptoms or having severe B symptoms. Binet stage A having B symptoms No previous treatment ECOG 0 to 2
Knauf (2007)[43]	**Bendamustine** **Chlorambucil**	Europe	Primary: overall response and progression-free survival Secondary: duration of remission, overall survival, safety and quality of life (QoL)	Binet stage B/C Untreated B-CLL
Eichhorst (2007)[44]	**F** **Chlorambucil**	Europe	Complete response Overall response, PFS, overall survival, rescue treatment	Age: > 64 years Binet A, B or C with advanced CLL

Table 21 continued

Ref	*Number of cycles*	*time points dose*	*Dose per month* (25 as BMI)	*Population*	*Quality (Jadad)*	**Comparison**
ML17102 (CLL-8)[27]	2 x 3 cycles	First days of monthly cycle	F: 75 mg/m2 C: 750 mg/m2 --- F: 75 mg/m2 C: 750 mg/m2 R: 375 mg/m2 (1st cycle), 500 mg/m2 (2-6 cycle)	810 persons, 74% male, median age 60 (43-77), 5% Binet A, 64% Binet B, 31% Binet C	3	R-FC versus FC
Catovsky (2007)[15]	F and FC 6 cycles, Chlorambucil up to 12 courses until maximum response	First days of monthly cycle	F: 125 mg/m2 iv or 200 mg/m2 orally --- IV: F: 75 mg/m2 C: 750 mg/m2 iv or Orally: F: 120 mg/m2 C: 750 mg/m2 --- Chlorambucil: 70 mg/m2	777 persons, 74% male, median age 65 (35-86), Binet A 25%, Binet B 45%, Binet C 30%	3	FC versus F --- F versus Chl
Hillmen (2007)[45]	Alemtuzumab: 12 weeks Chlorambucil: 12 months	First days of monthly cycle	Chlorambucil: 40 mg/m2 --- Alemtuzumab: 400 mg/m2 (90 mg/m2 per week)	294 persons, 72% male, median age 60 (35-86), Rai stage is used. 0-2: 66%, 3-4: 34%. Corrected hazard ratio is computed	5	Alemtuzumab versus Chl
Flinn (2007)[14]	6 monthly cycles	First days of monthly cycle	F: 125 mg/m2 iv --- F: 100 mg/m2 iv C: 600 mg/m2	278 persons, 70% male, median age 61 (33-86), Rai stage is used, 0-II or unknown: 56%, III-IV: 44%	3	FC versus F
Rai (2000)[46]	Continuation until no additional response or maximum of 12 cycles.	First days of monthly cycle	F: 100 mg/m2 --- Chlorambucil: 40 mg/m2	509 persons, 68% male, median age 63 (32-83), Rai stage is used; 0-II or unknown: 61%, III-IV: 39%	3	
Eichhorst (2006)[14]	6 monthly cycles	First days of monthly cycle	F: 90 mg/m2 C: 750 mg/m2 --- F: 125 mg/m2	362 persons, 73% male, median age 57 (30-65), Binet A: 10%, Binet B: 55%, Binet C: 35%; RAI 0-II: 60%, Rai III-IV: 40%	3	FC versus F
Knauf (2007)[47]	6 monthly cycles	BEN: first days of monthly cycle Chlorambucil: days 1 + 15 of monthly cycle	Bendamustine: 200 mg/m2 --- Chlorambucil: 40 mg/m2 (0.8 mg/kg on days 1+15)	305 persons, median age 64, Binet B: 70%, Binet C: 30%	2	Bendamustine versus chlorambucil
Eichhorst (2007)[48]	F: 6 monthly cycles Chlorambucil: 12 months	F: first days of monthly cycle Chlorambucil: 1 and 15th day of monthly cycle	F: 125 mg/m2 --- Chlorambucil: 20 -- 40 mg/m2 (0,4 - .8 mg/kg ideal bodyweight (BW) qd15)	206 persons, median age 70 (64-80), Binet A: 15%, Binet B: 47%, Binet C: 38%	3	F versus Chl

Results of the Mixed Treatment Comparison

To assess the heterogeneity, the credibility interval of the goodness of fit test for the fixed effects model was compared with the credibility interval of the goodness of fit test for the random effects model. The credibility intervals of the residual deviance for the fixed effects models and random effects models overlap each other for all outcomes (PFS, complete response and overall response) to a high extent. For PFS, the credibility intervals were [1.6; 12.2] for the fixed effects model and [1.1; 13.0] for the random effects model. The interval for the fixed effects model is therefore within the interval for the random effects model, so that the fixed effects model was preferred. This implied there is almost no gain in goodness of fit when a random effects model is used and that there seems to be no heterogeneity between studies.

For PFS, the hazard ratios were estimated. For complete response and overall response, the OR (Odds Ratio) and RR (Relative Risk) were estimated.

Progression-Free Survival

Of the eight identified studies, five reported hazard ratios with respect to the primary outcome, PFS, (see Table 22) allowing for comparison with results from CLL-8.

Table 22. Hazard ratios for PFS

Study	Treatment	Control	Hazard ratio	Lower bound	Upper bound
CLL-8	R-FC	FC	0.56	0.43	0.72
Catovsky (2007)	FC Fludarabine	Fludarabine Chlorambucil	0.45 0.86	0.35 0.71	0.59 1.04
Hillmen (2007)	Alemtuzumab	Chlorambucil	0.58	0.43	0.77
Flinn (2007)	FC	Fludarabine	0.51	P value 0.0003	
Eichhorst (2006)	FC	Fludarabine	0.56	0.40	0.80

Because chlorambucil was on average the treatment with the shortest PFS, this treatment was used as a reference treatment.
Table 23 provides the estimated hazard ratios of the different comparators in comparison to chlorambucil. R-FC shows the lowest hazard ratio in comparison to chlorambucil, implying that R-FC prolongs PFS the most.

Table 23. Hazard ratios with respect to chlorambucil

Treatment versus chlorambucil	Mean hazard ratio	Median hazard ratio	Lower bound	Upper bound
R-FC	0.24	0.24	0.17	0.34
Fludarabine	0.86	0.86	0.71	1.04
Alemtuzumab	0.59	0.58	0.43	0.78
FC	0.43	0.43	0.33	0.55

Table 24 provides the estimated hazard ratios of R-FC relative to different comparators. The upper bounds of the credibility intervals for the hazard ratios are all below 1, implying that R-FC prolonged PFS in comparison to all treatments.

Table 24. Relative efficacy of R-FC measured in hazard ratios for PFS

R-FC versus treatment	Mean hazard ratio	Median hazard ratio	Lower bound	Upper bound
Chlorambucil	0.24	0.24	0.17	0.34
Fludarabine	0.28	0.28	0.20	0.38
Alemtuzumab	0.42	0.41	0.26	0.66
FC	0.56	0.56	0.43	0.72

The probability for R-FC being the best treatment of the alternatives in terms of PFS results was 100% (versus 0% for chlorambucil and all other treatments), indicating that R-FC is the best first line treatment for CLL patients with regards to PFS.

Complete Response

All included studies reported information about complete response. In Table 25, the results on the relative effects of complete response are provided in terms of OR and RR. The OR of 2.71 (>1) for R-FC versus FC implies that R-FC increases the complete remission percentage with respect to FC. Similar conclusions can be drawn from the RR estimate (>1).

Table 25: Observed OR and RR on complete remission

	Treatment	OR	RR
CLL8	R-FC versus FC	2.7 (2.0-3.8)	2.09 (1.63-2.69)
Catovsky (2007)	FC versus fludarabine	2.3 (1.3-4.1)	2.5 (1.7-3.8)
Catovsky (2007)	F versus chlorambucil	3.5 (2.1-5.8)	2.1 (1.3-3.5)
Hillmen (2007)	Alemtuzumab versus chlorambucil	15.4 (4.6-51.3)	11.9 (3.8-37.9)
Flinn (2007)	FC versus F	6.4 (2.6-15.9)	5.1 (2.2-11.9)
Rai (2000)	Fludarabine versus chlorambucil	5.4 (2.4-12.1)	4.5 (2.2-9.5)
Eichhorst (2006)	FC versus F	4.3 (2.1-8.8)	3.5 (1.9-6.7)
Knauf (2007)	Bendamustine versus chlorambucil	17.6 (5.3-58.5)	12.6 (4.0-39.6)
Eichhorst (2007)	Fludarabine versus chlorambucil	7.2 (0.8-60.9)	6.7 (0.8-54.4)

These results resemble the results obtained for PFS. Chlorambucil is again the least preferable treatment. It is therefore used as reference treatment to compare to the other treatments. The following table provides information about the OR and RR of the different treatments compared with chlorambucil. R-FC shows the largest OR and RR in comparison to chlorambucil.

Table 26. Complete response in comparison to chlorambucil

Treatment versus chlorambucil	**OR**				**RR**			
	Mean	**Median**	**Lower bound**	**Upper bound**	**Mean**	**Median**	**Lower bound**	**Upper bound**
R-FC	31.6	30.3	17.5	53.4	16.1	15.7	10.8	23.3
Bendamustine	26.2	19.7	6.5	84.6	13.6	12.4	5.4	28.9
Fludarabine	3.1	3.0	2.0	4.6	2.9	2.8	1.9	4.2
Alemtuzumab	23.2	17.2	5.8	74.8	12.6	11.4	4.9	27.7
FC	11.5	11.1	7.2	17.7	8.6	8.4	5.8	12.4

Table 27 presents the OR and RR for complete response. With respect to complete response, it can be concluded that R-FC has a larger complete response rate than chlorambucil, fludarabine and FC. Based on available evidence, alemtuzumab and bendamustine perform worse, but not worse enough with respect to R-FC to conclude that R-FC is better. To show that R-FC is better than alemtuzumab and bendamustine, additional trials are needed to increase patient numbers and reduce the credibility interval.

Table 27. Relative effect on percentage of patients in complete response

R-FC versus treatment	OR				RR			
	Mean	Median	Lower bound	Upper bound	Mean	Median	Lower bound	Upper bound
Chlorambucil	31.6	30.3	17.5	53.4	16.1	15.7	10.8	23.3
Bendamustine	1.9	1.5	0.3	5.4	1.4	1.3	0.6	2.8
Fludarabine	10.4	10.1	6.3	16.4	5.7	5.6	4.0	7.8
Alemtuzumab	2.1	1.8	0.4	6.0	1.5	1.4	0.6	3.1
FC	2.8	2.7	2.0	3.8	1.9	1.9	1.5	2.3

Overall Response

Overall response (OR) was smaller for chlorambucil and all comparators (particularly R-FC) outperformed chlorambucil with respect to OR. The Odds Ratios (OR) for R-FC in comparison to the relevant comparators were between 2.4 (FC) and 14.8 (chlorambucil) (Table 8). The relative chance (RR) on overall response of R-FC with respect to the relevant comparators were between 1.1 (FC and Alemtuzumab) and 1.8 (chlorambucil).

Table 28. Relative effect of R-FC regarding overall response

R-FC versus treatment	OR				RR			
	Mean	Median	Lower bound	Upper bound	Mean	Median	Lower bound	Upper bound
Chlorambucil	14.8	14.2	8.3	24.7	1.8	1.8	1.6	1.9
Bendamustine	4.5	4.2	2.0	8.9	1.2	1.2	1.1	1.3
Fludarabine	6.0	5.8	3.5	9.8	1.3	1.3	1.2	1.4
Alemtuzumab	3.8	3.5	1.6	7.5	1.1	1.1	1.0	1.3
FC	2.4	2.3	1.6	3.4	1.1	1.1	1.0	1.1

Sensitivity analysis: Disregarding Catovsky (2007)

Table 29 shows that Catovsky et al. 2007 was the only paper providing a hazard ratio for the comparison of fludarabine with chlorambucil. Alemtuzumab, bendamustine and chlorambucil are therefore all linked to R-FC, due to this paper. Unfortunately, the Binet stage A group in Catovsky et al. 2007 was relatively large. Further, the dose of chlorambucil was relatively high. The high dose may imply why the median on PFS for chlorambucil found in this paper was relatively large in comparison to the other papers in which chlorambucil was used. The high dose chlorambucil therefore seemed to imply conservative estimates for the effect of R-FC in comparison to alemtuzumab, bendamustine and chlorambucil. To assess the influence of the Binet distribution in Catovsky et al. 2007 on the comparison of FC with fludarabine, two

other papers were used: Flinn et al. 2007 and Eichhorst et al. 2006. The results were presented in Table 29.

Table 29. Influence of Catovsky et al. 2007 on fixed effects model results

FC versus Fludarabine	Mean hazard ratio	Lower bound	Upper bound
With Catovsky (2007)	0.47	0.29	0.72
Without Catovsky (2007)	0.54	0.42	0.68

From Table 29 it can be concluded that Catovsky et al. 2007 has only small implications with respect to the estimated hazard ratio, but that the width of the credibility interval was almost doubled when Catovsky et al. 2007 was included. The difference in Binet distribution therefore implied a conservative evaluation of the effect of R-FC with respect to the other treatments.

Summary and Conclusion

Adding rituximab to FC significantly prolonged PFS and significantly increased overall response in comparison to all other comparators. It also significantly increased complete response with respect to chlorambucil, fludarabine and FC. The credibility intervals of residual deviance for the fixed effects models and random effect models overlap each other for all outcomes to a high extent. This implied there is almost no gain in goodness of fit when a random effects model is used and that the results can be considered valid estimates. When more eligible RCTs become available to be included in the network, heterogeneity will be tested again.

The results obtained from this study regarding the indirect comparison between R-FC and chlorambucil have been used to inform the economic analysis of R-FC versus chlorambucil (see Section 7). Section 7 also includes a more conventional indirect comparison to validate the findings of this MTC.

6.7 Safety

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

6.7.1 Introduction

The excellent safety and tolerability of rituximab added to conventional cytotoxic chemotherapy is well established and has been extensively reviewed in previous appraisals. To date, Roche estimates that worldwide, over 1.5 million patients have been treated with rituximab in all its indications and its safety profile is predictable and well understood. The commonest events seen are infusion-related events which can occur during and immediately after the completion of each infusion. The characteristic infusion-related symptoms typically consist of fever, chills and rigors but may rarely also include flushing, angioedema, nausea, urticaria, rash, fatigue, headache, throat irritation, rhinitis, vomiting, tumour pain and very rarely exacerbation of any pre-existing cardiac condition. Occasional bronchospasm and hypotension accompanies these symptoms in less than 10% of cases. More than 50% of patients suffer from an infusion reaction with their first dose, however this subsides rapidly with subsequent dosing. Premedication with an antihistamine and paracetamol is recommended prior to infusion. If a steroid is part of the

chemotherapeutic regime this is also given pre-rituximab to minimise potential reactions.

The evaluation of safety information for the CLL population (first-line treatment) is based on data from the phase III study CLL-8, together with a combination of safety data reported in four Phase II studies with different base chemotherapy regimes. In study CLL-8 a total of 397 patients received at least one treatment cycle of rituximab (in combination with FC). From phase II studies, safety data is available for a total of 498 extra patients.

6.7.2 Safety Data from CLL-8

6.7.2.1 Extent of Exposure

The safety population of CLL-8 consisted of 793 patients (396 patients in the FC arm, 397 patients in the R-FC arm).

Table 30. Number of Treatment Cycles Received

	FC N=396 No.(%)	R-FC N=397 No.(%)	ALL N=793 No.(%)
Patients Receiving At Least x Cycles*			
1	396 (100.0%)	397 (100.0%)	793 (100.0%)
2	366 (92.4%)	384 (96.7%)	750 (94.6%)
3	342 (86.4%)	364 (91.7%)	706 (89.0%)
4	313 (79.0%)	342 (86.1%)	655 (82.6%)
5	289 (73.0%)	317 (79.8%)	606 (76.4%)
6	273 (68.9%)	299 (75.3%)	572 (72.1%)

*: x corresponds to the number of cycles received.

Of those patients treated with R-FC, 75% received all scheduled cycles of therapy compared to 69% of those treated with FC. This difference was mainly because of higher numbers of patients in the FC arm with insufficient responses at interim staging or withdrawals for administrative reasons.

6.7.2.2 Adverse Events

Overview of Adverse Events

An overview of the overall safety results in CLL-8 is shown in Table 31 below. It is important to note that only grade 3 or 4 adverse events (AEs) or serious adverse events (SAEs) were collected in this study. At the time of the main analysis (clinical cut-off July 2007 – note last patient was randomised on April 4th 2006), the incidence of grade 3 or 4 AEs and SAEs was higher in the R-FC arm, while the number of all deaths was higher in the FC arm. AEs leading to dose modifications were more frequent in the R-FC arm than the FC arm. However, AEs leading to treatment

discontinuation occurred with the same frequency in both arms (18%). Importantly, there was no difference in the rate of deaths considered related to therapy. Overall, the safety profile of rituximab in CLL was consistent with the known safety profile of rituximab used in combination with chemotherapy in other indications. No new safety signals related to rituximab were detected.

Table 31. Overview of Adverse Events in Study CLL-8

	Number of Patients (%)	
	FC	**R-FC**
	N = 396	**N = 397**
Grade 3 or 4 AE	246 (62%)	304 (77%)
Serious AE	162 (41%)	182 (46%)
AE leading to treatment discontinuation	70 (18%)	71 (18%)
AE leading to dose modification/interruption	80 (20%)	133 (34%)
Treatment-related death	8 (2%)	6 (2%)

Common Grade 3 or 4 Adverse Events

The proportion of patients reporting at least one grade 3/4 AE was higher in the R-FC arm (77%) compared to the FC arm (62%), due to a higher incidence of blood and lymphatic system disorders (57% R-FC versus 41% FC), which were mostly neutropenia and leucopenia (see below).

Grade 3 or 4 AEs that occurred with an at least 2% higher incidence in one of the treatment arms were:

Higher incidence in the R-FC arm compared to the FC arm:

- Neutropenia: 19% in the FC arm versus 30% in the R-FC arm
- Leucopenia: 12% versus 23%
- Febrile neutropenia: 6% versus 9%
- Pancytopenia: 1% versus 3%

Higher incidence in the FC arm compared to the R-FC arm:

- Thrombocytopenia: 10% in the FC arm versus 7% in the R-FC arm
- Anaemia: 7% versus 4%
- Pyrexia: 5% versus 3%

The incidences of AEs in all other system organ classes (including infections and infestations) were balanced between the treatment arms. The balance of infections and infestations is very relevant and is in keeping with many other Phase III rituximab studies – an excess of *asymptomatic* neutropenia/ leucopenia did not lead to an excess of symptomatic, potentially serious infectious sequelae.

A summary of all grade 3 or 4 adverse events with an incidence of at least 1% in either arm is highlighted below:

Table 32: Grade 3 or 4 AEs with an Incidence of at Least 1% in Either Arm

Body System/Adverse Events	FC N = 396 (%)	R-FC N = 397 (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	75 (19)	119 (30)
LEUKOPENIA	46 (12)	93 (23)
THROMBOCYTOPENIA	39 (10)	26 (7)
FEBRILE NEUTROPENIA	22 (6)	37 (9)
ANAEMIA	26 (7)	16 (4)
PANCYTOPENIA	5 (1)	13 (3)
LYMPHOPENIA	6 (2)	7 (2)
GRANULOCYTOPENIA	5 (1)	7 (2)
INFECTIONS AND INFESTATIONS		
PNEUMONIA	19 (5)	14 (4)
HERPES ZOSTER	12 (3)	9 (2)
SEPSIS	8 (2)	5 (1)
BRONCHITIS	6 (2)	5 (1)
INFECTION	3 (<1)	6 (2)
SINUSITIS	3 (<1)	4 (1)
NEUTROPENIC INFECTION	-	4 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
PYREXIA	21 (5)	12 (3)
FATIGUE	(<1)	4 (1)
GASTROINTESTINAL DISORDERS		
VOMITING	7 (2)	6 (2)
NAUSEA	4 (1)	4 (1)
DIARRHOEA	3 (<1)	4 (1)
INVESTIGATIONS		
NEUTROPHIL COUNT DECREASED	4 (1)	4 (1)
NERVOUS SYSTEM DISORDERS		
SYNCOPE	3 (<1)	5 (1)
CARDIAC DISORDERS		
ANGINA PECTORIS	1 (<1)	6 (2)
IMMUNE SYSTEM DISORDERS		
HYPERSENSITIVITY	1 (<1)	6 (2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
DYSPNOEA	4 (1)	1 (<1)

Deaths, Serious Adverse Events and Events Leading to Treatment Discontinuation

Deaths

A total of 80/793 patients (10%) in the safety population had died at the time of the main analysis. There were more deaths in the FC arm than in the R-FC arm (12% versus 8%). The most common causes of death were infections (5% in FC versus 3% in R-FC) and neoplasms (including death due to PD; 4% in FC versus 3% in R-FC). Five patients in the FC arm and three patients in the R-FC arm (approximately 1%) died due to a cardiac disorder. The underlying cause of death was considered to be PD in 42 patients (25 [6.3%] in the FC arm and 17 [4.3%] in the R-FC arm). Most of those patients whose death was related to PD developed an infection and died (13 patients in the FC arm and 8 in the R-FC arm).

Of the 38 patients (22 [6%] in the FC arm and 16 [4%] in the R-FC arm) who died due to causes not related to disease progression, 8 FC patients and 6 R-FC patients (approximately 2%) died from infections. The most common infection AEs resulting in death were sepsis (5 patients in each arm, including bacterial sepsis, pulmonary sepsis, and septic shock). It is well appreciated that treatment for any haematological malignancy can lead to life-threatening sepsis and it is unsurprising to see this data. What is very reassuring with regards to rituximab is the complete lack of excess infective morbidity and mortality in the R-FC arm.

In 8 FC patients (2%) and 6 R-FC patients (2%), the investigator judged the death to be related to study treatment.

Serious Adverse Events

A slightly higher incidence of SAEs was observed in the R-FC arm (182 patients [46%]) compared to the FC arm (162 patients [41%]).Serious infections and serious blood and lymphatic system disorders were most commonly reported in both treatment arms. The incidence for serious infections was broadly similar (15% in FC versus 18% in R-FC); the incidence of serious blood and lymphatic system disorders was 6% higher in the rituximab arm (11% in FC versus 17% in R-FC). All other SAEs were balanced between the treatment arms.

Approximately half of the SAEs were considered by the investigators as related to treatment.

Adverse Events Leading to Treatment Discontinuation

The proportion of patients who discontinued study treatment due to AEs was balanced between the two treatment arms (70 patients [18%] in the FC arm, 71 patients [18%] in the R-FC arm). Consistent with the overall pattern of AEs, the most common AEs that led to withdrawal were blood and lymphatic system disorders (10% FC vs. 12% R-FC) and infections/infestations (9 patients [2%] on FC vs. 7 patients [2%] on R-FC)

Adverse Events by Organ System or Syndrome

Specific comment is appropriate on adverse events affecting the blood/bone marrow and infections which constitute the majority of the excess Grade 3 or 4 events amongst rituximab patients and also on infusion reactions, which are the characteristic toxicity associated with rituximab elsewhere. It is also relevant to analyse haemolytic anaemia, which is of particular interest in CLL.

Adverse Events Occurring on the First or Second Day of Cycle Treatment

AEs with a date of onset on the day of or the day after the start of any cycle treatment were analysed separately in order to describe the profile of potential infusion-related events.

More patients in the R-FC arm compared to the FC arm had a grade 3 or 4 AE on the day of or the next day after start of cycle treatment (9% of patients in the FC arm and 16% in the R-FC arm). The most common events reported were blood and lymphatic system disorders (4% and 5%), general disorders and administration site conditions (<1% and 2%), and immune system disorders (<0.1% and 2%). None of the events occurring on the first or second day of cycle treatment were fatal.

Subgroup analyses based on lymphocyte counts at baseline show that the overall incidence of grade 3/4 AEs slightly increased with increasing lymphocyte counts and that this trend was more pronounced in the FC arm than in the R-FC arm. The rate of SAEs also increased with lymphocyte count in the FC arm but not in the R-FC arm. These findings are reassuring since there was concern that patients with high levels of circulating CLL cells might be at increased risk of AEs when rituximab was first given. *This has not been the case.*

Infections

The incidence of grade 3 and 4 infections was comparable between the treatment groups (67 patients [17%] in the FC arm and 73 patients [18%] in the R-FC arm). There was no consistent increase in infection rates across different age categories or Binet stage. However, the rate of infections increased with decreasing creatinine clearance at baseline in the FC arm.

The most common infections reported were pneumonia (5% FC vs. 4% R-FC), herpes zoster (3% vs. 2%), sepsis (2% vs. 1%), and bronchitis (2% vs. 1%). Twelve percent of patients in each arm had an infection, in which the underlying pathogen was not specified. Approximately 4% of patients in both arms had a viral infection (mainly herpes virus). Fungal and bacterial infections were each reported in <1% of patients in the FC arm and in 2% of patients in the R-FC arm.

A total of 31 patients died from infections, 19 patients (5%) in the FC arm and 12 patients (3%) in the R-FC arm. In 5 patients in the FC arm and in 4 patients in the R-FC arm, death due to infection was considered treatment-related.

Most of the grade 3/4 infections in either arm were considered a SAE. The proportion of patients reporting a serious infection was virtually identical: sixty-seven FC patients (17%) had a grade 3 or 4 infection and 59 (15%) had a serious infection. In comparison, 73 R-FC patients (18%) had a grade 3 or 4 infection and 71 (18%) had a serious infection. The difference between the arms was not significant (p=0.68). The rate of discontinuation of treatment due to infections was low with no difference between treatment arms (2% in each arm).

This analysis is reassuring and in keeping with safety data that has been extensively seen in Phase III rituximab-chemotherapy lymphoma studies: They indicate that despite a higher incidence of blood and lymphatic system disorders (notably neutropenia/leukopenia) in patients treated in the rituximab arm, this did not translate into a significantly higher incidence of infections.

Blood and Lymphatic System Disorders

Overall, as was expected, there was a higher incidence of grade 3 or 4 blood and lymphatic system disorders in the R-FC arm (228 patients [57%]) compared to the FC arm (161 patients [41%]). The difference was mainly accounted for by a higher incidence of neutropenia and leukopenia. Two patients in the FC arm experienced an event leading to death (autoimmune thrombocytopenia and bone marrow failure). The differences in both neutropenia (R-FC 33.6%, FC 20.9%: p=0.0001) and leukopenia (R-FC 24%, FC 12.1%: p<0.0001) were statistically significant. There was no statistical difference seen in thrombocytopenia (R-FC 7.4%,FC 10.8%: p=0.09), and anaemia (R-FC 5.4%, FC 6.8%: p= 0.42). If anything there was a tendency for R-FC to protect against thrombocytopenia.

Autoimmune Haemolytic Anaemia

Patients with CLL are known to be at risk of autoimmune haemolytic anaemia (AIHA) (and other autoimmune cytopenias) and this risk increases in patients with uncontrolled disease. Moreover, AIHA may be precipitated or exacerbated by treatment with fludarabine (e.g. D'Arena and Cascavilla) [49]. More patients in the FC arm than in the R-FC arm experienced a haemolytic event: 8 patients (2%) in the FC arm and 4 patients (1%) in the R-FC arm. Most of these were of grade 3/4 intensity, none of them were fatal. Numbers are small and it is therefore difficult to speculate, however R-FC may offer additional control to preventing autoimmune haemolysis in CLL. This effect may be due to better or more rapid disease control and/or to the immune modulating effects of rituximab,.

Tumour Lysis Syndrome

A higher incidence of tumour lysis syndrome (TLS) was observed in the FC arm compared to the R-FC arm (9 patients FC vs. 3 patients R-FC). Almost all of these events were of grade 3 and 4 intensity, 5 events in the FC arm and 2 events in the R-FC arm were serious, none of them were fatal.

Again, these data are reassuring since the superior efficacy of R-FC might be expected to result in a higher incidence of tumour lysis syndrome due to a more rapid and/or dramatic onset of cell lysis with the initiation of therapy. This was part of the rationale for the dose reduction of rituximab for the first cycle. However, the incidence of tumour lysis syndrome appeared to be lower or similar in the R-FC arm of the study than the FC arm. This slight difference may have been due to chance or to greater vigilance by investigators (TLS prophylaxis) when administering R-FC.

Phase II Safety Data

These studies are fully analysed in section 6.8 below, but their safety analysis is included here. They add valuable information that reinforces the predictable and well understood safety profile of rituximab in combination with chemotherapy in CLL.

Treatment: R-FC; (Keating et al, Tam et al)

Patients with previously untreated CLL received rituximab combined with fludarabine and cyclophosphamide in this open-label phase II study. Three hundred patients with symptomatic or progressive disease as defined by NCI working group criteria were enrolled. Their median age was 57 years (range 17-86) and 30% were female. Interim results in 224 patients showed that the treatment regimen was well tolerated. The adverse events observed with R-FC were mainly myelosuppression and infections. Grade 3 or 4 neutropenia occurred in 24% and 28% of 927 assessable courses, respectively. Grades 3 or 4 thrombocytopenia occurred in 4% and less than 1% of courses, respectively. Despite the relatively high incidence of neutropenia, only 2.6% of the courses were associated with major infections, including pneumonia (20 episodes) or septicemia (11 episodes). Minor infections, such as fever of unknown origin, cellulitis, urinary tract infections, upper respiratory infections, sinusitis or bronchitis, were reported in 10% of the courses. One third of the 224 patients had more than one episode of infection, and 10% had a fever of unknown origin. Following completion of therapy, 19% of patients had persistent cytopenias lasting more than three months. Following recovery of blood counts, recurrent late cytopenia episodes occurred in 69 of 245 patients (28%). The risk of grade ≥3 infections or opportunistic infections was 10% and 4% during the first and second years of remission, respectively. From the third year of remission onwards, serious infections were uncommon (<1.5% per year).

Treatment: R-F; Source: Publications by Byrd et al

The Cancer and Leukemia Group B (CALGB) conducted a randomised study in 104 previously untreated CLL patients of induction treatment with either concurrent or sequential fludarabine and rituximab (CALGB9712). In a historical cohort comparison, patients randomised in this study were compared with a historical cohort of patients receiving fludarabine alone as initial therapy (CALGB9011). The two treatment cohorts were balanced with respect to age with a median age of 63-64 years (ranges between 37-88 years).
Compared to the fludarabine only group, the incidences of neutropenia, hypotension and dyspnoea was higher in the fludarabine and rituximab treatment group. No significant difference in other haematological toxicity (anaemia or thrombocytopenia) or infections was noted.

Treatment: R-FCM; Source: Conference Abstract by Faderl et al, 2007

The combination of rituximab with FCM chemotherapy plus pegfilgrastim as first-line treatment for untreated patients with CLL was presented by Faderl et al at the American Society for Clinical Oncology (ASCO) 2007 meeting and updated at the American Society for Hematology (ASH) 2007 meeting. Thirty patients were included. The median age was 57 years (range 38-69), and more than half the patients were female.
Grade 3-4 neutropenia occurred in 19/30 patients (63%) and grade 3-4 thrombocytopenia in 2/30 (7%). Infectious episodes were seen in 13/30 patients (43%). Seven patients (23%) did not complete six treatment courses because of ongoing cytopenias. A further full publication is expected next year.

Treatment: R-PC; Source: Publication by Kay et al, 2007

In a study by Kay et al, 64 previously untreated patients with CLL received induction treatment with pentostatin, cyclophosphamide and rituximab. Most patients enrolled in this trial exhibited high risk factors (Rai stage 3-4) at study entry. The median age was 63 years (range 38-80), 18 patients were older than 70 years, and 15 patients were female (23%).
The treatment was equally effective and tolerated in young and older (>70 years) patients. Reasons for premature discontinuation of some patients were disease progression (three patients [4.7%]), refusing further treatment (four patients [6.3%]), unacceptable toxicity (three patients [4.7%]), other medical problems (one patient) and death during treatment (two patients [3.2%]). While on treatment, 25 patients (39%) had the dose held or modified, and 14 of these patients had dose delays or modifications due to hematological adverse events.
Overall, 34 patients (53%) had a grade 3-4 hematological AE, and 28 patients (44%) had a grade 3 non-hematological AE. The most common severe toxicities were hematological: 26 patients (41%) had grade 3 or 4 neutropenia, and 13 patients (21%) had grade 3 or 4 thrombocytopenia. The most common grade 3 or greater non-hematological toxicities included nausea, infection (six patients each), vomiting and fever without neutropenia (four patients each). The infections were related to upper respiratory tract sites. Two patients died during the study. One patient developed fever, hypoxia, and hypotension following the first cycle of therapy and died. The other patient experienced grade 5 hypoxia and pneumonia. Both deaths were considered possibly related to study treatment. Both patients had comorbid illnesses including chronic obstructive pulmonary disease and uncontrolled diabetes that may have contributed to the risk of AEs. Two patients had possible autoimmune haemolytic anemia; one patient developed haemolysis during cycle 2 but completed therapy, the other patient developed haemolysis during cycle 1 and had to stop treatment because of disease progression.

6.7.3 Overall Conclusions on Clinical Safety

The safety profile of rituximab is well known. The excellent safety and tolerability of rituximab added to conventional cytotoxic chemotherapy is predictable and well established. The antibody has been available for clinical use for more than 10 years, and Roche estimates that over 1.5 million patients have been treated to date in all its indications. The safety profile of rituximab plus FC seen in CLL-8 was very acceptable with only the expected addition of rituximab-related side effects to those of FC. No new safety concerns were identified and the addition of rituximab did not increase the rate of treatment discontinuations compared to patients treated with FC alone or the incidence of treatment related deaths. As has been seen in numerous other Phase III rituximab studies, the excess asymptomatic neutropenia/leukopenia seen did not translate into an increased risk of infection.

The safety profile of other R-chemotherapy regimes as seen in the published Phase II studies is in keeping with what was seen in the Phase III study and support the notion that the safety profile is predictable and in keeping with other approved indications in Non Hodgkin lymphoma.

It must be noted that there is not Phase III safety data available for all chemotherapy regimes, as it would have been impractical and logistically impossible to carry out the number of trials required, but after 10 years of use and cumulative Phase III studies there is enough safety data across all indications with different regimes that allows confidence with the broad ‘R-chemotherapy’ indication, and it is anticipated that the regulatory authorities will endorse this.

6.8 Non-RCT evidence

6.8.1 Details of how the relevant non-RCTs have been identified and selected

See section 6.2.4 for list of studies and section 6.2.5 for CONSORT flow diagram detailing how non-RCTs have been identified. As noted in Section 6.2.2 a randomised, non-comparative Phase II study with rituximab in both arms (Byrd et al, 2003, 2005) is analysed in this section as well.

6.8.2 Summary of methodology of relevant non-RCTs

6.8.2.1 Overview

For the specific population relevant to this submission, there are four supporting studies that highlight the efficacy and tolerability of rituximab in combination with different chemotherapy regimes. These are detailed below in Table 33. Two of the studies also present historical cohort comparisons to estimate survival differences across regimes used in earlier trials.

Table 33: Supporting Phase II Studies

Study: Keating et al (2005)19, Tam et al (2008)20 R-FC as initial treatment for CLL	
Rationale and Purpose	To test the efficacy and tolerability of adding rituximab to the combination of fludarabine and cyclophosphamide for the initial treatment of CLL, with the hope of increasing CR rates to greater than 50%.
Design	Single-arm, open label Phase II study of 300 patients.
Participants	300 patients aged 18 years or older with previously untreated CLL requiring therapy as indicated by NCI 1996 guidelines. Median age was 57, with 14% being 70 or older. 61% of patients had Rai stage I-II disease, and 36% had Rai stage III-IV disease. Cytogenetics via conventional karyotyping was available for 222 patients (FISH was not available); of these 30% had clonal abnormalities and 4% had abnormalities involving chromosome 17. FISH, IgvH and ZAP-70 were not clinically available at the time of study recruitment.
Interventions	6 cycles of R-FC given every 28 days. All medication given i.v. Rituximab : 375mg/m2 cycle 1, 500mg/m2 cycles 2-6; Fludarabine 25-30mg/m2 for 3 days each course and cyclophosphamide 250-300mg/m2 for 3 days each course.
Outcomes	Responses as according to NCI criteria, overall survival, failure-free survival, time to progression.
Added comments	A historical comparison of R-FC against previous frontline fludarabine-based regimes at the MD Anderson Cancer Center is also presented.
Study: Kay et al, 200750 R-PC as initial treatment for CLL	

Rationale and Purpose	To evaluate the efficacy and tolerability of pentostatin in combination with cyclophosphamide and rituximab for the initial treatment of CLL.
Design	A Phase II, single arm non-randomised study.
Participants	65 patients with progressive CLL requiring treatment for the first time, as defined by NCI criteria. Median age was 63 years, 34/64 patients (53%) had high risk disease according to Rai stage (i.e. stage 3 or 4 disease), 71% had unmutated IgVH, 34% were CD38-positive, and 28% were ZAP-70-positive. Thirty patients (47%) had one anomaly detected by fluorescence in situ (FISH) hybridisation, and 21 (33%) had complex FISH defects.
Interventions	6 cycles of treatment, given every 21 days consisting of Pentostatin 2mg/m2, cyclophosphamide 600mg/m2, and rituximab 375mg/m2 all given on day 1 of cycles 2-6. In cycle 1 , more doses of rituximab were given, with 100mg/m2 on day 1 and 375mg/m2 on days 3 and 5.
Outcomes	Responses graded according to NCI criteria, and all patients followed up for 5 years or until disease progression. Minimum residual disease was also tested for in responding patients.
Added comments	Pentostatin is a purine analogue similar to fludarabine but is also a potent transition state inhibitor of the enzyme adenosine deaminase (ADA). This inhibition, as well as direct inhibition of RNA synthesis and increased DNA damage contributes to the overall cytotoxic effect of pentostatin.
Study: Faderl et al, 200751 R-FCM as initial treatment for CLL	
Rationale and Purpose	To evaluate the efficacy and tolerability of fludarabine, cyclophosphamide, mitoxantrone and rituximab for the initial treatment of CLL
Design	A Phase II, single arm non-randomised study.
Participants	30 patients with progressive CLL requiring treatment, as defined by NCI criteria. The median age was 57 years (range 38-69). Fourteen patients (48%) were male. Four patients (14%) had Rai stage ≥ 3 disease. Median β2-microglobulin was 2.6 mg/L (range 1.4-4) and the median WBC was 59.9 x 109/L (range 5.6-355). Two patients had 11q23 and 17p- abnormalities by cytogenetics/fluorescent in situ hybridisation (FISH). Unmutated IgVH was reported in 12/17 patients (71%) and ZAP-70 was positive in 11/19 patients (58%).
Interventions	Fludarabine (25 mg/m2 i.v. d 2-4), cyclophosphamide (250 mg/m2 i.v. d 2-4), mitoxantrone (6 mg/m2 i.v. d 2), rituximab (375 mg/m2 i.v. d 1) and pegfilgrastim (6 mg s.c. d 4) in cycle 1. For cycles 2 to 6, FCM started on day 1 together with 500 mg/m2 of rituximab followed by pegfilgrastim on day 3. Cycles were repeated every 4 to 6 weeks.
Outcomes	Responses graded according to NCI criteria, at 3 and 6 months post starting therapy.
Added comments	Further publication on this study expected next year.

Study: Byrd et al, 200329 and 200552 Combining Rituximab and Fludarabine for the initial treatment for CLL	
Rationale and Purpose	To investigate the efficacy, tolerability and optimal schedule of administration of rituximab with fludarabine in previously untreated patients. Two schedules of rituximab were presented: concurrent, or sequential.
Design	Non-comparative, randomised Phase II study.
Participants	104 patients with 51 in Arm A (concurrent), and 53 in Arm B (sequential). All required treatment for CLL as defined by NCI criteria. Median age was 64. 59% of patients had Rai Stage I-II disease, the rest had Stage III-IV.
Interventions	Concurrent Regime: 6 monthly courses of fludarabine (25mg/m2 iv for 5 days) concurrently with rituximab (375mg/m2 – 2 doses in cycle one and one in each of the subsequent 5), followed 2 months later by 4 weekly doses of rituximab (375mg/m2) for consolidation therapy. Sequential Regime: Treatment with fludarabine alone followed by rituximab consolidation therapy 2 months later, doses as described above. Consolidation therapy was only given to those who responded to initial treatment.
Outcomes	Response rates, progression-free and overall survival were all measured for both concurrent and sequential groups. Please note that this was study was not designed to compare both arms and contained rituximab in both arms, and is therefore not appropriate for discussion in section in 6.3.
Added comments	The 2004 publication compared all the pooled results of CALGB 9712 versus an older CALGB study (9011) of fludarabine monotherapy in a similar population.

6.8.3 Critical appraisal of relevant non-RCTs

The limitations of Phase II studies are understood; centre bias, selection bias and the lack of an adequately controlled comparator arm all mean that one should not over-interpret Phase II data.

However, it must be appreciated that the studies presented in this section were designed and executed for specific reasons – to explore the efficacy and tolerability of different rituximab combination chemotherapies before moving into a Phase III setting. These add valuable extra information to support the broad R-chemotherapy licence that is expected and they highlight that the base regime does not preclude efficacy and does not cause alarming or unexpected toxicity (see section 6.7). The next logical step on from the Phase II studies (which was taken), was to analyse and confirm the benefit of adding rituximab to the most appropriate base regime in a Phase III setting.

The heterogeneity around the dose of rituximab across the Phase II studies should be highlighted. Only the MD Anderson study used the dosing (500mg/m^2) of rituximab which was used in CLL-8 (the GCLLSG based their dosing regime on this Phase II study), and this will be the approved dosing in the SmPC.

6.8.4 Results of the relevant non- RCTs

Tam et al.[19], Keating et al.[20]

In the publication by Tam et al., the long-term results of the open label, phase II study of R-FC in 300 patients with previously untreated CLL were reported. Early results of this study were reported by Keating et al. in 2005.

At a median follow-up of six years, the overall response rate was 95%, with complete response (CR) in 72%, nodular partial response (nPR) in 10%, partial response (PR) due to cytopenia in 7%, and PR due to residual disease in 6% of patients. Two patients (<1%) died within three months after starting therapy. Six-year overall survival (OS) and failure-free survival (FFS) were 77% and 51%, respectively. Median time to progression (TTP) was 80 months.

Pre-treatment characteristics independently associated with inferior response were: age $\geq$ 70, β2-microglobulin ≥ twice upper limit of normal (ULN), white cell count (WBC) ≥150 x 10^9/L, abnormal chromosome 17, and lactate dehydrogenase (LDH) ≥ 2xULN. No pre-treatment characteristic was independently associated with decreased complete remission duration. The risk of late infection was 10% and 4% for the first and second years of remission, respectively, and <1.5% per year for the third year onwards. In a multivariate analysis of patients receiving fludarabine-based therapy, R-FC therapy emerged as the strongest independent determinant of survival.

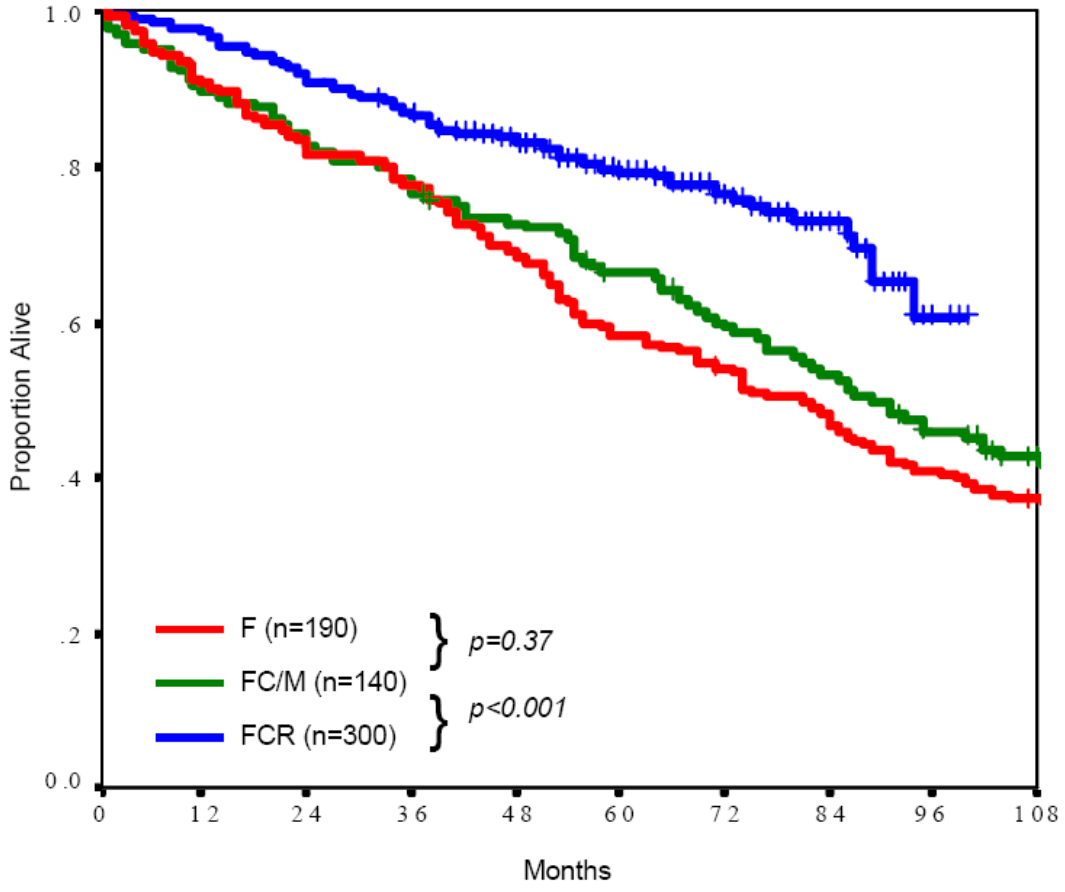
Give the open label, phase II design of this study, the treatment effect of the R-FC observed in this study is likely to be a reasonable proxy for the community effectiveness obtained in the real world. Nevertheless, there may be factors, such as diagnosis accuracy, patients' and healthcare professionals' compliance that cause this study to differ from routine clinical practice. The comparative Phase III R-FC trial already presented provides a more rigorous analysis of the efficacy of R-FC versus FC, however this Phase II data gives an idea of the what longer term follow-up of the R-FC arm in CLL-8 may end up looking like, as to date the maximum median follow-up in CLL-8 is 25 months (compared to 6 years in this study).

Risk of over-interpreting a Phase II study is noted, but it is very interesting and encouraging to have a potential glimpse into the future of what may happen to the R-FC arm of CLL-8.

Retrospective Cohort Analysis

Using CLL patient cohort data collected at the same institution, Tam et al. compared the treatment effect of first line R-FC with previous generations of frontline fludarabine-based regimes (Fludarabine monotherapy, FC and FC + mitoxantrone (FCM)). Their analysis showed a significantly superior overall survival associated with R-FC (Figure 10).

Figure 10: Historical Comparison with Patients Receiving F or FC/M



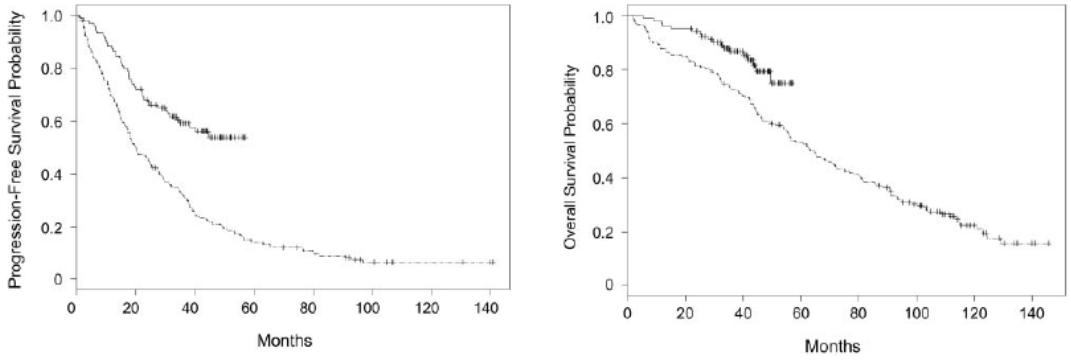
After adjusting for differences in pretreatment variables using Cox regression multivariate analysis, R-FC therapy emerged as the strongest independent predictor of survival (p<0.001, HR 0.48).

Results from Byrd et al.[29,48]

The overall response rate with the concurrent regimen was 90% (47% CR, 43% PR; 95% confidence interval [CI], 0.82-0.98) compared with 77% (28% CR, 49% PR; 95% CI, 0.66-0.99) with the sequential regimen. With a median follow-up time of 23 months, the median response duration and survival had not been reached for either regimen at the time of reporting. The authors concluded that rituximab administered concurrently with fludarabine in previously untreated patients with CLL demonstrated marked clinical efficacy and acceptable toxicity.

A retrospective analysis published in 2005 compared the results of the combination of R-F in study CALGB 9712 (n=104) with the treatment outcome of patients with similar clinical characteristics enrolled in a study evaluating fludarabine monotherapy in the same clinical setting (CALGB 9011, n=178). In multivariate analyses controlling for pre-treatment characteristics, the patients receiving R-F had a significantly better PFS (p<0.0001) and OS (p=0.0006) than patients receiving fludarabine (F) monotherapy (figure x below). Two-year PFS probabilities were 0.67 for R-F versus 0.45 for F alone, and 2-year OS probabilities were 0.93 for R-F versus 0.81 for F alone. Infectious toxicity was seen to be similar between with the two treatment approaches.

Figure 11: PFS and OS for Patients Assigned to Rituximab and Fludarabine on CALGB 9712 versus fludarabine on CALGB 9011.



Results from Faderl et al.[47]

29 patients were evaluable for response at 3 months and 30 patients at completion of therapy. Twenty-eight patients (97%) responded at 3 months (41% CR, 17% nPR, 39% PR); 10 patients (34%) had <1% detectable residual CLL cells in the bone marrow. Response rates at completion of therapy were: 77% CR, 10% nPR, 10% PR (overall response rate [ORR] = 97%). Seventeen patients (57%) had < 1% residual CLL cells in the marrow at the end of therapy.

In conclusion, this study highlighted that R-FCM was able to elicit a high CR rate in symptomatic, previously untreated patients with CLL. A further analysis and publication on this study is expected next year.

Results from Kay et al.[46]

Responses occurred in 58 patients (91%), with 26 (41%) CRs, 14 (22%) nPRs, and 18 (28%) PRs. Examination of prognostic factors demonstrated poor response in the 3 patients with del(17p). In contrast, this regimen was found to be equally effective in young versus older (> 70 years) patients and in patients with del(11q22.3) versus other favourable prognostic factors. The median PFS was 32.6 months.

24 responding patients had no evidence of minimal residual disease by 2-colour flow cytometry at the end of treatment(19 with CRs and 5 with a nodular PR). Interestingly, patients who were MRD negative after treatment had a PFS advantage over those who did not (HR 0.22, p=0.003).

Overall, the authors concluded that the novel regimen of pentostatin, cyclophosphamide, and rituximab for previously untreated patients with CLL had

significant clinical activity in previously untreated patients with CLL, with modest toxicity. Efficacy was seen despite poor risk-based prognoses, including achievement of minimal residual disease in some patients.

Summary

These data highlight the efficacy of rituximab in combination with a range of chemotherapy regimes. The limitations associated with over-interpreting Phase II data are noted, however these results highlight that the background chemotherapy regime can be altered and rituximab combinations still provide efficacy and tolerability, in the relevant population

It is important to note that on the basis of the three fully published Phase II studies, the American NCCN guidelines recommend the use (Category '2A' evidence – by their definition Category 2A is " based on lower-level evidence in clinical experience and uniform consensus) of R-PC, FC+/-R and F+/- R for the initial treatment of CLL – as discussed in section 4.6. A summary table of results highlights the response rates obtained from the Phase II studies discussed.

Table 34: Summary Table of Response Rates from Phase II Studies

Study	**Keating et al.,Tam et al.**	**Byrd et al.**		**Faderl et al.**	**Kay et al**
Regimen	**R-FC N= 300**	**F→R N=53**	**RF→R N=51**	**R-FCM N=30**	**R-PC N=64**
ORR	95%	*77%*	*90%*	97%	91%
CR	72%	28%	47%	77%	41%
PR	23%	49%	43%	20%	50%
Median Follow-up	72 months	23 months		6 months	53 months

6.8.5 Safety of the relevant non-RCTs

This is covered in section 6.7

6.9 Interpretation of clinical evidence

6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The Relevance of the Evidence Base to the Decision Problem

The decision problem relates to appraising rituximab in CLL in line with its expected marketing authorisation, that is in combination with (any) chemotherapy. In some

parts of the world, rituximab combinations have become standard treatments, but in those patients where non-rituximab therapy is used, single agent chlorambucil and fludarabine combination therapy (FC) are generally preferred as first-line options (as highlighted for the United Kingdom by market research data presented in section 4). FC is steadily becoming the standard of care in the United Kingdom for many patients, with chlorambucil remaining a choice for the very frail and elderly. Very rarely, clinicians may use combinations such as CVP (cyclophosphamide, vincristine and prednisolone) or CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone). Therefore ideally, there would be comparative Phase III data comparing every baseline chemotherapy with its rituximab combination counterpart, and more pragmatically with relevance to this decision problem there would be Phase III data relating to fludarabine combination therapy and chlorambucil (the two comparators noted in the decision problem). However there is only one Phase III trial available but the following analysis explains how a combination of this study, supporting Phase II data and the mixed-treatment comparison combine to give a full evidence base entirely pertinent to the decision problem. It should be noted at this point that with regards to the population, all the studies presented included patients with CLL who were symptomatic and needed treatment according to standardised criteria only, which is exactly the population being appraised, as stated in the decision problem.

Evidence Base Relevant to Fludarabine Combination Therapy

After the publication of the three randomised Phase III fludarabine combination studies it has become widely accepted that the optimal non-antibody approach to obtaining the best remission and progression-free survival is FC combination treatment. The evidence base presented in this submission includes the sole comparative Phase III study to have been carried out with rituximab in the relevant population with FC as the comparator – which is highly pertinent.

Evidence Base Relevant to Chlorambucil

With regards to the other main comparator in this submission (chlorambucil), there is data presented (in terms of the mixed-treatment comparison- MTC), which helps to appraise the benefit of R-FC compared to chlorambucil. In the UK CLL-4 study, the superior efficacy of FC compared to chlorambucil was clearly demonstrated. However due to the multiple co-morbidities and frailty of many CLL patients, chlorambucil remains a popular disease control treatment strategy, even though its use appears to be declining in the UK following the publication of the CLL-4 trial. There is no published phase II or III study data with rituximab and chlorambucil, however in the United Kingdom there is an ongoing Phase II combination trial of rituximab and chlorambucil (UK CLL201) for first-line patients who are not appropriate for fludarabine-based treatment. A Phase III study for analysis would be the ideal data to have (R-FC versus chlorambucil and/or R-chlorambucil versus chlorambucil), however the MTC provides a network meta-analysis which highlights the superiority of R-FC over chlorambucil. The MTC highlights that compared to chlorambucil, R-FC has the best chance of prolonging PFS, obtaining a CR and results of both fixed and random effects analyses suggest there was no significant heterogeneity across the network of studies analysed in the comparison.

Summary

It is appreciated that the most rigorous form of Phase III data is not available for every chemotherapy regime. However the Phase III trial presented compares against the most relevant comparator for the UK, and the mixed-treatment comparison clearly highlights the superiority of R-FC compared to chlorambucil. The supporting phase II studies add some information that is readily interpretable – they highlight that changing the base regime still allows efficacy with an acceptable toxicity profile. Previous experience in follicular lymphoma Phase III studies with rituximab (eg Marcus et al.[53], Hiddemann et al.[54]) have consistently highlighted that varying the base regime does not alter the additional benefit that rituximab gives to these patients. Thus the evidence base does cover the comparators and population appropriately.

The Relevance of Outcomes Assessed in Clinical Trials to the Clinical Benefits Experienced by Patients in Practice

As highlighted in section 4, CLL is generally considered incurable (a small number of may be cured by allogenic bone marrow transplantation) and patients are treated when they become symptomatic with a view to inducing a remission, thereby alleviating symptoms, which one would intuitively believe improves quality of life. The criteria for treatment are standardised and have been re-endorsed in the updated NCI guidelines (Hallek et al., 2008).

Patients in remission are not only free of the symptoms caused by overt disease, but also from the inconvenience and toxicity of the chemotherapy that will be required when they relapse, not to mention the psychological trauma that attends relapse. However there is a balance that needs to be maintained between obtaining a remission and the subsequent time-free from disease with the morbidity of potentially toxic chemotherapy. As discussed in section 4, increasing evidence is accumulating suggesting that the depth of remission is directly linked to prognosis, and it is clear that the deeper the remission the longer the progression-free survival. For each individual patient, a risk-benefit analysis has to be undertaken to estimate the effect of potential treatment-related morbidity versus the potential time free of disease/progression following treatment.

Endpoints in CLL Trials and their Relevance to Patients

In the pivotal randomised Phase III study that is supporting this submission, the endpoints assessed (both primary and secondary) are of direct relevance to benefits that would be experienced by patients in practice. Time progression-free is highly relevant as discussed above and all the secondary endpoints are usually measured in oncology trials. The phase II studies also analysed a number of these standard endpoints. The direct relevance of overall survival is obvious to patients and clinicians alike, and the trend towards overall survival shown in the R-FC arm of CLL-8 is highly encouraging.

Health-related Quality of Life (HR-QoL)

It is entirely logical to assume that the HR-QoL of patients with active CLL will be directly linked to a) the treatment that they are given and b) the response that they obtain from treatment. Treatments that are more likely to cause a response are more likely to improve immediate HR-QoL by relieving the often very debilitating signs and symptoms of the disease (e.g. night sweats, weight loss, painful and/or disfiguring lymphadenopathy, issues surrounding bone marrow failure etc). It would also be reasonable to assume that longer-term HR-QoL will be maintained by preventing relapse. However the counterpoint of aiming to get the best chance of response is

potential morbidity (and mortality) related to toxicity of treatment. There is an increasing body of evidence that more efficacious treatment is directly leading to improved HR-QoL. In the HR-QoL analysis arising from the German CLL-4 trial (Eichhorst et al.,2007[55]) , the German study group found a small (but not significant) improvement by 2 years in patients given the more efficacious regime (FC). This has been confirmed by the analysis coming from the UK CLL-4 trial (Else et al., 2008[56]), where they found that patients who responded to treatment had a global HR-QoL score of 9.1 months higher at 3 months than of non-responders (p=0.0001), and 10.5 points higher at 2 years (p=0.0004). It is therefore reasonable to assume that giving the patients the best chance of response (which from CLL-8 and supporting data has been shown to be rituximab-based chemotherapy) will lead to the best health-related quality-of-life. There is a fully-planned HR-QoL analysis coming out from the CLL-8 study, however this has not been completed yet, and is not available for discussion.

[redacted]

Gaining 'real-life' utilities in CLL

The actual utility for CLL patients in different disease states is highly pertinent and to gain valid, prospective data on this, Roche have commissioned a questionnaire based (EQ-5D and QLQC-30) study. The aim of this study is to get prospective quality-of-life data for patients with CLL (sample size 200) who are at different time points in their disease profile and to gain data on the HR-QoL in different states e.g. stable disease, progressed disease/relapse, progression-free survival. The study will be carried out in 6-8 centres in the United Kingdom, and the study has already received ethics approval through The Royal Bournemouth Hospital, and the pilot study is underway. It is anticipated that the first data from this study will be available in January 2009 and when complete, the study will be put forward for publication in a peer-reviewed haematology journal. To our knowledge, this type of data in CLL patients does not exist to date and represents an important opportunity to obtain HR-QoL information in this disease. All utilities obtained in this study will be available for use in the economic model and the Q-TWisT, and as soon as this data is available it will be submitted to the Evidence Review Group. The utility study is discussed further in the economic section (7) below.

Summary

In this submission, evidence has been presented from a pivotal, well-conducted comparative Phase III study which forms the core of the application to extend the marketing authorisation for rituximab to cover the first-line treatment of symptomatic patients with CLL. Data from supportive Phase II trials highlight the benefit of adding rituximab to a variety of chemotherapy regimes. The essence is that rituximab, when added to induction chemotherapy in CLL increases the proportion of patients entering remission (doubling of the complete response rate in CLL-8) and as is being found in all ongoing Phase III studies in indolent B-cell malignancies, the depth of remission is directly linked to the durability of remissions. In the CLL-8 study, rituximab added to FC led to a highly significant 44% risk reduction in progression or death which has very clear benefits to patients. As has been highlighted above, remission and time-progression free is of central importance in managing this disease. The differences seen between arms in CLL-8 were not only highly statistically significant, but also of a magnitude that would be expected to make a real difference to patients, especially as the "cost" to patients in terms of additional treatment burden is minimal – rituximab infusions are administered at the same time as patient visits for chemotherapy and add little to treatment toxicity, with the statistically significant increase in grade 3/4 neutropenia/leukopenia (asymptomatic adverse events), not matched by an increase in the Grade 3/4 infection rate. The data on MRD negativity is also highly encouraging, with adding rituximab improving the chance of an MRD-negative CR by 18%. It has been repeatedly shown that MRD negativity after treatment is a very favourable prognostic factor.

HR-QoL is of critical importance in this disease. The evidence presented is highlighting how the best HR-QoL is linked to the most efficacious treatment.

Prospective utility data for CLL patients is being collected in an ongoing study and this will give real-life utility scores which will help further validate this concept.

6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

As highlighted throughout this submission, the pivotal Phase III study that forms the core of this submission, was a very well run comparative trial that clearly highlights the significant clinical superiority of R-FC over FC. Supportive Phase II data highlights that the base regime can be altered, but rituximab combinations still offer good efficacy and tolerability. There are however a few points that need to be highlighted with regards to the applicability primarily of the Phase III study to routine clinical practice in the United Kingdom:

Routes of Administration

In the key fludarabine-based study analysed to frame the decision problem (CLL-8), both fludarabine and cyclophosphamide were administered intravenously (i.v.). An oral formulation of fludarabine became available in 2001, and bioavailability studies identify that a higher oral dose is required to obtain the equivalent iv dose (55% bioavailability, Foram et al., 1999[58]). There is widespread Phase II clinical data and general consensus that as long as a dose adjustment is made for oral fludarabine there is no difference in efficacy or side effects (eg Rossi et al., 2004[59]) The investigators in the UK LRF CLL-4 study amended their protocol so that from 2001, patients were allowed to be given single agent fludarabine or FC orally. The fall-out from this is that in The United Kingdom today, 99% of all FC is administered orally (Roche CLL Monitor, Genactis 2008[65]). An analysis comparing the two groups of patients separated by the protocol amendment in the UK study (i.e. the IV F/FC cohort and the fully oral cohort) of the data suggested that an observed difference in response rates between intravenous and oral fludarabine in the LRF CLL4 trial was probably not due to the route of administration of fludarabine but is more likely to be explained because older patients with a poorer prognosis were entered later in the study when all patients were guaranteed to receive oral therapy.(Hillmen et al.[60]). It is important to note that response rates for chlorambucil also went down after the protocol amendment allowing oral fludarabine, supporting the notion of selection bias that the protocol amendment led to. Although a randomised controlled trial would be required to formally prove that oral fludarabine is not inferior to intravenous

fludarabine the data suggested that there are unlikely to be significant differences in response rates between routes of administration of fludarabine. This is accepted worldwide. Therefore even though FC has been given intravenously in the studies analysed, there would be anticipated to be no difference in efficacy or tolerability if they were given orally, and the results of the German CLL-8 study would have looked almost identical if FC had been given orally. Pragmatically the mode of administration is not a clinical issue, but it would change a fully oral regime (oral FC) into a partially intravenous regime (R+oral FC).

Choice of Eligible Patients, Age and Co-morbidities

The median age of patients presenting with CLL is around 70, and with advancing age, co-morbidity and frailty treatment of any malignancy can become increasingly difficult. It is generally a feature of all oncology studies that there are not enough older patients enrolled and this is applicable to CLL-8, where the median age of patients was 59, and only 58 patients in the trial population were greater than 70 years old. The phase III study also only selected patients with an ECOG performance status of 0 and 1, which helps explain the median age of the trial group, with an expected decrease in performance status with increasing age. ECOG 0 and 1 may not reflect the true performance status of a number of frailer CLL patients who need treatment for the first time.

However, modern oncology practice is changing and patients are being treated in line with their 'biological' age rather than their 'chronological' age. It is possible that clinicians may only choose fitter patients for rituximab based treatment with fludarabine/cyclophosphamide as the base regime and they may consider other adaptive rituximab-based strategies in frailer patients with co-morbidities. Chlorambucil monotherapy will still play a role in the management of the frailest with numerous co-morbidities. There is also encouraging recent evidence suggesting that rituximab combinations including smaller doses of fludarabine and cyclophosphamide (R-FC 'lite') may be effective (Tarhini et al.,2007[61]).

In the United Kingdom, it is felt that on the basis of the evidence base, rituximab-based chemotherapy in this population can be appropriately used in a wide population with the most rigorous data in patients who would be eligible for fludarabine-based treatment. The actual size of the 'fludarabine eligible' population is not clearly defined but one would anticipate that this would be over 60% of patients at first treatment. It should be noted that in terms of the selection of patients to actually start treatment in the clinical trials (i.e. symptoms that necessitated treatment), this would be entirely in keeping with routine clinical practice and all the patients treated in the studies would have been initiated on treatment if they had presented to UK haematologists.

1.1.1.2 Relevance of Dosing Schedules Used in Clinical Trials

The main study used in support of this submission (CLL-8) used a regime that will become the licensed dosing schedule for rituximab in CLL and as such will be documented in the SmPC. Some of the supportive Phase II studies used the lymphoma dose only (375mg/m^2), but as explained above it was thought that a higher dose was required for CLL and 500mg/m^2 will become the standard licensed combination dose.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

The search strategy aimed to identify all publications relating to rituximab and chronic lymphocytic leukaemia. Keyword strategies were developed using key references retrieved through initial scoping searches. Search strategies did not include search terms or filters that would limit results to specific publication types or study design. In addition to broad medical databases (e.g., Medline and EMBASE), health economic databases and websites of health technology assessment (HTA) agencies were searched. All databases and websites searched are listed in Table 35. The search strategy is provided in Appendix 3.

Table 35. Literature review Databases

General Databases
Medline
EMBASE
HTA/health economic databases and websites
NHS EED
International Society For Pharmacoeconomics and Outcomes Research (ISPOR) Research Digest
National Institute for Clinical Excellence (NICE)
Scottish Medicines Consortium (SMC)

7.1.2 Description of identified studies

There were no studies or research papers that examined the health economic evaluation of rituximab in CLL. Please see Appendix 3 for a description of the excluding studies identified and the rationale behind their exclusion.

Three conference abstracts that will be presented in the forthcoming months have been identified.

1. Keating, M. J., Lerner, S., Aultman, R. Treatment of chronic lymphocytic lymphoma with the rituximab, fludarabine and cyclophosphamide regimen – An economic evaluation based on observational data (presented in the annual congress of the International Society For Pharmacoeconomics and Outcomes Research, ISPOR 2008)[62]

2. Carr, E., Lerner, S., Aultman, R., Weisgerber-Kriegl, U., Keating, M. Treatment effect of first line rituximab, fludarabine and cyclophosphamide in a chronic lymphocytic leukemia patient cohort: an evaluation of prognostic factors, estimated life expectancy and economic outcomes (presented in ASH, American Society of Hematology, Annual Meeting 2008)[63]

3. Papadakis, K., Oscier, D., Carr, E., Lewis, G., Aultman, R. A UK Cost-Effectiveness Analysis Comparing First Line Treatment with Rituximab in Combination with Fludarabine and Cyclophosphamide Versus Fludarabine and

Cyclophosphamide Alone in Chronic Lymphocytic Leukemia (CLL) Patients (presented in ASH, American Society of Hematology, Annual Meeting 2008)[64]

The first two abstracts, (1) and (2), present the economic analysis based upon the MD Anderson observational data. The method used for the analysis was cost-effectiveness comparing FC to R-FC. The incremental cost-effectiveness ratio for R-FC compared to FC was $12,382 per QALY gained.

The third abstract, (3), which will be presented at the American Society of Haemtalogy meeting in Decemeber 2008 is a provisional cost utility analysis using the same model structure as utilised within this submission and based upon the phase III randomised controlled CLL8 data. The model compares FC to R-FC and it has been adapted to the reflect UK costs and benefits. The resulting ICER was £12,387 per QALY gained. The difference in the ICER reported in this abstract and that reported within this submission is due to further updates to the base-case parameters since it was used to calculate this provisional ICER. These differences include a comparison of intravenously infused FC (whilst the base case in this submission assumed orally administered FC) and different unit costs for health care resource use.

7.2 De novo economic evaluation(s)

Manufacturer economic model described in detail below.

7.2.1 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

The technology (rituximab) is assumed to be used as indicated in its draft UK Summary of Product Characteristics (SPC). Rituximab (R) is administered by infusion in combination with fludarabine and cyclophosphamide (FC) for a maximum of 6 cycles or until disease progression. FC was assumed to be administered orally as per standard practice in the UK (Genactis CLL Monitor - Q2 2008[65]). Each cycle was 28 days in length. The assumed doses for each drug are described in the table below. The dosage information relating to the second comparator, chlorambucil, is also included:

Table 36: Drug dose and frequency included within the economic model

Drug	Dose	Dose Frequency
Rituximab (infusion)	375mg/m^2 500mg/m^2	Day 0 of the first cycle Day 1 of each subsequent cycle (Cycles 2-6)
Fludarabine (oral)	24mg/m^2	Day 1-5 of each cycle (6 cycles)
Cyclophosphamide (oral)	150mg/m^2	Day 1-5 of each cycle (6 cycles)

Chlorambucil (oral)	10mg/m^2	Day 1-7 of each cycle (12 cycles)
Fludarabine (IV)*	25mg/m^2	Day 1-3 of each cycle (6 cycles)
Cyclophosphamide (IV)*	250mg/m^2	Day 1-3 of each cycle (6 cycles)

*Intravenously administered FC was included in the sensitivity analysis

The doses listed in this table for intravenously administered rituximab, fludarabine and cyclophosphamide were taken from the ML17102 (CLL-8) phase III randomised control trial. The doses listed for oral fludarabine, cyclophosphamide and chlorambucil were taken from the CLL-4 trial (Catovsky et al 2007[15]).

Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

The base case assumes all patients in PFS receive the recommend treatment course of six cycles unless disease progression occurs before this time point. This assumption may overestimate the incremental drug cost of rituximab in the base case ICER as it does not adjust for those patients stopping treatment after 3 cycles.

However, the model scenario based on observed trial dosing in CLL-8 accounts for any patients stopping treatment after 3 cycles (see Section 6.3.4).

7.2.2 Patients

What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The patient cohort within the economic evaluation are assumed to have the same baseline characteristics as those observed in CLL-8. As the trial represented the main registration study, it can be claimed that the economic evaluation is reflective of the licensed indication. The baseline characteristics of the trial are described in greater detail in Section 6.

Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach?

For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

No sub-group cost effectiveness analysis was conducted. The CLL-8 study was not powered to show significant differences between subgroups. Consequently, any subgroup analyses are exploratory in nature. Only two subgroups in CLL-8 did not show a numerical improvement in PFS with R-FC: patients greater than 70 years of age and those who were diagnosed 6–12 months before study entry. However, patient numbers in both of these groups (58 and 73 patients, respectively) were too small to draw statistically meaningful conclusions. The multivariate analysis within the clinical trial illustrated that outcomes were comparable across all selected sub-groups (see the forest plot in Figure 8). Furthermore, the licensed indication for rituximab is not restrictive in terms of the population and hence the intention to treat (ITT) population within the CLL-8 trial was considered the most appropriate population upon which to base the economic evaluation. It was also considered that this population is representative of the likely patient group that will receive rituximab in the UK.

Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

As described in Section 7.2.2.2, CLL-8 study was not powered to show significant differences between subgroups, thus due to the low patient numbers and their non-randomised nature, it is therefore not possible to draw statistically meaningful conclusions.

At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients enter the evaluation at the start of treatment receiving either R-FC or the comparator treatment. Patients may only then exit the evaluation due to death from either the progression-free or progressed health states. Patients who failed to respond to either treatment will not have been classed as being "progression-free" within the trial and will therefore make the transition to the progressed health state. The assumed points of entry and exit within the evaluation are the same for both treatment interventions. The risk of death from the progressed health state is also assumed to be the same in both treatment arms. While the model does not make any assumption of patients being re-staged, the PFS curves from CLL-8 reflect this restaging (as described in Section 7.2.1.2). Details on these probabilities and the design of the model are described in more detail in Section 7.2.6.1 below.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The base case choice of comparators within the economic evaluation were FC and chlorambucil. FC is the comparator regimen within the main registration trial. As described in Sections 4 and 6 above, UK treatment options are dominated by fludarabine-based regimens and chlorambucil (Genactis CLL Monitor - Q2 2008[65]). Consequently FC and chlorambucil can be considered an adequate representation of the standard of care in the UK for the first line treatment of CLL, as reflected in the final scope.

Since FC is usually provided orally in the UK, the base case assumed that the planned dose of oral FC was administered during each cycle. However, the model is informed by clinical results from the pivotal trial CLL-8, where both fludarabine and cyclophosphamide were administered intravenously (IV). Therefore, it was necessary to assume that the mode of administration did not impact upon clinical effectiveness of FC. The rationale for this assumption is discussed in more detail in Section 6.9.2 above. The sensitivity analysis also provides results based upon the actual clinical trial setting, assuming both the actual IV doses of R-FC and FC and accounting for the associated drug and administration costs for both arms. This is described further in Section 7.2.11.2.

Because of the lack of direct (head to head) evidence, an indirect comparison was necessary for evaluating the relative efficacy of any alternative comparators. To inform the comparison with chlorambucil, a mixed treatment comparison, as recommended in the latest Guide to Methods of Technology Appraisal (June 2008[66]) was adopted, which was described previously in Section 6.6. Chlorambucil is also administered according to the planned oral dose for a maximum of 12 cycles or until disease progression.

7.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The economic analysis reflects the perspective of the NHS and Personal Social Services.

7.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

The analysis took lifetime time horizon (equating to 15 years) in order to follow the vast majority of the original cohort of patients within the model to death (i.e. only 1.3% of the cohort are estimated to survive past this period in the two arms). This was to ensure all lifetime costs and benefits of both interventions could be evaluated.

7.2.6 Framework

1.1.1.3 a) Model-based evaluations

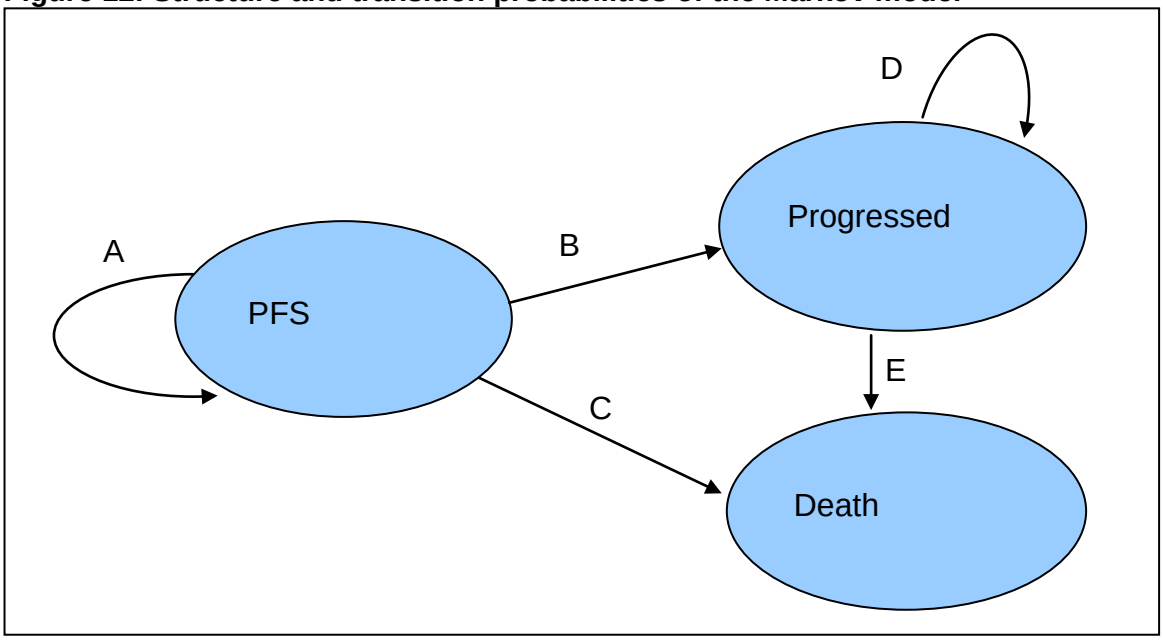
Please provide the following.

- **A description of the model type.**

The model mirrors the key outcomes of the CLL-8 clinical trial, and is designed for the purposes of extrapolating the trial outcomes beyond the last follow-up and accounting for future costs and clinical outcomes. The model is a 3-state Markov model constructed using Excel™ with a cycle length of 1 month, reflecting a very common structure for oncology economic evaluations. Patients are assumed to be within 1 of 3 possible discrete health states at any given time; "progression-free survival"(PFS), "progressed" or "death". The "progressed" health state represents the time period from 1st treatment relapse until death and therefore includes the possible sequence of remission and relapse of 2nd and subsequent lines of treatments common to this disease area.

- **A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.**

Figure 12: Structure and transition probabilities of the Markov model



All patients were assumed to start in the progression-free health state which is defined by the criteria within the CLL-8 study. At the end of each cycle a patient could either remain in PFS (A) or move to the progressed health state (B) or die (C). Once a patient is within the progressed health state, a patient may either remain within the progressed health state (D) or die at the end of each cycle (E). Patients could not move from the progressed health state back to PFS within the model. Death is an absorbing health state within the model. Monthly transition probabilities are listed in the table below with their exact derivation described in more detail in Section 7.2.6.8.

The main differences in model assumptions between the R-FC and comparator arms of the model (apart from drug cost and administration costs) is the transition probability from PFS to "progressed" (B) and PFS to Death (C). The Progressed health state has identical costs, treatment options, transition probabilities and utility scores for both the R-FC and comparator arms. The rationale for this assumption is provided in Section 7.2.6.8.

- **A list of all variables that includes their value, range (distribution) and source.**

Table 37. Model Parameters and Values

Model Variable	Value	Source
Transition Probabilities (tp)		
PFS to PFS	Time dependent based upon Weibull extrapolation of PFS trial curves	CLL-8[27]
PFS to Progression	1 – [tp(PFS to PFS) + tp(PFS to death)]	CLL-8[27]
PFS to death	Maximum value of either age-specific background mortality or monthly rate at which patients died (all cause) while in PFS	Office of National Statistics[67] or CLL-8[27]
Progression to Progression	1 - tp(Progression to death)	CLL-8[27]
Progression to death	Constant hazard of dying obtained from modelling the CLL-8 post-progression population survival as a single population due to the non-significant difference in survival between the treatment arms	CLL-8[27]
Costs		
Supportive-care costs		
Monthly PFS health state supportive care • Consultation	£28	Eichhorst et al. 2008[68]; NHS reference costs, 2006/7[69]
• Blood Transfusion 1- Per one unit pack 2- Per infusion	£161.11 £289.73	Agrawal et al, 2006[70] inflated by PSSRU 2007[71]
• Bone Marrow Transplant	£47,565	NHS reference costs, 2006/7[69]
Monthly Progressed health state supportive care • Consultation • 2nd-line and later therapy	£84 £257.66	NHS reference costs, 2006/7[69] BNF 56[72], CLL-8[27]

Drug costs[†]		
Rituximab per cycle • For Cycle 1 • For Cycles 2-6	 £1,397.03 £1,746.30	 BNF 56[72]
FC per cycle	£450.00	BNF 56[72]
Chlorambucil per cycle	£23.41	BNF 56[72]
Drug administration costs[†]		
Rituximab administration per cycle • For Cycle 1 • For Cycles 2-6	 £437.50 £157.50	 NHS reference costs, 2006/7[69]; PSSRU 2007[71]
FC administration per cycle	£371.50	NHS reference costs, 2006/7[69]; PSSRU 2007[71]
Chlorambucil administration per cycle	£371.50	NHS reference costs, 2006/7[69]; PSSRU 2007[71]
Utilities		
Progression Free Survival Health State	0.8*	Hancock et al, 2002[57]
Progressed Health State	0.6*	Hancock et al, 2002[57]
Discount rates		
Costs	3.5%	Guide to Methods, NICE[66]
QALYs	3.5%	Guide to Methods, NICE[66]

[†]Costs are provided by cycle. However, as the Markov model utilised a cycle length = 1 month, the costs provided in this table have been adjusted to account for the total number of cycles which occur in each month (30.4375 days per month / 28 days per cycle = 1.08).
*Utilities values are planned to be updated in Q1 2009 with results from an ongoing utility study in UK CLL patients (see section 7.2.8.3)

The calculation for relevant values as well as further detail on the references is provided in the appropriate sections below. The assumed ranges for each model parameter are listed in Section 7.2.11.3 when describing the probabilistic sensitivity analysis (PSA). Further details on the calculation of costs is provided in Section 7.2.9.

- **A separate list of all assumptions and a justification for each assumption.**

1. Rituximab is assumed to delay progression of disease (as observed in the CLL-8 trial) but is not assumed to impact on time to death once progression (treatment failure) occurs.

Following treatment failure, patients enter the progressed health state. The subsequent monthly risk of death from this health state is assumed equal in both arms of the model.

2. Following first relapse, all patients are assumed to have the same sequence of further health care resource use.

Once patients in the R-FC and comparator arms have progressed they are subject to the same treatment options at 2nd and subsequent lines. Consequently, monthly healthcare costs, utility scores and transition probabilities are assumed to be the same for both arms following first-line relapse. The rationale for this assumption is provided in 7.2.6.8. The assumed healthcare costs for the "progressed" health state are outlined in more detail in Section 7.2.9.2 below.

3. Orally administered FC has the same safety and efficacy profile as IV administered FC.

As described in the clinical section (Section 6.9.2), comparable outcomes may be assumed with either mode of administration after making the necessary dosage adjustment for fludarabine and cyclophosphamide.

4. No differences in treatment-related adverse events are assumed between the R-FC and FC arms.

As the results of the CLL-8 study illustrated, no major differences in treatment related adverse events were observed between the R-FC and FC arms of the trial. A small but significant difference in neutropenia/leukopenia was observed, however neutropenia/leukopenia are asymptomatic on their own and this was not associated with an increase in the incidence of severe infection (Hallek et al, 2008[28]). Because this did not translate into any meaningful differences in infection rates, whilst some differences will occur, no significant incremental costs or quality of life impact can be expected between R-FC and FC patients in clinical practice. Therefore to fully account for all costs and possible QoL impacts was considered an un-necessary complication in model design given the scale of its impact upon the final ICER.

Whilst the differences in febrile neutropenia (FN) events were not significant across the two arms, due to the significant costs associated with FN, sensitivity analysis did evaluate the impact of including the cost of febrile neutropenia on the final ICERs, if the exclusion of adverse events from the base case was considered an unreasonable assumption.

5. Chlorambucil is assumed to have a similar adverse events profile and probabilities of mortality as FC.

Due to lack of patient level data, it was assumed that chlorambucil was not associated with a change in treatment-related adverse events rates compared to FC and therefore no treatment related adverse event costs were included in the comparison to chlorambucil. Changes to the adverse events profile (specifically, assuming an improved adverse events profile of chlorambucil compared to FC) was explored in the sensitivity analysis. The main clinical difference incorporated in the chlorambucil arm is the treatment effect derived from the adjusted indirect comparison (described further in Section 7.2.6.8).

Why was this particular type of model used?

The disease area of chronic lymphocytic leukaemia has a long term progression with survival rates long exceeding the time frame of the main clinical trials. Therefore in order to estimate clinical outcomes and the resulting costs beyond the follow-up of the main trial (median 2.2 years, maximum observed follow-up = 4.6 years), some form of modelling exercise was required. A Markov model was considered the most

appropriate as CLL is a chronic long-term disease which can be easily classified into a few discrete health states.

What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The structure of stratifying the clinical outcomes of oncology patients into progression-free, progression, and death is common practice in the economic evaluation of oncology. The health states align with one of the key objectives of treatment within this disease area: to place a patient into a progression-free health state for the longest period possible. Furthermore, the main outcomes of the clinical trial could be stratified into one of these 3 heath states: progression-free survival, progressed patients and death. Disease progression was represented by all patients no longer being classified as “progression free” within the CLL-8 trial, as defined by the CLL-8 protocol.

What were the sources of information used to develop and inform the structure of the model?

The main sources that informed the model structure was the CLL-8 clinical trial for R-FC and FC and the mixed treatment comparison for chlorambucil. This trial provided the probability of a patient remaining within the PFS health state for each cycle of the model. Due to the very low number of events observed in the study for patients dying within the PFS health state, UK mortality rates[67] were used to supplement the trial data sources. The mixed-treatment comparison (described in Section 6.6) was utilised to calculate the probability of a patient remaining within the PFS state for chlorambucil.

Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The 3 health states within the model capture all conditions relevant to the decision problem.

For discrete time models, what was the model’s cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The cycle length of the Markov model is monthly. Rarely is clinical assessment and consequently diagnosed clinical status performed on a more regular basis than every month. Therefore it is unreasonable to assume that costs or clinical outcomes could change on a more frequent basis than every month.

Was a half-cycle correction used in the model? If not, why not?

A half cycle correction was applied within the model.

Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

At the time of the pre-planned interim analysis (July 2007) of CLL-8, the median follow-up was 1.7 years (20.7 months), which is relatively short in light of the long disease course of CLL, which has a median survival of 5 to 10 years. Therefore, the most recent additional observation period was included by utilising a more recent analysis of the trial (July 2008) to help improve the maturity of the data set for the purposes of extrapolation. Therefore the economic model attempts to utilise the most current follow-up information (July 2008) compared to the data set for EMEA filing (described in Section 6) to minimise any uncertainty associated with the required extrapolation of clinical outcomes.

At the time of analysis (2.2 years median follow-up), 87.04% and 89.22% of patients in the FC and R-FC arm of the CLL-8 study were still alive. Consequently, to estimate the lifetime clinical outcomes and associated NHS costs, assumptions of the future disease progression of these patients have been made.

Table 38. CLL-8 results: median follow-up 2.2 years

CLL-8	R-FC (n= 409)	FC (n=408)
Mean progression free survival (months)	37.12 (se 0.9538)	30.84(se 0.9765)
Median progression free survival (months)	42.809	32.230
p value Log-Rank test	P<0.001	
Hazard ratio (unadjusted / unstratified)	0.595 (CI 0.473-0.748)	
p value Log-Rank test	P<0.001	
Hazard ratio (adjusted /stratified)	0.577 (CI 0.457-0.729)	
Percentage of patients censored for overall survival	87.04% (n=364)	89.22% (n=356)
Mean overall survival (months)	47.65 (se 0.6922)	48.15 (se 1.0544)
p value Log-Rank test	p=0.1842	

The clinical results reported on OS and PFS were non-parametrically (Kaplan-Meier) generated and were under the assumption of proportional hazards. Diagnostics were performed to ensure that this assumption was reasonable.

Figure 13. Progression Free Survival of R-FC versus FC: median follow-up 2.2 years

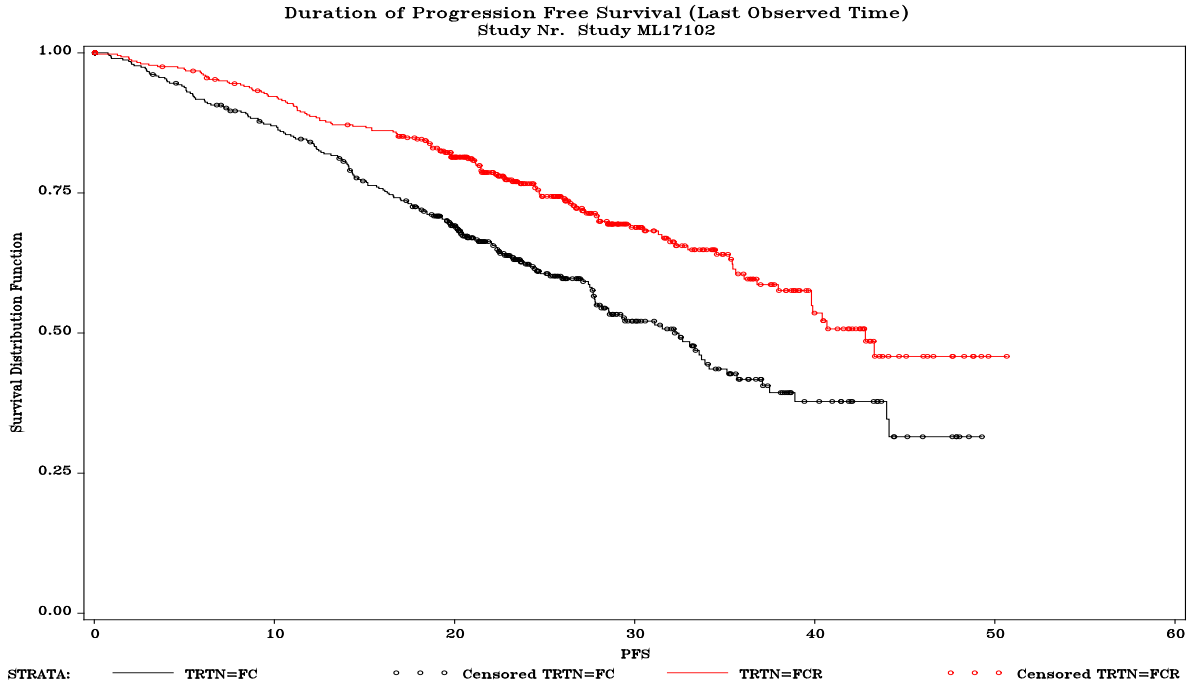
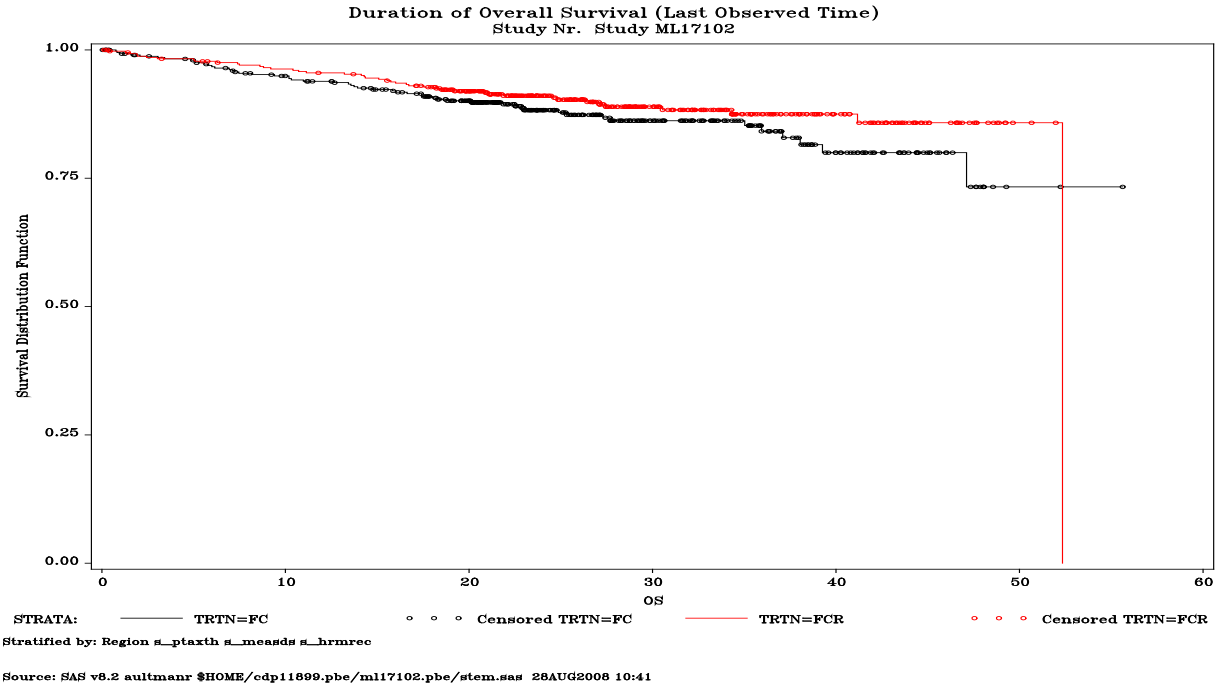


Figure 14. Overall Survival of R-FC versus FC: median follow-up 2.2 years



Extrapolation beyond the clinical follow up period can only be performed if one assumes that the data originated from a parametric distribution. The use of a parametric function requires that its unknown parameters (e.g. λ, γ parameters of a Weibull survival function) can be estimated. Various parametric functions were

available and each function was assessed for its goodness of fit to the data using Akaike (AIC) and Bayesian Information Criteria (BIC), the mean squared deviance and graphical inspection of fit (e.g., Martingale residuals) to the data before deciding on the final functional form. The parametric model structures assessed for goodness of fit to the data were: Log Logistic, Weibull, Log Normal, Gompertz and Exponential.

- **Estimating long-term Progression-free survival**

R-FC/FC

To estimate future progression free survival (PFS) an extrapolation of the PFS curve from the CLL-8 study for both R-FC and FC was performed. A monthly, treatment- and time-dependent probability of remaining within the PFS health state could then be calculated from these extrapolated curves to populate the Markov model (transition probability A and B from Figure **12**).

Extrapolation of the progression free (PFS) data was carried out under the assumption that the data followed a parametric model structure. The parameters were estimated using patient level clinical data from the CLL-8 study (July 2008 data cut). As reported in Section 6, the unstratified and stratified results were consistent and so the parametric parameters were determined using an unstratified model. The various models were assessed for goodness of fit. The same shape Weibull function was found to be the best fit to the PFS data. Independently shaped parametric models are assessed whenever there is an indication that the shape of the treatment arms differ. There was no indication of differences in the shapes of the treatments and no violation of the underlying assumption of proportional hazards was noted in the diagnostics (e.g. Martingales) plots. Thus a same shape Weibull model was selected as the best fit parametric function to model the PFS data. Table 4 gives the goodness of fit results for PFS for all functions evaluated.

Table 39: Summary of Parametric Functions' Goodness of Fit for PFS

Parametric Model	**Rituximab + FC versus FC Alone AIC / BIC (MSD: R-FC / FC) Progression Free Survival**
Exponential	-756.26 / -757.61 (0.004 / 0.0122)
Log Logistic	-745.07 / -747.78 (0.0012 / 0.0019)
Log Normal	-755.64 / -758.35 (0.00 / 0.00275)
Weibull	-742.19 / -744.89 (0.00021/ 0.00071)
Gompertz	NC (0.00061 / 0.00191)

NC = not calculated because not available in current tools. The value of the maximum likelihood is not calculated in Proc NLIN procedure in SAS. MSD = Mean Square Deviance.

The decision for the Weibull function was based on the AIC / BIC for PFS and graphical inspection of the fit. Mean squared deviation (MSD) is also reported so that some assessment of goodness of fit can be assessed for the Gompertz function. The SAS institute is developing a procedure to assess the Gompertz function and report the value of the likelihood which can then be assessed for fit using AIC and BIC methods.

The Weibull survival function is defined as

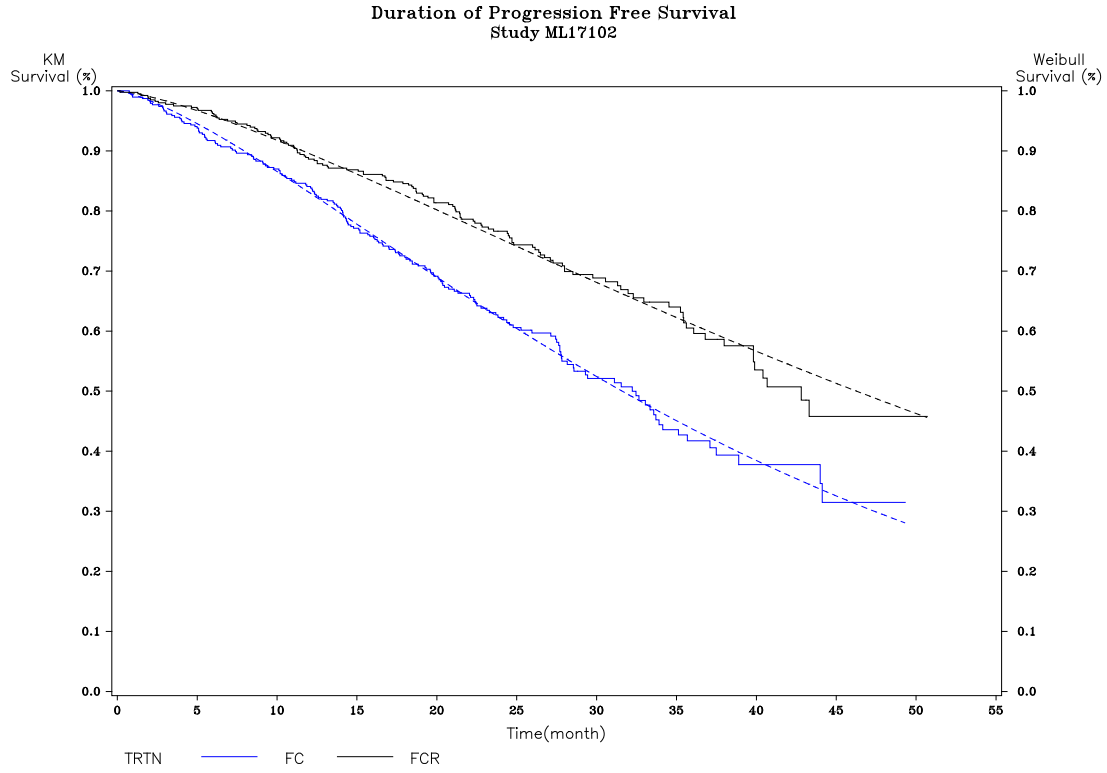
$$S(t) = \exp(\lambda t^{\gamma}),\ \lambda, \gamma > 0,\ t \geq 0$$

The probability of staying in this health state is determined by the cumulative ½-cycle corrected survival probabilities obtained from same shaped Weibull function for PFS. Table 40 summarizes the Weibull parameter estimates used to determine the distributions specifying the monthly probability of transitioning from PFS to progressed or death by treatment arm. Figure 15 represents the KM PFS curves from CLL-8 and extrapolated PFS curves for R-FC and FC using the Weibull function. The impact on the ICERs of using alternative parametric curves was explored in the sensitivity analysis.

Table 40. Weibull parameters for PFS progression

Efficacy Endpoint	Rituximab + FC	FC Alone
Progression Free Survival (PFS)		
Lambda	0.003724939	0.006262217
Gamma	1.362977234	1.362977234

Figure 15. Extrapolated Progression Free Survival curves (Weibull)



Source: SAS v8.2 aultmanr $HOME/cdp11899.pbe/ml17102.pbe/stem.sas 25AUG2008 10:05

Chlorambucil

Two relevant RCTs for first line CLL therapy with either chlorambucil or R-FC with a common comparator were identified. The LRF CLL4 study (Catovsky et al., 2007[15])

provided the hazard ratios for chlorambucil versus FC, while hazard ratios for R-FC versus FC were obtained from CLL-8 (July 2008, 2.2 years median follow-up). The method suggested by Bucher (Bucher et al. 1997[73]) for adjusting indirect comparisons was used to validate the results of the mixed treatment comparison. The indirect comparison of R-FC and Chlorambucil was adjusted by the results of their direct comparisons with a common intervention, FC (Table 41). This adjusted method aims to overcome the potential problem of different prognostic characteristics between study participants among trials. It is validated if the relative efficacy of interventions is consistent across different trials (McAlister et al., 1999[74]; Bucher et al. 1997[73]; Song et al.,2003[75]).

Table 41. Comparison of R-FC versus Chlorambucil

Trial results	**HR**	**LCL**	**UCL**	**Reference**
HR(FC vs. Chlorambucil)	0.45	0.37	0.54	Catovsky et al. 2007
HR(R-FC vs. FC)	0.53	0.41	0.68	CLL-8
HR (Chlorambucil vs. FC)	2.22	1.85	2.7	Catovsky et al. 2007
Indirect Method	**HR**			
HR(R-FC vs Chlorambucil) = **A / B**	***0.2385***			Bucher et al 1997 method
Mixed treatment comparison	**HR**	**LCL**	**UCL**	
HR(R-FC vs Chlorambucil) = **A / B**	***0.24***	0.17	0.34	Mixed-treatment comparison - Section 6.6
CHL vs R-FC probabilistic HR	**4.166667**			

The hazard ratio 0.2385 derived from the adjusted indirect comparison above validates the mixed treatment comparison (see section 6.6), where the estimated mean hazard ratio of R-FC (CLL-8 interim analysis) relative to chlorambucil was 0.24 (CI 0.17-0.34). The mean hazard ratio from the MTC was used in the base case and the confidence intervals from the MTC were used in the probabilistic analysis Table 41).

The same model structure for the comparison of R-FC to chlorambucil was used, with identical assumptions for adverse events, death in PFS and death from the progression health state (Table 42). To incorporate the treatment effect of chlorambucil, the hazard ratio (1/0.24 derived from the MTC) was applied to the best fitting parametric function (Weibull) fitted to the R-FC PFS KM curve in the comparator arm.

Table 42. Transition probabilities, mortality rates and hazard ratios

Markov Transition	**Monthly probability**	**Data source**
PFS to death	R-FC = 0.00119627 FC = 0.00138823	Maximum of age-specific background mortality[67] or monthly rate at which patients died while in PFS from the CLL-8 study
Progression to death	0.0405144	Progression to death population from CLL-8 treated as a single population with mean time to death converted to a constant hazard of dying

Parameters used to determine the distributions specifying the monthly probability of transitioning from PFS to progressed or death (FC)*

	Lambda (λ) Mean (SE)	Gamma (γ) Mean (SE)	Type of Function
R-FC[1]	0.003724939 0.006262217	 1.362977234	Weibull

	R-FC vs. CHL Hazard Ratio	Duration of treatment effect (months)
Chlorambucil	0.24	12

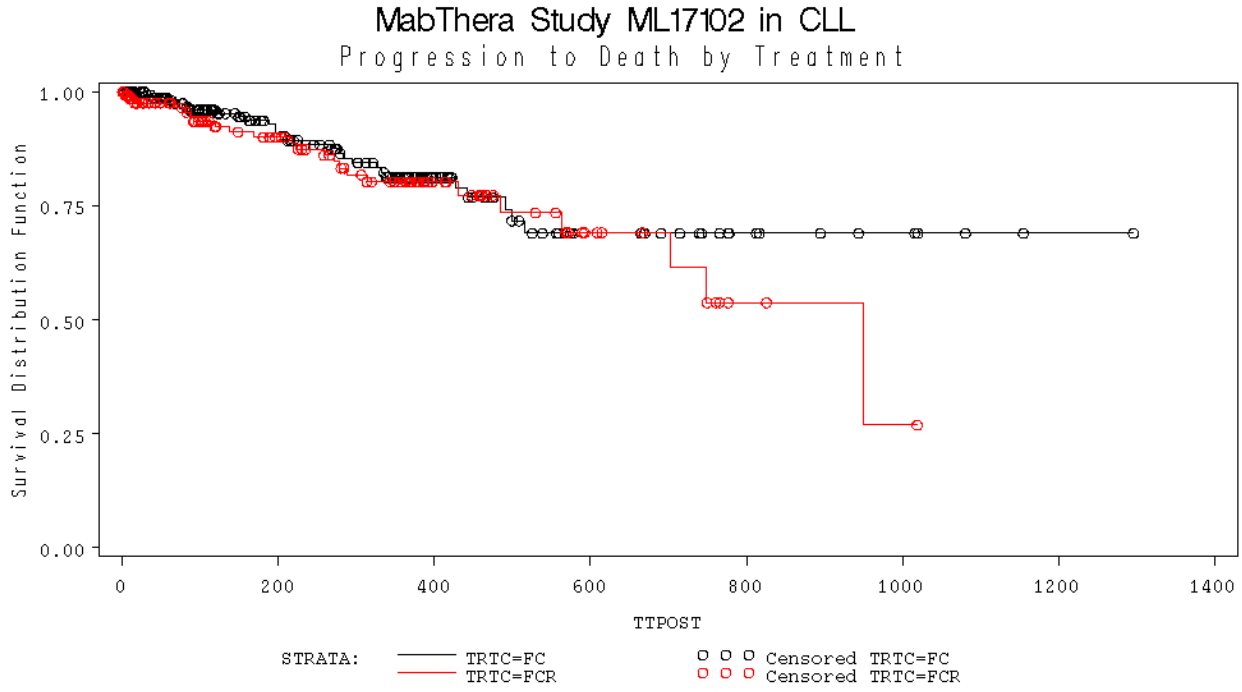
[1] Uncertainty in the R-FC parameter estimates are obtained via Choleski decomposition of the variance-covariance matrix.

*Parameter estimates (λ and γ) of the functions were obtained by regression analysis of the PFS Kaplan-Meier data from the CLL-8 trial

- **Estimating Survival for Progressed patients**

The progressive health state is defined by surviving patients having experienced disease progression. Patients will transition from this state to the absorbing state (Death) at a constant rate determined by having modelled progression to death for patients having experienced at least one day of progression before dying or being censored. The patients in this health state were first stratified by protocol treatment regimen (R-FC or FC) and assessed for treatment differences using the Kaplan-Meier method. The log-rank was found non-significant (p=0.3947) for treatment differences (Figure 14). The relevant Kaplan Maier curves for this analysis are illustrated below. By the clear overlapping nature of these curves it was considered a reasonable assumption to assume an equal risk of death for R-FC and FC patients following disease progression.

Figure 16. Post Progression Survival by Treatment (CLL-8, July 2008 cut)



Given that the overall survival follow-up is incomplete for both study treatment arms in CLL-8 (Table 38), a simple Markov process was chosen to model progression to death. Because the log-rank was non-significant, the progression to death population was modelled as a single population with the mean time to death converted to a constant hazard of dying. The inverse of the mean from the Kaplan-Meier is a suitable estimate of the rate of death (constant) assuming that the underlying distribution is exponential. The mean time in progression was 24.1791(se=0.9019) months. The rate of death obtained from modelling the progression to death population converted to a monthly probability, P(death | progression) is 0.0405. This was applied throughout the specified time horizon for the R-FC, FC, and chlorambucil arms. Uncertainty in the rate of progression to death is assessed with PSA. It was considered reasonable to assume that this mean rate and its associated uncertainty encompass the age-specific increase in mortality.

The graph in Figure 17 is taken from the Excel model reflecting PFS and OS for R-FC versus FC alone based on the Markov process. In the extrapolated PFS and PS curves for the indirect comparison of R-FC versus chlorambucil is provided.

Figure 17. Extrapolated PFS and OS curves of R-FC versus FC

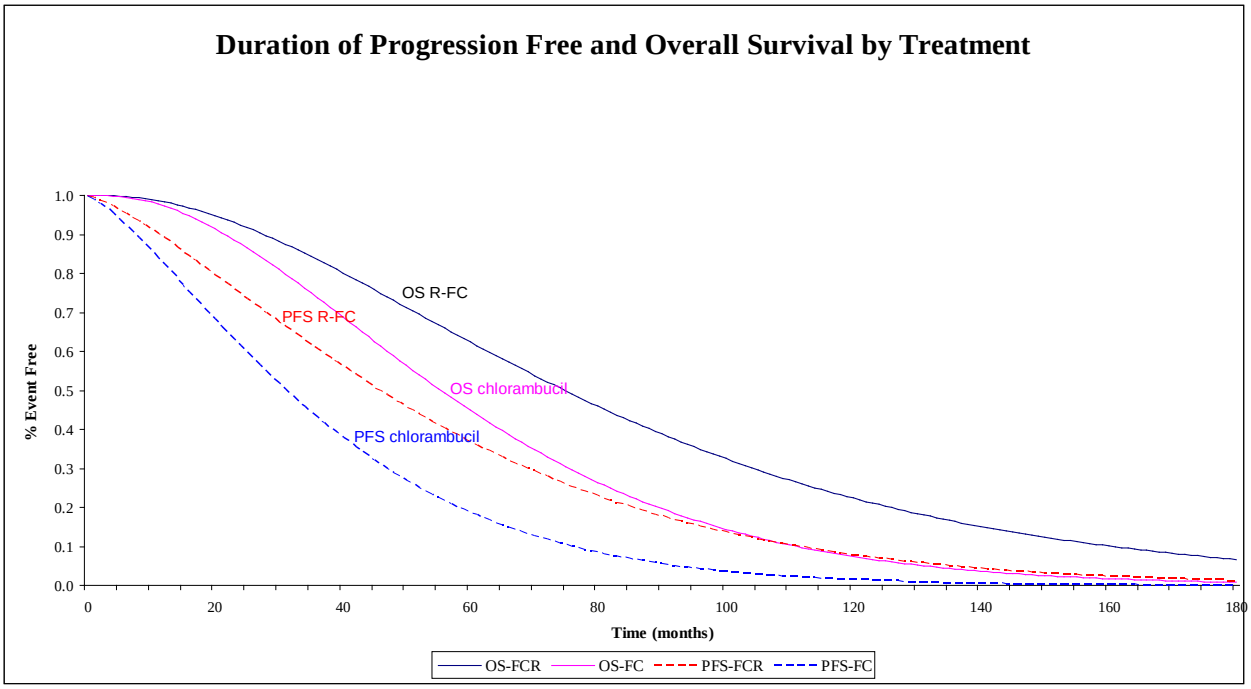
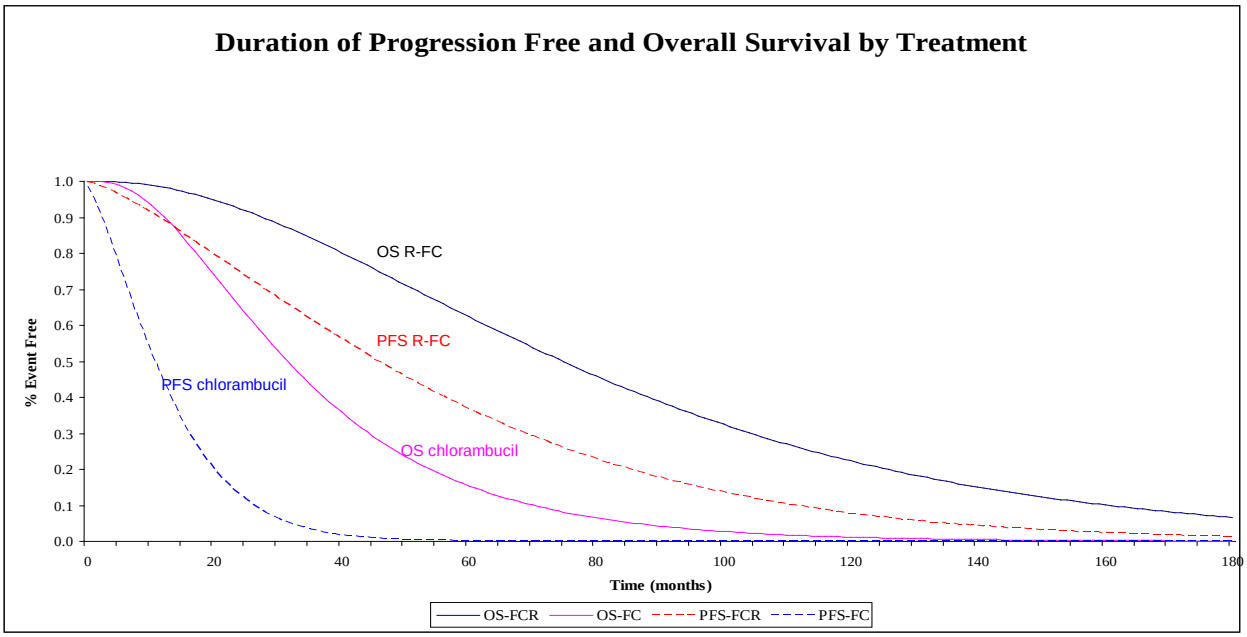


Figure 18. Extrapolated PFS and OS curves for an indirect comparison of R-FC vs. Chlorambucil



- **Estimating Death**

This state includes those patients who died from any cause (standard UK all-cause background mortality) or due to advanced disease. No costs are attached to this health state and the utility attached is zero. A number of patients die while in PFS and, along with those patients that die while in progression, will collectively represent the total number of deaths in the Markov process. The methodology employed for patients dying while in the progression health state has been described above.

The number of patients that die, expressed as a monthly rate, while in PFS is determined by either background mortality or by the monthly rate at which patients died (any cause) while in PFS from the study (CLL-8). For example, 21 of the 408 patients in the R-FC arm died whilst in PFS. These deaths occurred over a period of 43 months. The rate of death in the R-FC arm is calculated as 21/(408*43) = 0.00119699. Thus the monthly number of patients that die while in PFS is the maximum of either background mortality or the monthly probability of death calculated as 1 – exp(-rate of death) = 0.00119627 (Table 42). This approach was preferred to utilising the trial data alone; due to the low number of events in CLL-8, it seemed unreasonable to assume that mortality rates would at times be lower than the average all cause mortality rate. Background mortality was taken from UK national statistics[67] and was weighted 1.6 to 1 on male versus female age-specific mortality rates, taking into account the higher prevalence of CLL among men (Watson et al, 2008[76]).

1.1.1.4 b) Non-model-based economic evaluations

Not Applicable. Only model-based economic evaluations were performed for this submission.

7.2.7 Clinical evidence

How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

Assuming that the "baseline risk" of disease progression relates to the comparator treatments within the evaluation, this was derived directly from the CLL-8 trial results for FC and a mixed-treatment comparison (Section 6.6, validated by an indirect comparison, Section 7.2.6.8) for chlorambucil.

How were the relative risks of disease progression estimated?

The relative risk reduction of moving from PFS to the Progressed health state are described in section 7.2.6.8 above. No relative risk reduction of transitioning from progressed health state to death for R-FC patients was assumed within the model. A single point estimate of the relative risk reduction of disease progression was not an explicitly required parameter within the existing model structure in order to estimate long term disease progression as this varied over time. Instead, disease progression for each treatment in the evaluation was modelled separately (albeit with a same shape assumption) based on their respective extrapolated PFS curves.

Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The health state of progression free survival and "progressed" were linked to the final outcome of QALYs in the model. The utility scores were informed by an estimate from the literature in patients requiring first-line treatment for CLL (see Section 7.2.8.3).

Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

No health effects associated with adverse events were included within the model. While there were some significant differences in rates of neutropenia and leukopenia, this did not translate into a significant different in grades 3 or 4 infections. As no significant incremental adverse event differences likely to impact quality of life or costs were observed between R-FC and FC within the CLL-8 trial, this was not considered necessary. As described earlier, chlorambucil was assumed to have the same adverse events profile as FC. Alternative assumptions concerning the costs associated with adverse events were explored in the sensitivity analysis.

Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

No expert opinion was used to estimate clinical parameters. However, expert opinion was used to determine some NHS resource utilisation. This includes the assumption of one visit with a clinical oncologist during each cycle of chemotherapy, the pharmacist time required to prepare different chemotherapy regimens, and validation of the international CLL-8 trial reported subsequent treatment for a UK setting. These are described further in Section 7.2.9.2.

What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

All assumptions relating to clinical evidence have been previously described in Section 7.2.6.1.

7.2.8 Measurement and valuation of health effects

If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health benefits were expressed as QALYs within the model.

Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The health effect associated with the PFS state and progressed state were measured via survival analysis and valued via utility scores. This allowed for different health benefits to be calculated for patients in the R-FC and comparator arms by taking into account the difference in life expectancy and the duration of time spent in the progression free health state relative to the progressed health state.

How were health effects measured and valued?

A utility score was applied to each health state in the model (Table 43). We assume that the utility in PFS is not affected by the treatment the patient receives. Utility losses due to adverse events are not taken into account. The impact of a variation in the assumed utility score was evaluated in the PSA.

Table 43. Health state utilities

	Utility	*Reference*
PFS Health State	0.80	Hancock 2002[57]

Progressed Health State	0.60	Hancock 2002[57]
Death	0.00	Assumption

These values were obtained from a previous health technology assessment report for the first-line treatment of fludarabine in CLL patients (Hancock et al 2002[57]), and were originally derived from expert opinion. As they were estimated, they may not reflect societal preferences. In order to obtain more robust and realistic values for the UK CLL population, a utility study is currently underway, with first results expected in Q1 2009. The following describes the protocol for this ongoing study.

Utility Measurement Study for Patients with Chronic Lymphocytic Leukaemia

Objective: The purpose of this study is to estimate the health related quality of life of patients with chronic lymphocytic leukaemia (CLL).

Instruments: This ongoing utilities study will include the following instruments to measure HRQL: EQ-5D, EORTC QLQ-C30 and patient-completed socio-demographic. Clinical profile forms will be completed by the site research nurse.

Recruitment and number of subjects: Recruitment will take place in 8 clinical sites in the UK. A total of 250 patients with chronic lymphocytic leukaemia will be recruited. The clinical sites will prospectively sample patients who are currently receiving therapy, those who have finished therapy and who have undergone an assessment of the treatment. These people will be classified in 4 CLL responses to treatment categories (Complete Responder, Partial Responder, Progressive Disease and Stable Disease (neither response nor progression)).

Procedures: This is a questionnaire-based study of 250 patients. Participants will be recruited in one of two ways. The primary investigator for each site will decide which methods to implement at his/her site. Firstly, a site can choose to recruit patients by reviewing medical charts or patient databases and will screen patients for eligibility using an enrolment form. Patients who meet the clinical inclusion/ exclusion criteria will be sent, the Patient Information Sheet, a copy of the consent form and a letter inviting them to take part in the study. When the patients next attend their outpatients' appointments, a Research Nurse will find out whether these patients are willing to take part in the study or whether they require more time to consider their decision. Should the patients wish to take part in the study informed consent will be obtained. After signing the informed consent form, the patients will be asked whether they wish to complete the questionnaires at the clinic or to take home for completion, a pre-reply paid envelope will be provided. If a participant fails to return his/her questionnaires within a two week period, a reminder will be sent. If a patient does not return the questionnaire, the data will be treated as missing data. Alternatively, the site can choose to adopt the second recruitment protocol. This method requires the consultant physician to identify the participants during the patients' outpatients visit. The consulting physician will know which patients meet the inclusion criteria from their medical records. Consequently, during the consultation the consultant will ask the patient whether they wish to participate in the study. If the participants are interested in taking part, the consultant will give the patient a copy of the consent form, patient information sheet and a stamped pre-addressed envelope. The consultant will ask whether the research nurse can telephone the participant in seven days time so that she can answer any queries that the patient may have regarding their participation. With the participant's permission, the research nurse will call to

answer any queries, and find out if the participant wishes to take part. The research nurse will also ask whether the participants require more time to consider their decision. If the patients are happy to take part in the study, the research nurse will ask them to sign and return the consent form in the reply paid envelop. In addition, the research nurse will ask whether the participant would wish to complete the questionnaires by telephone. If the participants wish to complete the questionnaires by telephone, on receipt of the signed consent form the research nurse will contact the patient and administer the questionnaire. It is expected that it will take the participants approximately 20-30 minutes to complete the questionnaires. After completing the questionnaires, for each patient, Oxford Outcomes will arrange for a £25 donation to be made to the cancer charity CancerBackup. Arrangements have been made to accommodate individuals that have difficulties in understanding English.

Sites will be asked to monitor the recruitment of patients and attempt to recruit roughly equal numbers of people in each of the four response states.

In addition, to the questionnaire data, the research nurse will complete a clinical profile form for each of their patients.

Analysis: The data will be aggregated and analysed by treatment responses, so that differences in health related quality of life at different points in the disease process will be revealed.

Roche will make these utility scores available to both the ERG and appraisal committee as soon as they become available. However as the sensitivity analysis will demonstrate, we do not expect any uncertainty around the utility values to fundamentally affect the cost effectiveness conclusions.

Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis.

Two quality of life measures were used in the CLL-8 trial, however this data is not currently available to Roche for analysis and discussion. Quality of life was measured by the attending physician at every visit using The Spitzer Quality of Life Index. This index documented the patient's activity level, independence/ dependence, general well-being, social support and mental state. In addition the EORTC-QLQC30 (European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30) was taken before therapy, after cycle 6 (initial staging), final staging and at months 6,12, 24, 36, 48, 60 and subsequent annual assessments in the follow-up period, regardless of progression or alternative therapy being initiated.

However as these represent disease specific instruments; they are not adequate for informing the requisite generic measure of health or subsequent utility scores.

Were any health effects excluded from the analysis? If so, why were they excluded?

The effect of adverse events upon health benefit and quality of life was excluded from the evaluation as described in Section 7.2.7.4.

7.2.9 Resource identification, measurement and valuation

What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

1) Drug costs for R, FC, and chlorambucil
2) Drug administration costs for R, FC, and chlorambucil
    a) Administration cost
    b) Consultation cost (face-to-face with clinician with white cell count test)
    c) Hospital pharmacist time for drug preparation
3) Blood transfusion events
4) Bone marrow transplant events
5) Outpatient consultations
6) Subsequent (2nd-line and later) CLL treatment costs

The following section describes each resource in detail.

How were the resources measured?

1) Drug costs for R, FC, and chlorambucil

Drugs costs were calculated according to the recommended adult dose and wastage was assumed for all therapies. Actual doses from the CLL-8 trial were limited to the sensitivity analysis due to the additional differentiating factor of infused FC treatments in the trial compared to oral FC treatments in the base case.

Table 44. Drug doses and costs for rituximab

Assumptions	Value	Description
Body surface area m^2	1.93	Average body surface area (from CLL-8)
Unit price per vial (£) • 100mg • 500mg	 174.63 874.15	BNF 56[72]
Recommended dose (mg/m^2) • Cycle 1 • Cycle 2-6	 375 500	Recommended adult dose as per SPC
Average adult Dose (mg) including wastage • Cycle 1 • Cycle 2-6	 800 1,000	 $1.93mg/m^2$ * 375mg = 725mg (round-up) $1.93mg/m^2$ * 500mg = 965mg (round-up)
Cost per infusion/cycle (£) • Cycle 1 • Cycle 2-6	 1,397.03 1,746.30	 500ml @ £873.15 + 3* 100ml @ £174.63 2 * 500ml @ £873.15
Number of infusions cycles	6	Administered on day 0 in Cycle 1 and day 1 of each subsequent cycle of

		chemotherapy in 28 day cycles for a total of 6 cycles
Total rituximab drug cost per patient (£)	**10,128.53**	£1,397.04 + 5 * £1,746.30

Table 45. Drug doses and costs for FC and chlorambucil

Assumptions	F (oral)	C (oral)	Chl	Description
Body surface area m^2	1.93	1.93	1.93	Average adult body surface area
Unit price per mg (£)	1.86	0.0024	0.17	BNF 56[72]
Recommended dose (mg/m^2)	24	150	10	Recommended adult dose
Average adult daily dose (mg) including wastage	50	300	20	F: 24mg*1.93m^2 = 46.32mg (round to nearest 10mg) C: 150mg*1.93m^2 = 289.50mg (round to nearest 50mg) Chl: 10mg*1. 93m^2 = 19.3mg (round to nearest 2mg)
Days of treatment per cycle	5	5	7	Recommended adult dose
Cost per infusion/cycle	465.00	3.60	23.80	F: £1.86 * 50mg/day *5 days C: £0.0024 * 300mg/day *5 days Chl: £0.17 * 20mg/day *7 days
Number of cycles of treatment	6	6	12	Administered on day 1 of each cycle of chemotherapy in 28 day cycles
Total drug cost per patient (£)	2,790	21.60	285.60	F: £465 * 6 cycles C: £3.60 * 6 cycles Chl: £23.80 * 12 cycles

For the sensitivity analysis, a similar calculation can be performed to calculate the total drug cost per patient of IV fludarabine and cyclophosphamide, approximately £430 and £10 per cycle, respectively. This is based on the BNF cost of £156 per 50ml vial and £3.54 per 500ml vial, respectively, and actual dosages from the CLL-8 trial. This analysis is described further in Section 7.2.11.2.

2) Drug administration costs for R, FC, and chlorambucil

a) Administration cost

To estimate the resource utilisation associated with the drug administration of R-FC and the comparators, the appropriate reference costs (National Schedule of Reference Costs 2006-07[69]) associated with inpatient chemotherapy administration were utilised.

Table 46. Drug Administration costs

Applied to:	HRG label (Code)	National average unit

		costs
FC (oral) on day 1 of each cycle	Deliver exclusively Oral Chemotherapy (SB11Z)	£280
R (in combination with FC or on its own during cycle 1)	Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance (SB14Z)	£430
Sensitivity analysis: FC infusion for day 1	Deliver simple Parenteral Chemotherapy at first attendance (SB12Z)	£309
Sensitivity analysis: FC infusion for days 2-3	Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£255

In the base case scenario, it was assumed that on day 0 of cycle 1, rituximab incurred a marginal cost of £430. On day 1, the patient returned to collect their oral FC (or chlorambucil) therapy which they then took at home over the following 5 (or 7) days for a cost of £280. In cycles 2 through 6, the patient in the R-FC arm entered the hospital on day 1 for rituximab infusion for £430 and on the same day collected their FC (or chlorambucil) treatment to administered at home over the next 5 (or 7) days (for no additional costs). In this case, rituximab can be considered to incur a marginal cost of £150 (the difference between the R-FC and comparator arms as illustrated in the table below). Once again, patients in the comparator arms with solely oral therapies will enter the hospital on day 1 to collect their oral chemotherapy regimens, incurring a cost of £280. For patients in the chlorambucil arm, they will return to the hospital for 6 additional cycles (or until progression) to receive their remaining indicated treatments, incurring an additional £280 for each visit.

Table 47. Drug administration cost by treatment

Base case (oral FC)	**R-FC**	**FC**	**Chlorambucil**
Cycle 1	£710 = £430 + £280	£280	£280
Cycle 2 – 6	£430	£280	£280
Cycle 7 - 12	NA	NA	£280
Scenario analysis (IV FC)	**R-FC**	**FC**	
Cycle 1	£1,249 = £430 + £309 + 2*£255	£819 = £309 + 2*£255	
Cycle 2 – 6	£940 = £430 + 2*£255	£819 = £309 + 2*£255	

In the scenario analysis where FC is assumed to be administered intravenously (as in the CLL-8 trial), the cost in cycle 1 of FC would increase to £309 on day 1. As IV FC requires 3 days of treatment, the patient would return on days 2 and 3, incurring a cost of £255 each day. Therefore the total cost per cycle of a patient taking FC would be £819. The marginal cost of administering rituximab would remain the same (at £430) as this is administered on day 0. In Cycles 2 through 6, an FC patient would again incur a total cost of £819 over days 1 to 3. As rituximab would be administered on day 1 as well, the marginal cost of administering rituximab would be reduced to £121.

b) Consultation cost (face-to-face with clinician with white cell count test)

Each cycle was associated with one consultation with a clinical oncologist. A cost of £84 per cycle was taken from the National Schedule of Reference Costs 2006-07 -

consultant led follow up attendance outpatient face to face with a clinical oncologist[69]. As this visit occurred regardless of the treatment selected, there were no marginal consultation costs assumed to be associated with rituximab.

c) Hospital pharmacist time for drug preparation

Pharmacist time for drug preparation was derived from expert opinion and costed using an assumed hospital pharmacist unit cost of £30/hour. This was derived from the PSSRU, Section 12.6, Hospital pharmacist: Unit costs available 2006/2007[71]. It was assumed that oral preparations (FC or chlorambucil) take 15 minutes to prepare, while IV rituximab takes an additional 15 minutes to prepare (thus R-FC requires 30 minutes of pharmacist time total per cycle). In the sensitivity analysis, where IV FC is considered, FC still required 15 minutes to prepare, but as this is given over 3 days, 45 minutes total is required for preparing 3 bags of infusion. Thus the total pharmacist time required for R-FC in this scenario is assumed to be 1 hour.

3) Blood transfusion events

Blood transfusions (BT) associated with CLL patients were recorded in the CLL-8 study and included in the model in the supportive care costs for the progression-free health state. A total of 318 and 269 transfusions events occurred in the R-FC and FC arms of the trial, respectively.

Due to the lack of reference costs or tariffs associated with blood transfusions, a focused literature search was performed to identify relevant and recent UK costing studies. A paper assessing the total costs of blood delivery to hospital oncology patients in 2004(£)[70] was identified and the relevant costs were inflated to 2007 level (HCHS pay and price inflation index from PSSRU 2007[71]). An average cost of £161.11 was applied to each unit of blood dispensed as well as an average cost of £289.73 was applied to each blood transfusion event.

4) Bone marrow transplant events

Bone marrow transplant (BMT) associated with CLL patients were recorded in the CLL-8 study and included in the model in the supportive care costs for the progression-free health state. Only 5 and 3 BMT events occurred in the R-FC and FC arms of the trial, respectively.

An average cost of £47,565 was applied to this event. This cost was taken from the National Schedule of Reference Costs 2006-07 - NHS Trusts Elective Inpatient HRG Data for a Bone Marrow Transplant - Allogeneic Graft (Volunteer Unrelated Donor) 19 years and over[69].

5) Outpatient consultations

The recent ESMO guidelines (Eichhorst et al., 2008[68]), recommend that follow up of asymptomatic patients should include a blood cell count every three months, as well as a regular examinations of lymph nodes, liver and spleen. Patients who were progression-free were attributed the cost of an outpatient visit every 3 months (£28 per month; £84/3). This cost was taken from the National Schedule of Reference Costs 2006-07 - consultant led follow up attendance outpatient face to face with a clinical oncologist[69].

It was assumed in the progressed health state that the frequency of visits would increase to one per month. Therefore a cost of £84 per month was applied to the supportive care cost in the progressed state in combination with the 2nd-line CLL treatment costs described below. Due to lack of reliable data, no additional health care related cost (for example, primary care, non-chemotherapy medication, etc.) were included in the base case. Uncertainty in the cost of supportive care is assessed with one-way sensitivity analysis and PSA.

6) Subsequent (2nd-line and later) CLL treatment costs

The CLL-8 trial collected data on CLL treatments given post-progression (i.e. 2nd-line and later therapies for all patients who received at least one subsequent CLL treatment). However, only patient numbers were collected and not dosage information for each therapy. Therefore those therapies representing resources used by more than 2% of the patient population were costed by utilising standard doses for each therapy of interest and applying unit costs from BNF 56. The average patient cost for 2nd-line treatment was £5,179. In order to include a monthly figure into the cost of supportive care in the progressed state, this value was divided by the average months spent in the progression state (as predicted by the model) between the R-FC and comparator arms (20.1 months). This resulted in a monthly cost applied to the progressed state of £257.66. The table below presents the subsequent therapies from the CLL-8 trial which were used to determine the cost of subsequent CLL treatments.

Table 48. Subsequent CLL treatments from the CLL-8 trial included in the costing

Progression Therapy	Number of Patients		Cumulative days on treatment		Average number of days per patient on treatment	
	FC	R-FC	FC	R-FC	FC	R-FC
ALEMTUZUMAB	8	5	550	251	68.75	50.2
ALEMTUZUMAB/CYCLOPHOSPHAMIDE/FLUDARABINE	1	2	120	145	120	72.5
CHLORAMBUCIL	1	3	5	157	5	52.33
CYCLOPHOSPHAMIDE	3	0	33	0	11	0
CYCLOPHOSPHAMIDE/DOXORUBICIN/PREDNISOLONE/RITUXIMAB/VINCRISTINE	12	7	881	213	73.42	30.43
CYCLOPHOSPHAMIDE/DOXORUBICIN/PREDNISONE/VINCRISTINE	9	1	645	105	71.67	105
CYCLOPHOSPHAMIDE/FLUDARABINE/RITUXIMAB	4	2	287	146	71.75	73
FLUDARABINE	2	1	32	195	16	195
RADIOTHERAPY	2	0	18	0	9	0
RITUXIMAB	5	2	155	84	31	42
STEM CELL TRANSPLANT	1	4	9	0	9	0

Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Selected resource utilisation data was captured within the CLL-8 trial therefore it was possible to align some resource utilisation data with the source of evidence used to

estimate disease progression. This included bone marrow transplants, blood transfusion events, and therapies used beyond progression. Assumptions relating to routine patient monitoring and drug administration resources were estimated outside of the trial setting, as described above in more detail.

Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

The progressed health state represents the period from 1st relapse until death. It should therefore include the costs and effects of future treatments. The relevant costs are estimated based on those treatments observed in the CLL-8 trial following disease progression, with the corresponding effectiveness captured in the derivation of the post progression risk of death based upon both arms of the trial. As the subsequent costs including the supplementary monitoring costs are applied for each cycle of the model until death, resources used for treatment in all relevant years has been accounted for within the model.

What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

National reference costs were the preferred means of valuing resources. Where these reference costs did not apply (i.e. blood transfusion costs) a focused literature search was conducted to obtain applicable UK costs. Where data gaps existed (i.e. the dosage information associated with 2nd-line therapies collected in the trial), internal expert clinical opinion from a former NHS haematologist was used to assign standard dosages in UK clinical practice to different therapies. Drug preparation costs, which were assumed to differ between the rituximab arm and the oral competitor arms, are not captured in the national reference costs, and therefore expert opinion was again sought to approximate the pharmacist time for differing preparations, and this was then costed according to PSSRU.

What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations

with which the discount has been agreed for the whole of the NHS in England and Wales.

As described in Section 7.2.9.2, the NHS list price of Rituximab (ex VAT) is, 10-mL vial = £174.63, 50-mL vial = £873.15 (10 mg/mL).

Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

No additional infrastructure would be required for the administration of rituximab.

Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Only costs relating to resources under control of the NHS and PSS were included. Emphasis was placed on identifying resource use where differential effects between the R-FC and comparator arms were applicable, such as the drug administration costs. Prices were taken from National reference costs 2006/2007, BNF 56, and PSSRU 2007. Only when costs could not be identified from these sources were alternative sources, such as literature review or expert opinion, utilised to inform the model.

Were resource values indexed to the current price year?

For those costs obtained from sources prior to 2007 (i.e. blood transfusion costs), values were inflated to 2007 levels using the HCHS pay and price inflation index obtained from the PSSRU 2007.

Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

The resource costs of patients in the PFS health state were assumed equal regardless of whether the patient received R-FC or FC, with the exception of the frequency of blood transfusion cost or bone marrow transplantation costs, which were taken from the CLL-8 trial. The resource costs of patients in the progressive health state were assumed equal regardless of whether the patient received R-FC or FC due to the relatively equal balance observed in the 2nd-line treatments utilised in the CLL-8 trial.

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

A discount rate of 3.5% was applied to both costs and QALYs in the model.

7.2.11 Sensitivity analysis

Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

Selection of the correct parametric function to inform the survival analysis may be considered a source of structural uncertainty and therefore alternative functions were evaluated. Extrapolation of the progression free data was carried out under the assumption that the data followed a parametric model structure. The various models were assessed for goodness of fit. The same shape Weibull function was found to be the best fit to the PFS data and was therefore selected for the base case analysis for the comparison of R-FC versus FC. Alternative parametric survival functions (Exponential, Log Logistic, Log Normal, and Gompertz) were evaluated in the sensitivity analysis.

The following figures present the parametric plots of alternative survival function overlain onto the KM plots for the PFS.

Figure 19. Extrapolated Progression Free Survival curves (Exponential)

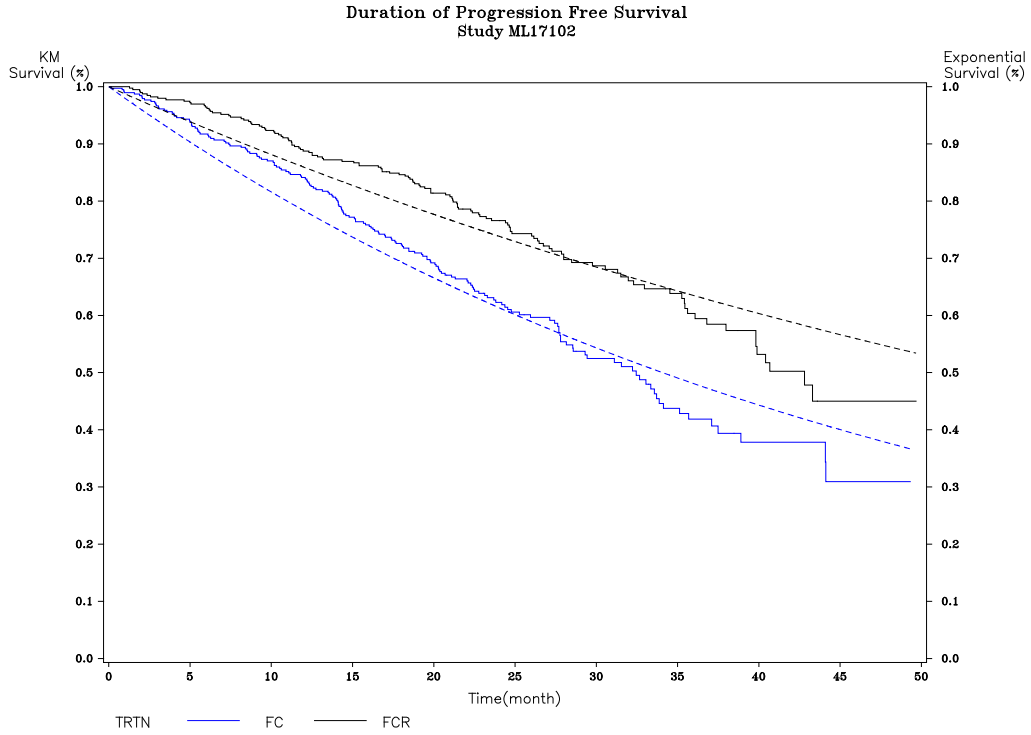
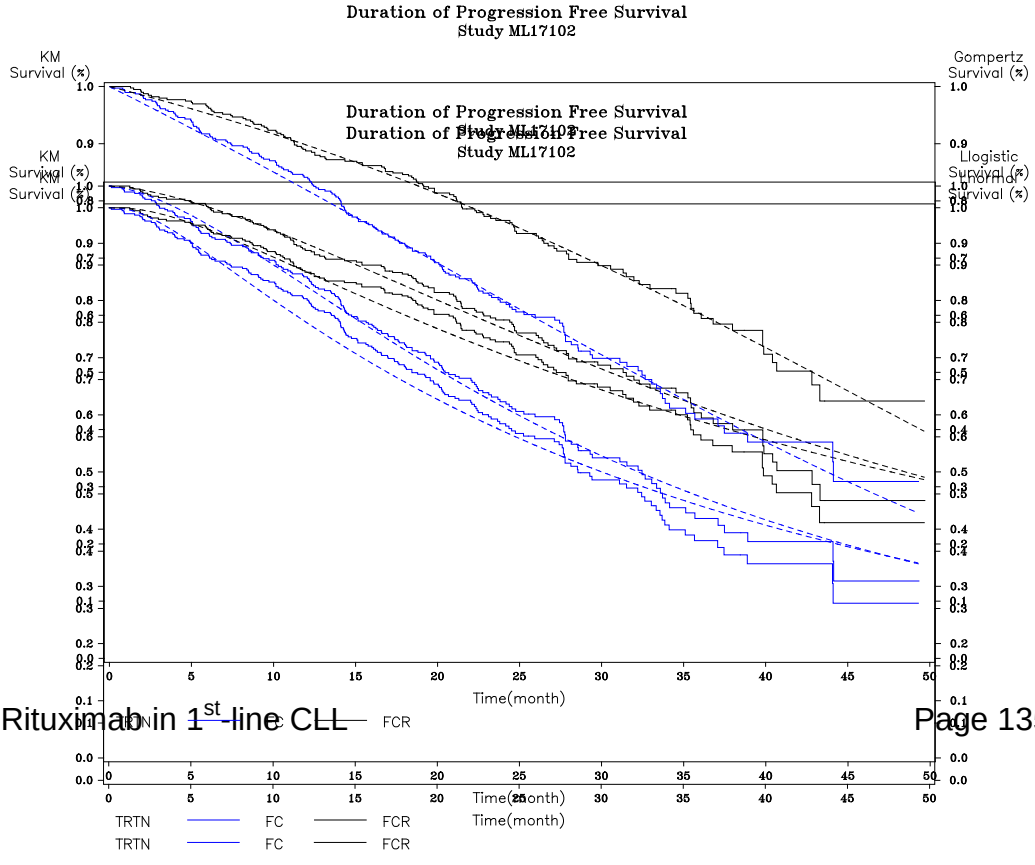


Figure 20. Extrapolated Progression Free Survival curves (Log Logistic)

Figure 21. Extrapolated Progression Free Survival curves (Log Normal)

Figure 22. Extrapolated Progression Free Survival curves (Gompertz)



Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

1.) Intravenously administered FC and actual doses (simulation of the CLL-8 clinical trial).

The utilisation of actual dosages of R-FC and FC from the clinical trial (including any wastage) were explored in this analysis as opposed to the base case assumption of oral FC at the planned licensed dose. As the mean trial dosages are lower than the planned dosages, this may reflect the true dosages in clinical practice. In addition, the drug dosages and administration cost of IV FC were utilised (for both the R-FC and FC arms) and these values were previously described in Section 7.2.1.1 and 7.2.9.2. Wastage is determined by calculating the number of vials used for the administration under the assumption that any residual medication would be discarded. Wastage is calculated for Rituximab only.

Table 49. Drug utilization – R-FC versus FC based on CLL-8 (July 2008)

	Rituximab + Fludarabine / Cyclophosphamide			Fludarabine / Cyclophosphamide Alone		
Study Medication	Rituximab	Cyclophosphamide	Fludarabine	Rituximab	Cyclophosphamide	Fludarabine
Nr. of Patients (ITT)	404	404	404	398	396	396
Nr. of Patients (SAF)	402	402	402	0	396	396
Nr. of Administrations	2'115	6'327	6'343	0	5'898	5'897
Average Nr. of Administrations (ITT)	5.24	15.66	15.70	0.00	14.60	14.60
Average Nr. of Administrations (SAF)	5.26	15.74	15.78	0	14.89	14.89
Average Nr. of Administration Months	4.84	4.83	4.84	0.00	4.57	4.57
Total Cumulative Dose (mg)	1'852'319.50	2'843'335.32	286'710.92	0.00	2'712'043.95	272'019.84
Average Dose (mg) per Administration	875.80	449.40	45.20	0	459.82	46.13
Median Dose (mg)	5'120.00	7'650.00	774.00	0	7'730.00	776.40
Mean Total Dose (mg) - SAF	4'607.76	7'072.97	713.21	0	6'848.60	686.92

Because the base case already assumed the clinical results of the CLL-8 trial were applicable, this sensitivity analysis only includes changes in fludarabine and cyclophosphamide drug cost and drug administration in both the R-FC and FC arms.

2.) IV FC – recommended dose.

A similar sensitivity analysis to that described above was performed which assumed the costs associated with IV FC were incurred in the model, without in addition assuming that actual dosages from the clinical trial were used.

3.) Inclusion of severe adverse event costs

While neutropenia and leukopenia were found to be statistically different between the two arms in the trial, as they are often asymptomatic, and because there was no different in infection rates between the two arms, no costs was applied to these events. While the difference between febrile neutropenia in the two arms was not found to be statistically significant (17 versus 24 Grade 3 events and 8 versus 15 Grade 4 events for FC versus R-FC, respective), the event is associated with a high event cost, and therefore the cost associated with the observed number of events was included in this sensitivity analysis. The cost associated with febrile neutropenia of £2,286 was taken from a recent UK costing exercise (NICE DSU 2007[77]).

In addition, chlorambucil is considered by clinicians to have good tolerability. Because there was no comparable data between R-FC and chlorambucil adverse events rates, this was not included in the base case. In lieu of reliable data, this sensitivity analysis explores the ICERs resulting from the following assumptions:

- No BMTs for chlorambucil (compared to 3 in the base case, same as FC)
- 50% fewer transfusions for chlorambucil than for FC in the trial (269 transfusions in the base case)
- 66.6% fewer cases of febrile neutropenia than for FC (17 Grade 3 events and 8 Grade 4 events)

4.) Monthly supportive care costs

For both the PFS and progressed health states, costs were both increased and decreased by 50%.

5.) Utility values

Sensitivity to the utility values was tested by widening and narrowing the differential between the PFS and progressed health states: the absolute difference was doubled and halved as shown in the table below.

Table 50. One-way sensitivity analysis for utility values

	PFS	Progressed	Absolute difference
Base case	0.8	0.6	0.2
Sensitivity analysis	0.9	0.5	0.4
Sensitivity analysis	0.75	0.65	0.1

6.) Drug administration costs

The upper (£482 and £795) and lower (£174 and £210) quartiles for "Deliver exclusively Oral Chemotherapy" and "Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance" respectively (from reference costs 2006/07[69]) were tested.

In addition, a scenario analysis was performed to consider the impact of R-chemo on potential cost-effectiveness results.

Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

PSA was undertaken. An assumption of 1,000 samples was used in order to achieve reasonably tight distributions around the mean estimate. Lower sample numbers result in very wide and flat distributions, which were deemed to be meaningless. The table below summarizes the assumptions relating to distributions and ranges of each parameter included within the PSA analysis. Distributions are applied around the following parameters to reflect parameter uncertainty in the model:

- **Utilities for PFS (=0.8) and progression (=0.6)**: The parameters for the distributions used for the probabilistic sensitivity analysis are calculated as follows (beta (0.80 *1000, (1-0.80) *1000):

- **Monthly supportive care costs** in the PFS health state (£28) and in the progressed health state including 2nd and further line treatments and supportive care costs (£341.66). Values were varied by means of a Beta Pert function within an assumed range of 50% of the base case.

- **Drug administration costs** Values were varied by means of a Beta Pert function within the lower and upper quartile for "Deliver exclusively Oral Chemotherapy" and "Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance" (from reference costs 2006/07[69]).

- **Bone marrow transplant and blood transfusions** (event numbers obtained from CLL-8 study). Values were varied by means of a Beta Pert function within the lower and upper quartile for bone marrow transplant costs (from reference costs 2006/07[69]) and an assumed range of 40% of the base case for costs associated with blood transfusions.

Table 51. PSA values for monthly supportive care costs and resource utilisation events

Cost	Base case	Minimum	Maximum
PFS	£28	£14	£42
Progressed	£341.66	£170.83	£512.49
Administration - Deliver exclusively Oral Chemotherapy	£280	£174	£482
Administration - Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance	£430	£210	£795
Bone marrow transplant	£47,565.05	£34,318.25	£54,646.47
Blood transfusion	£289.73	£173.84	£405.62
1 Unit of blood	£161.11	£96.67	£225.26

- **Parameter estimates for the parametric (e.g. Weibull) PFS and OS functions**

Table 52. PSA values for the Weibull parametric function for PFS and PS

	Deterministic analysis	
	Lamda	**Gamma**
R-FC PFS	0.003724939	1.7723436298
FC PFS	0.006262217	1.7723436298
R-FC OS	0.356089100208	1.021971227
FC OS	0.004798433	1.021971227

- **The R-FC Chlorambucil hazard ratio** (obtained by indirect comparison): the hazard ratio applied to the parametric functions to reflect the treatment impact vs. Chlorambucil was varied using the Beta Pert function

- **Monthly probability of death** (applicable to the progressed health state): the probability of moving to the death state was assumed to originate from an exponential function and thus is calculated as the inverse of the restricted means from the Kaplan-Meier based on last observed time . This was varied by the Beta Pert function.

Table 53. PSA values for R-FC Chlorambucil hazard ratio and monthly probability of death from the progressed state

Hazard ratio	HR	LCL	UCL
HR to reflect treatment impact of R-FC v. Chl	0.2385	0.17	0.34
HR of the exponential (to be converted into a probability of dying)	24.1791	22.411376	25.946824

For a more detailed description of the beta-pert distribution please see: http://www.decisioneering.com/support/risktips/risktip-3.html.

7.2.12 Statistical analysis

How were rates or probabilities based on intervals transformed into (transition) probabilities?

Please see Section 7.2.6.8 above.

Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The best-fit for the PFS curves from the CLL-8 was the Weibull function. PFS is modelled with a proportional hazard (PH) Weibull survival function under the assumption that the transition probabilities for both treatment arms will vary over time. The Chlorambucil PFS curve is also modelled as a PH Weibull survival function varying with respect to R-FC in the location parameter as a consequence of the indirect comparison. Therefore time dependent transition probabilities were applied in the model.

7.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The internal validation and debugging of the model was performed by Outcomes International, an independent consultant company specialized in the development and validation of decision analytic models used for health economic analyses. The following validation procedures were performed:

- Check of completeness of reported results (health outcomes, economic outcomes) as compared to other published economic evaluations targeting the same indication

- Execution of selected extreme tests to check the plausibility of model outcomes. Extreme testing was applied to the following parameters: treatment efficacy, adverse event costs, cost of study drugs and administration, discount rates, and health utilities

External validation of the model was also performed. Tam (Tam et al. 2008[20]) reported on data from an open-label phase II study in 300 chronic lymphocytic leukaemia (CLL) patients treated with Rituximab combined with Fludarabine and Cyclophosphamide (R-FC) at the MD Anderson Cancer Center in Houston, Texas (USA), with the majority receiving therapy under the care of community physicians. A six-year follow-up, cohort comparison with first-line Fludarabine-based regimens showed that R-FC was associated with superior overall survival (p=0.0011) compared to FC alone, confirming that R-FC is an effective first-line therapy for CLL. Moreover, given the open label design of the Tam et al. study, the observed treatment effect of R-FC is a reasonable proxy for the real world effectiveness obtained in the clinical setting. Nevertheless, there may be factors, such as diagnosis accuracy, patients' and healthcare professionals' compliance that cause this study to differ from routine clinical practice. The comparative Phase III R-FC trial (CLL-8) provides a more rigorous analysis of the efficacy of R-FC versus FC, however the Tam et al. (2008) data gives an idea of the potential impact of longer term follow-up of the R-FC arm, as to date the maximum median follow-up in CLL-8 is 2.2 years. This study is described in greater detail in section 6.8.3.

To validate the outcomes based upon the phase III clinical trial, the cost effectiveness model was modified based on the data from Tam et al. (2008) using the same model structure and assumptions as that used for CLL-8 (detailed in this submission). The main difference was that the monthly post-progression probability of death observed in the Tam et al. (2008) study was four times lower than that observed in CLL-8. In addition, because 22% of patients in the R-FC arm and 12% of patients in the FC arm were still alive after 15 year, the MD Anderson model base case extended to a 30 year time horizon. However for the purposes of this comparison, the results from a 15 year time horizon rare presented below.

Table 54: Transition probabilities, mortality rates and hazard ratios from US MD Anderson study

Markov Transition	Monthly probability	Data source
PFS to death	R-FC = 0.000428951[$] FC = 0.001191076[$]	Maximum of age-specific background mortality^ or monthly rate at which patients died while in PFS from the Tam et al., 2008 study[$]
Progression to death	0.01960644	Progression to death population from Tam et al., 2008 treated as a single population with mean time to death converted to a constant hazard of dying

Parameters used to determine the distributions specifying the monthly probability of transitioning from PFS to progressed or death (FC)*

	Lambda (l) Mean (SE)	Gamma (g) Mean (SE)	Type of Function
FC	0.008842377	1.144723461	Weibull (W lamba, gamma)

R-FC[1]	0.004756676	1.144723461	Weibull (W lamba 2, gamma)

[1] Uncertainty in the R-FC parameter estimates are obtained via Choleski decomposition of the variance-covariance matrix.
^ Life tables for the whole of US (2003).US CDC website accessed Friday 23 May 2008. Weibull = 1-exp(-l * time ^{g}). For the Weibull function, monthly transitions are time-dependent,
[$] Parameter estimates (l and g) of the functions were obtained by regression analysis of the PFS Kaplan-Meier data from the Tam et al. (2008) cohort study

In general, the additional mean life expectancy and QALYs predicted when utilising the MD Anderson study to inform clinical outcomes (Keating et al 2008[62]) were consistent with that observed in the CLL-8 economic evaluation (to be detailed in Section 7.3).

Table 55. Comparison of outcome measure in the economic model based on the MD Anderson Study and the UK economic model based on CLL-8 trial data

	MDA results	UK CLL-8 results
Total FC life years	7.56	4.65
PFS life years	4.32	2.93
Progression life years	3.24	1.73
Total R-FC life years	8.89	5.73
PFS life years	6.36	4.11
Progression life years	2.54	1.62
Incremental life years	**1.34**	**1.07**
Total FC QALYs	5.4	3.38
PFS QALYs	3.45	2.34
Progression QALYs	1.95	1.04
Total R-FC QALYs	6.61	4.26
PFS QALYs	5.08	3.29
Progression QALYs	1.52	0.97
Incremental QALYS	**1.21**	**0.88**

7.3 Results

7.3.1 Base-case analysis

What were the results of the base-case analysis?

The model base-case results are presented below for the following combinations:

(1) Rituximab plus Fludarabine and Cyclophosphamide (R-FC) compared with Fludarabine and Cyclophosphamide (FC)
(2) R-FC compared with Chlorambucil

R-FC versus FC

Costs

Table 56 indicates that rituximab given in combination with fludarabine and cyclophosphamide is associated with an additional average per-patient costs of £11,617 over the analyzed patients' lifetime period (15 years) when compared to fludarabine and cyclophosphamide therapy alone. These results are based on the recommended dose of 6 cycles.

Table 56: Total average per-patient cost for the two compared treatment groups over a lifetime period of 15 years (deterministic analysis) using CLL-8 trial data

Cost component (£)	R-FC	FC	Incremental
Mean cost of PFS	**£18,965**	**£6,891**	**£12,074**
Costs of Rituximab	£10,113	£0	£10,113
Administration costs of Rituximab	£1,224	£0	£1,224
Cost of Fludarabine	£2,776	£2,790	-£14
Administration costs of Fludarabine	£1,109	£1,115	-£6
Costs of Cyclophosphamide	£21	£22	£0
Administration costs of Cyclophosphamide	£1,109	£1,115	-£6
Cost of supportive care in PFS	£1,381	£983	£398
Cost of Bone Marrow Transplantation	£592	£360	£231
Cost of Blood Transfusions	£640	£507	£133
Mean cost of Progression	**£6,630**	**£7,088**	**-£458**
Mean Total Cost	**£25,595**	**£13,978**	**£11,617**

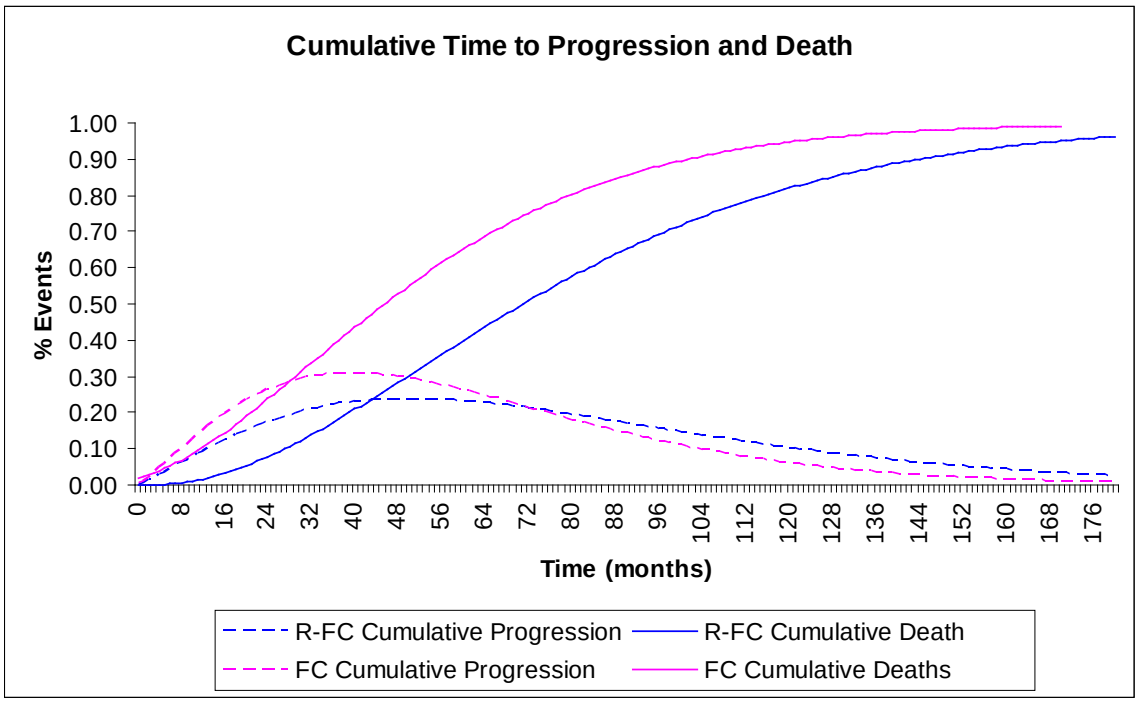
Life Years and Quality-Adjusted Life Years

Table 57 shows that the combination of rituximab plus fludarabine and cyclophosphamide results in a mean gain of 1.07 life years and 0.88 quality-adjusted life years (QALYs) when compared to Fludarabine and Cyclophosphamide alone over the analyzed lifetime period of 15 years. This finding is mainly 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 23 where patients in the FC arm progress quicker and have a shorter time to death than R-FC patients. The model estimates 1.18 additional life years in PFS for the R-FC arm compared to the FC arm which is comparable to the difference in the median PFS duration observed in the CLL-8 trial of 0.88 years (10.6 months).

Table 57: Total mean QALYs per patient for the two compared treatment groups over a lifetime period of 15 years (deterministic analysis) using CLL-8 trial data

Outcome measure	R-FC	FC	Incremental
Mean Life Years (yrs)	5.73	4.65	1.07
Mean Life Years in PFS (yrs)	4.11	2.93	1.18
Mean life Years in Progression (yrs)	1.62	1.73	-0.11
Mean QALYs	4.26	3.38	0.88
Mean QALY in PFS	3.29	2.34	0.95
Mean QALY in Progression	0.97	1.04	-0.07

Figure 23: Cumulative time to progression and death for R-FC and FC using CLL-8 trial data



Incremental Cost-Utility Ratio

Based on the assumptions used for the core model analysis, a cost per QALY of £13,189 for the RF-C combination therapy relative to FC therapy was calculated (Table 58)

Table 58: Cost per life year/cost per QALY gained ratios for R-FC versus FC over a lifetime period of 15 years (deterministic analysis) using CLL-8 trial data

Cost-utility results	R-FC	FC	Incremental
Mean Life Years (yrs)	5.73	4.65	1.07
Mean QALYs	4.26	3.38	0.88
Mean Total Cost	£25,595	£13,978	£11,617
Cost per Life Year Gained (£)			**£10,825**
Cost per QALY Gained (£)			**£13,189**

R-FC versus Chlorambucil

Table 59 indicates that Rituximab given in combination with Fludarabine and Cyclophosphamide is associated with incremental average per-patient costs of £12,250 over the analyzed patients' lifetime period (15 years) when compared to chlorambucil therapy.

Table 59: Total average per-patient cost for R-FC versus chlorambucil over a lifetime period of 15 years (deterministic analysis) using an indirect comparison

Cost component (£)	R-FC	Chl	Incremental
Mean cost of PFS	**£18,964.98**	**£5,851.86**	**£13,113.12**
Costs of Rituximab	£10,113	£0	£10,113
Administration costs of Rituximab	£1,224	£0	£1,224
Cost of Fludarabine	£2,776	£0	£2,776
Administration costs of Fludarabine	£1,109	£0	£1,109
Costs of Cyclophosphamide	£21	£0	£21
Administration costs of Cyclophosphamide	£1,109	£0	£1,109
Costs of Chlorambucil	£0	£0	£0
Administration costs of Chlorambucil	£0	£4,458	-£4,458
Cost of supportive care in PFS	£1,381	£527	£854
Cost of Bone Marrow Transplantation	£592	£360	£231
Cost of Blood Transfusions	£640	£507	£133
Mean cost of Progression	**£6,630**	**£7,493**	**-£863**
Mean Total Cost	**£25,595**	**£13,345**	**£12,250**

Life Years and Quality-Adjusted Life Years

Table 60 shows that the combination of Rituximab plus Fludarabine and Cyclophosphamide results in a mean gain of 1.91 quality-adjusted life years (QALYs) when compared to chlorambucil over the analyzed lifetime period of 15 years. This finding is mainly related to a QALY gain due to a longer stay in the health state of progression-free survival (PFS) (2.55 years) for the patients assigned to Rituximab plus Fludarabine and Cyclophosphamide than that observed for patients with chlorambucil therapy.

Table 60: Total mean QALYs per patient for R-FC versus chlorambucil over a lifetime period of 15 years (deterministic analysis) using an indirect comparison

Outcome measure	R-FC	Chl	Incremental
Mean Life Years (yrs)	5.73	3.40	2.33
Mean Life Years in PFS (yrs)	4.11	1.57	2.54
Mean life Years in Progression (yrs)	1.62	1.83	-0.21
Mean QALYs	4.26	2.35	1.91
Mean QALY in PFS	3.29	1.25	2.03
Mean QALY in Progression	0.97	1.10	-0.13

Incremental Cost-Utility Ratio

Based on the assumptions used for the core model analysis, a cost per QALY of £6,422 for the Rituximab plus Fludarabine and Cyclophosphamide combination therapy relative to chlorambucil was calculated (
Table 61).

Table 61: Cost per life year/cost per QALY gained ratios for R-FC versus chlorambucil over a lifetime period of 15 years (deterministic analysis) using an indirect comparison

Cost-utility results	R-FC	Chl	Incremental
Mean Life Years (yrs)	5.73	3.40	2.33
Mean QALYs	4.26	2.35	1.91
Mean Total Cost	£25,595	£13,345	£12,250
Cost per Life Year Gained (£)			**£5,253**
Cost per QALY Gained (£)			**£6,422**

7.3.2 Subgroup analysis

What were the results of the subgroup analysis/analyses if conducted?

No sub-group analysis was performed for the reasons outlined in Section 7.2.2.2.

7.3.3 Sensitivity analyses

What were the main findings of the sensitivity analyses?

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 and R-FC versus chlorambucil. The following tornado diagram ranks these scenarios in terms of impact on the ICER.

Table 62. One-way sensitivity analyses: R-FC . FC

Sensitivity analyses	R-FC v. FC
Base case	**£13,189**
Exponential function	**£10,249**
Log logistic function	**£13,164**
Log normal function	**£12,426**
Gompertz function	**£22,661**
IV Infusion of FC = Actual dose from trial	**£12,236**
IV Infusion of FC = Recommended dose	**£13,006**
Utilities: PFS=0.9; Progressed = 0.5	**£11,497**
Utilities: PFS=0.75; Progressed = 0.65	**£14,236**
Inclusion of adverse event costs	**£13,283**
Monthly supportive care cost increase by 50%	**£13,155**
Monthly supportive care cost decrease by 50%	**£13,223**
Drug administration cost upper quartile	**£14,519**
Drug administration cost lower quartile	**£12,298**

Figure 24. Tornado diagram of one-way sensitivity analyses: R-FC v. FC

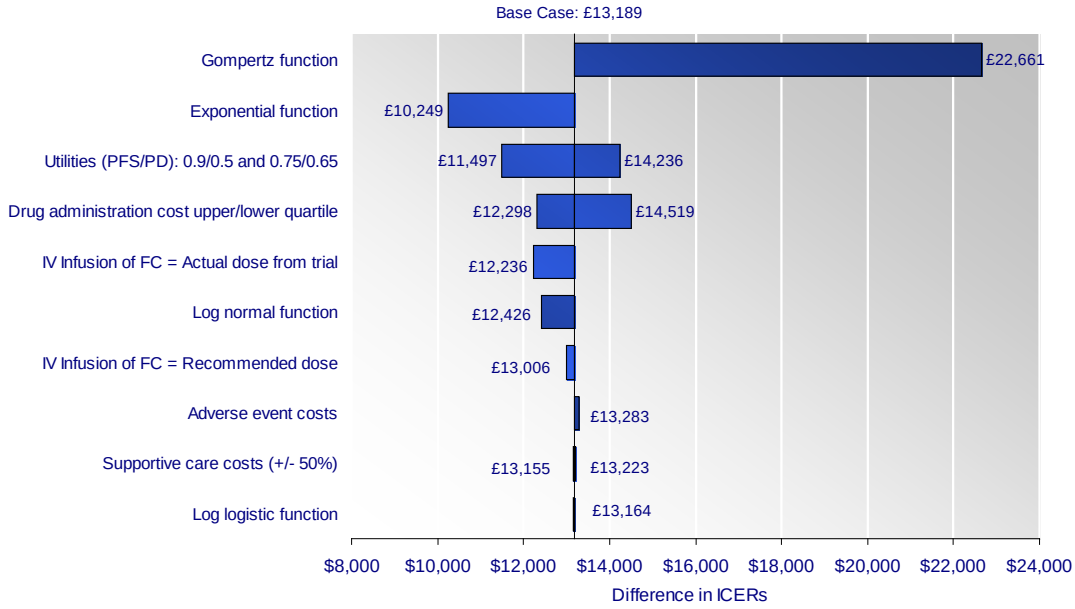
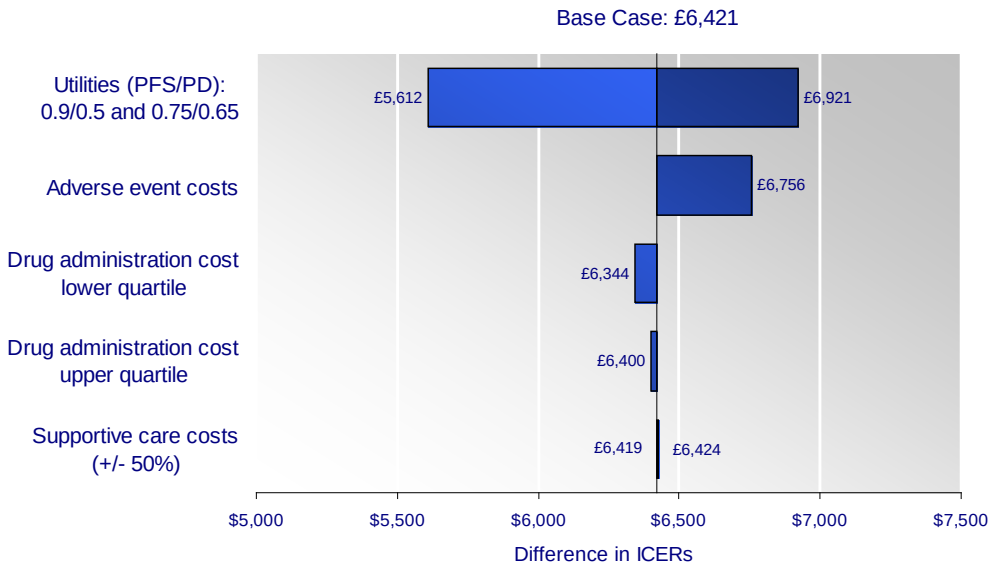


Table 63. One-way sensitivity analyses: R-FC v. Chlorambucil

Sensitivity analyses	R-FC v. Chl
Base case	**£6,422**
Utilities: PFS=0.9; Progressed = 0.5	**£5,612**
Utilities: PFS=0.75; Progressed = 0.65	**£6,921**
Inclusion of adverse event costs	**£6,756**
Monthly supportive care cost increase by 50%	**£6,419**
Monthly supportive care cost decrease by 50%	**£6,424**
Drug administration cost upper quartile	**£6,400**
Drug administration cost lower quartile	**£6,344**

Figure 25. Tornado diagram of one-way sensitivity analyses: R-FC v. chlorambucil



Scenario analysis: FC administered intravenously (as per CLL-8 trial)

A scenario analysis considered the drug dosage and administration information from the CLL-8 indicates that Rituximab given in combination with Fludarabine and Cyclophosphamide is associated with incremental average per-patient costs of £10,777 over the analysed patients' lifetime period (15 years) when compared to Fludarabine and Cyclophosphamide therapy alone.

Two adjustments were made to the base case in this analysis (1) the cost of oral FC treatment (and administration costs associated with delivering oral chemotherapy) was replaced with the cost of IV FC treatment (and administration cost associated with simple parenteral chemotherapy) and (2) recommended UK dosages were replaced with actual dosages observed in the trial. Both of these changes result in a decrease to the incremental difference between the R-FC and FC arms. The main driver of this decrease is the estimated cost of rituximab which has decreased from £10,113 to £8,868 when using the actual trial dosage data.

Table 64. Sensitivity Analysis: FC IV - Costs for FC comparison

Cost component (£)	R-FC	FC	Incremental
Mean cost of PFS	**£19,887**	**£8,652**	**£11,235**
Costs of Rituximab	£8,868	£0	£8,868
Administration costs of Rituximab	£947	£0	£947
Cost of Fludarabine	£2,449	£2,184	£265
Administration costs of Fludarabine	£2,481	£2,212	£269
Costs of Cyclophosphamide	£55	£53	£3
Administration costs of Cyclophosphamide	£2,474	£2,353	£121
Cost of supportive care in PFS	£1,381	£983	£398
Cost of Bone Marrow Transplantation	£592	£360	£231
Cost of Blood Transfusions	£640	£507	£133
Mean cost of Progression	**£6,630**	**£7,088**	**-£458**
Mean Total Cost	**£26,517**	**£15,740**	**£10,777**

Because no clinical inputs nor utility values were changed in this sensitivity analysis, results for the number of QALYs remain the same and are not replicated here. Due to the decrease in the incremental costs, there is also an associated decrease in the ICER from £13,189 to £12,236. Once again, this is attributed to the use of actual dosages from the clinical trial which were lower than the recommended planned dosages utilized in the base case scenario.

Table 65. Sensitivity Analysis: FC IV - Cost-utility results for FC comparison

Cost-utility results	R-FC	FC	Incremental
Mean Life Years (yrs)	5.73	4.65	1.07
Mean QALYs	4.26	3.38	0.88
Mean Total Cost	£26,517	£15,740	£10,777
Cost per Life Year Gained (£)			**£10,043**
Cost per QALY Gained (£)			**£12,236**

For the comparison against chlorambucil, the incremental total cost of the R-FC arm increase to £14,163 from £12,250. This was due primarily to the increase in the R-FC arm due to the increase in the drug and administration cost of IV FC. This effect was not as pronounced as it could otherwise have been as the actual dose of R-FC was simultaneously decreased to reflect actual dosages used in the trial which cancels out much of the incremental administration costs.

Table 66. Sensitivity Analysis: FC IV - Cost for chlorambucil comparison

Cost component (£)	R-FC	Chl	Incremental
Mean cost of PFS	**£19,887.10**	**£4,861.20**	**£15,025.91**
Costs of Rituximab	£8,868	£0	£8,868
Administration costs of Rituximab	£947	£0	£947
Cost of Fludarabine	£2,449	£0	£2,449
Administration costs of Fludarabine	£2,481	£0	£2,481
Costs of Cyclophosphamide	£55	£0	£55
Administration costs of Cyclophosphamide	£2,474	£0	£2,474
Costs of Chlorambucil	£0	£0	£0
Administration costs of Chlorambucil	£0	£3,467	-£3,467
Cost of supportive care in PFS	£1,381	£527	£854
Cost of Bone Marrow Transplantation	£592	£360	£231
Cost of Blood Transfusions	£640	£507	£133
Mean cost of Progression	**£6,630**	**£7,493**	**-£863**
Mean Total Cost	**£26,517**	**£12,354**	**£14,163**

The ICERs increased slightly in this sensitivity analysis from £6,422 to £7,404. This was driven by the incremental increase in mean total cost compared to the base case assuming FC is administered orally.

Table 67. Sensitivity Analysis: FC IV - Cost-utility results for chlorambucil comparison

Cost-utility results	R-FC	Chl	Incremental
Mean Life Years (yrs)	5.73	3.40	2.33
Mean QALYs	4.26	2.35	1.91
Mean Total Cost	£26,517	£12,354	£14,163
Cost per Life Year Gained (£)			**£6,073**
Cost per QALY Gained (£)			**£7,424**

Scenario analysis: Considerations for R-chemo

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.

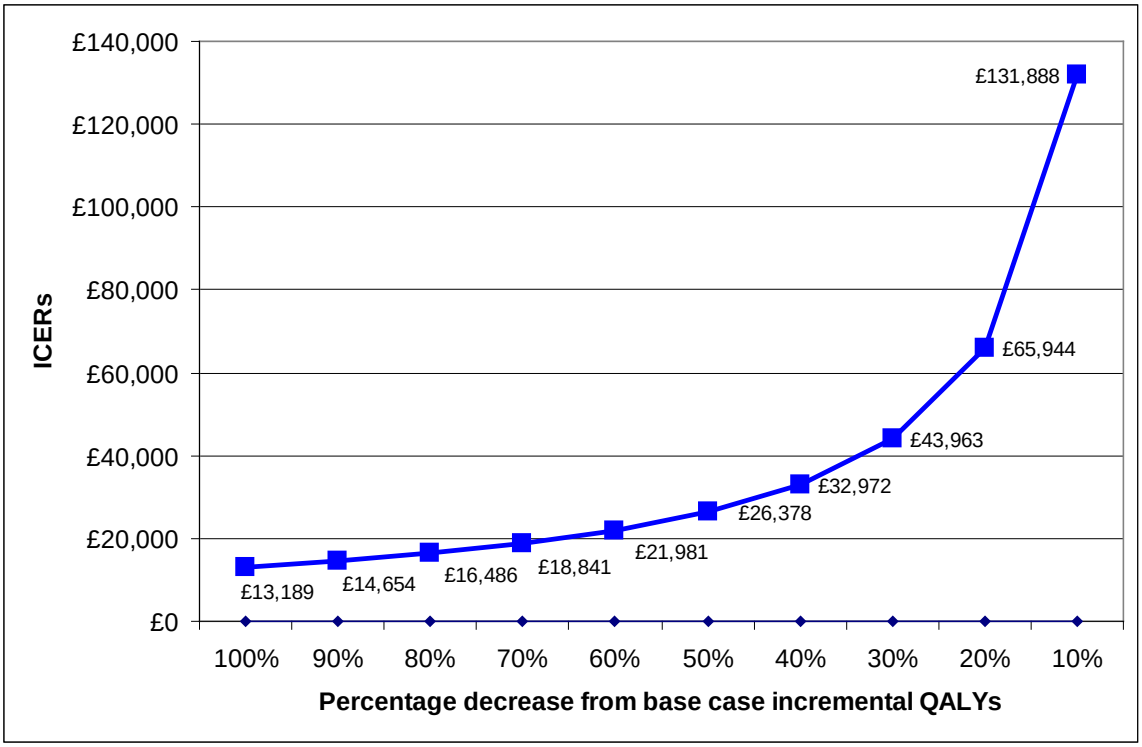
The results from the Phase II trials (section 6.8) describe the assessment of efficacy and tolerability of other rituximab combination chemotherapy. This included R-F (rituximab and fludarabine -104 patients), R-PC (rituximab, pentostatin and cyclophosphamide – 65 patients) and R-FCM (R-FC and mitoxantrone – 30 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 or Chlorambucil; 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 of adding rituximab to other chemotherapy regimens. 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 analysis.

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 26. 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 to 40% 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 Rituximab in combination with other chemotherapies is likely to also be cost effective.

Probabilistic sensitivity analyses

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. Below are the mean cost and outcome results from 1,000 runs.

Table 68. Mean Cost Effectiveness results for R-FC versus FC (1000 runs)

Cost-utility results	**R-FC**	**FC**	**Incremental**
Mean Life Years (yrs)	5.73	4.66	1.07
Mean QALYs	4.26	3.38	0.88
Mean Total Cost	£25,691	£14,002	£11,689
Cost per Life Year Gained (£)			**£10,916**
Cost per QALY Gained (£)			**£13,295**

Table 69. Cost Effectiveness results for R-FC versus Chlorambucil (1000 runs)

Cost-utility results	**R-FC**	**Chl**	**Incremental**
Mean Life Years (yrs)	5.72	3.41	2.31
Mean QALYs	4.26	2.37	1.89
Mean Total Cost	£25,536	£13,289	£12,247
Cost per Life Year Gained (£)			**£5,302**
Cost per QALY Gained (£)			**£6,482**

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.

Figure 27: Scatter plot of cost per QALY for R-FC vs. FC (example:1,000 Monte Carlo simulations)

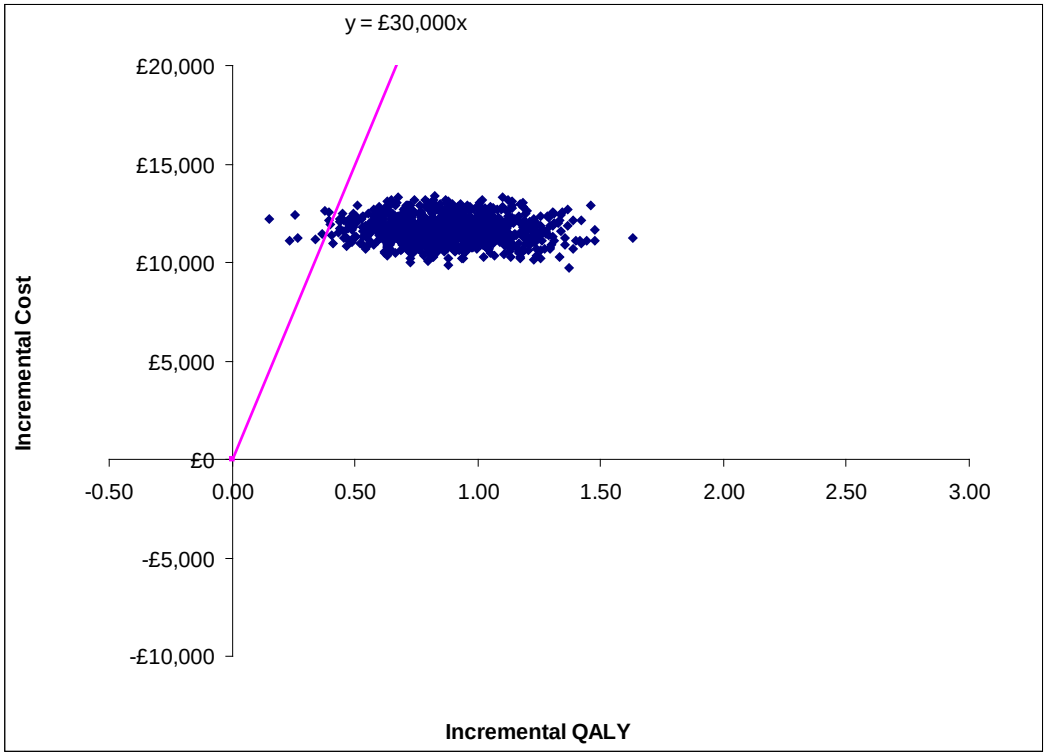
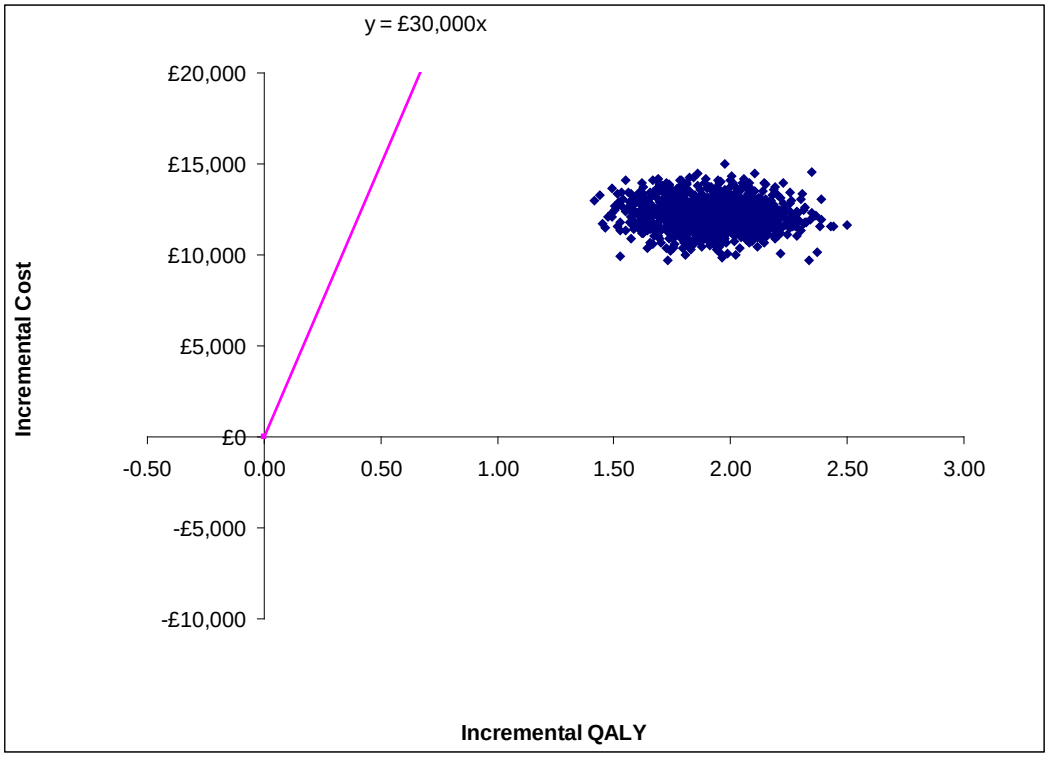


Figure 28: Scatter plot of cost per QALY for R-FC vs. Chlorambucil (example:1,000 Monte Carlo simulations)



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 91.9%, and the probability of not surpassing the £30,000 threshold is 98.6%. The probability of R-FC not surpassing either threshold of £20,000 or £30,000 compared to chlorambucil is 100%. Therefore, the PSA illustrates the robustness of the cost-effectiveness of R-FC compared to FC and chlorambucil.

Figure 29: Cost-effectiveness acceptability curve of R-FC vs. FC (example: 1,000 Monte Carlo simulations)

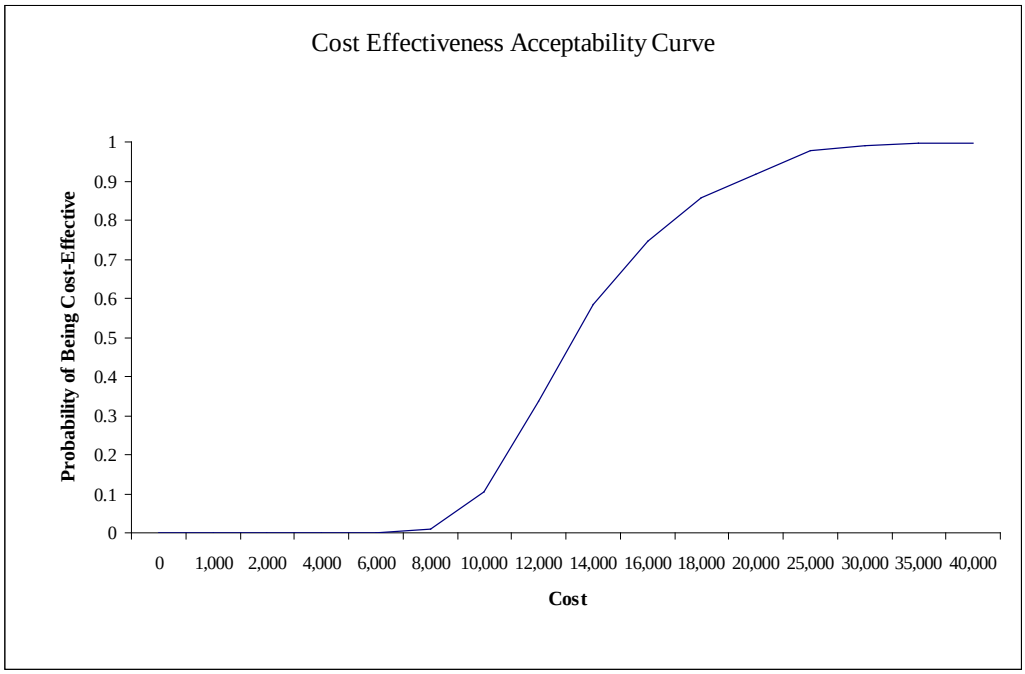
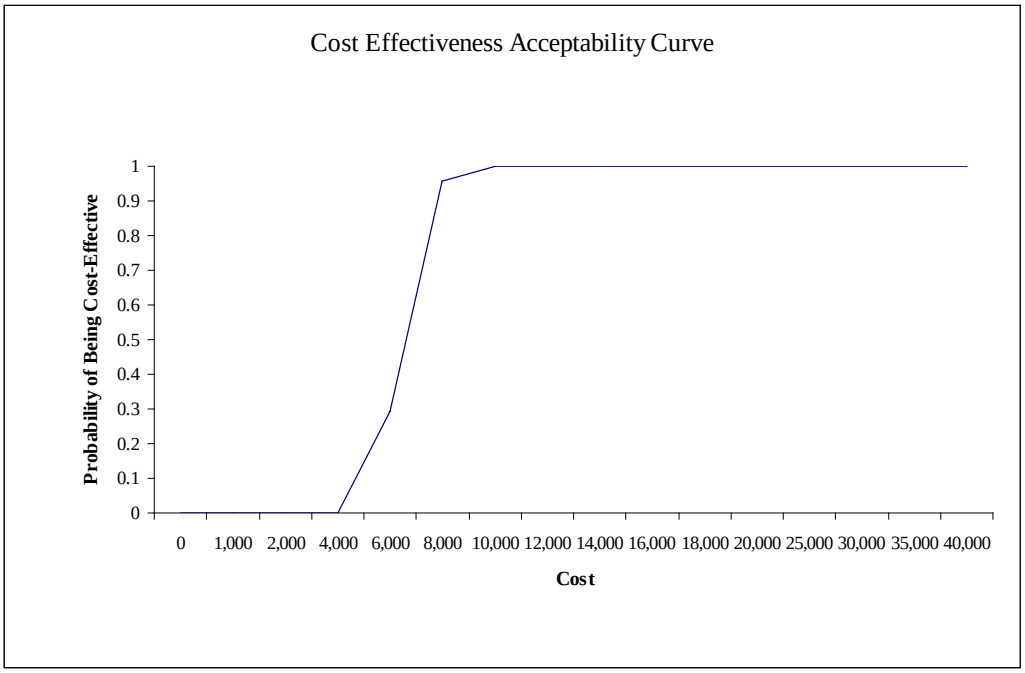


Figure 30: Cost-effectiveness acceptability curve of R-FC vs. chlorambucil (example: 1,000 Monte Carlo simulations)



What are the key drivers of the cost effectiveness results?

Utilising different parametric functions for survival extrapolation (specifically the exponential or gompertz functions) and large changes to the utility value had the largest impact on the ICERs. However, these values still remained well within commonly accepted cost-effectiveness thresholds. Supportive care cost, drug administration cost and the inclusion of potential adverse event cost had a marginal impact on the ICERs.

7.3.4 Interpretation of economic evidence

Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No previous economic evaluation of R-FC have been published (though several abstract will become available in the near future). However, results are still quite comparable to other indications previously evaluated by NICE for the combination of rituximab with chemotherapies in B-cell lymphoma and follicular lymphoma which all resulted in cost-effectiveness ratios less than £30,000 per QALY gained.

Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The economic evaluation was based upon its licensed indication and aligned with the baseline characteristics of those patients included within the CLL-8 study. There is no evidence to suggest that this is not a reasonably representative sample of the likely recipients of rituximab in England and Wales. Furthermore, a phase II trial with six-years median follow-up indicates that the observed benefits of rituximab on PFS may be larger than that observed in 2.2 years medium follow-up in the CLL-8 trial (Tam et al. 2008[20]).

What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

a) The incremental clinical effects of R-FC compared to FC are based upon a large randomised head to head controlled trial demonstrating a significant treatment effect of adding rituximab to standard chemotherapy. Consequently the certainty of the treatment effect of rituximab and the subsequent incremental clinical advantages of R-FC compared to FC is strong. As this is the key driver of the cost effectiveness of rituximab, it is important that the clinical predictions of the model are based on a robust clinical evidence and foundation. Utilising this data results in ICERs comfortably below the lower NICE threshold of £20,000 per QALY gained, thus

providing a strong case for the cost-effectiveness of rituximab in 1st-line treatment of CLL.

b) The extrapolation of the primary endpoint, PFS, from the CLL-8 study is based on a relatively long and the very latest follow up period of over 2.2 years with follow-ups for some patients extending to nearly 5 years.

c) A mixed-treatment comparison was used to populate and validate the indirect comparison of R-FC versus chlorambucil.

d) The final base case ICER is based upon 2 conservative assumptions. The selected Weibull curves are statistically the best fit, whilst also slightly overestimating the tail of the FC curve and underestimating the curve of the R-FC arm using a 15 year time horizon. Secondly, the clinical outcomes are based on the CLL-8 trial, however, drug costs in the model are associated with the full recommended dose of the drug instead of the actual (lower) doses observed within the trial. If actual doses were included, this would provide a disproportionate cost saving in favour of R-FC whilst not affecting the health outcomes, consequently the ICER for R-FC would improve further.

e) All possible uncertainties have been evaluated in both one-way and probabilistic sensitivity analysis. The resultant ICER has been demonstrated to be very stable to wide variations in model parameters.

f) Validation of clinical outcomes via real world effectiveness data in CLL in advance of final EU marketing authorisation. In addition an economic model constructed upon this registry data confirmed the cost effectiveness conclusions of the phase III registration trial analysis, providing a unique level of validation for an intervention yet to be licensed.

<u>Weaknesses</u>

a) Utility calculation should (and will) be based on more appropriate methods than the current expert opinion.

b) While some resource data was collected in CLL-8, these were not very 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 and not expert opinion.

c) The assumption of a constant risk of death from the progressed health state may not appear the most reasonable of assumptions. To overcome this limitation, uncertainty was built into this estimate.

d) The aggregated nature of the progressed health state may appear an over-simplification of the natural disease progression of a CLL patients. However as the sensitivity analysis illustrates, despite a wide variation in the assumed value of these particular parameters (cost and utility of the progressed health state) the ICER remains relatively insensitive to this issue. The effect of re-treatment can still be argued to be captured based upon the types of costs included and the risk of death utilised for this health state.

What further analyses could be undertaken to enhance the robustness/completeness of the results?

As described in Section 7.2.8.3, an outcomes study to estimate the health related quality of life of patients with CLL is currently underway. Results are expected early in Q1 2009.

In addition to utilities, the following analyses would further enhance the model results:

a) Extrapolation of PFS outcomes for R-FC and FC based upon longer follow-up of the CLL-8 study as it emerges. When further follow-up data is available, patients in progression should be re-stratified and the log-rank for post progression survival re-tested for non-significance.

b) A comprehensive audit and/or survey of the treatment strategies currently utilised in the UK stratified by line of treatment for CLL. This would help inform the likely lifetime costs per patient following failure of first line treatment. However the model appears relatively insensitive to this parameter.

c) A more detailed understanding of the proportion of time a CLL patient spends with and without active disease, following relapse of their 1st line of CLL treatment.

d) A prospective time and motion study capturing the resource requirements and consequent health care costs of administering both R-FC and common comparator treatments. This would help understand the marginal costs involved in administering R in addition to chemotherapy alone in greater detail.

e) An estimate of the risk of death for those 1st line patients in remission from CLL.

f) A direct RCT comparison with chlorambucil

8 Assessment of factors relevant to the NHS and other parties

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

Assuming a staggered additional uptake of 30%, 50%, and 100% per annum over the next three years respectively the estimated budget impact of the addition of rituximab to the current treatment regimens for the treatment of CLL patients is £4,995,671 in the 1st year, £8,390,318 in the 2nd year and £16,919,490 in the 3rd year. All the above figures include administration costs and VAT.

An additional £13,250 is needed for every eligible CLL patient treated with rituximab each year.

The budget impact estimates presented above represent the maximum possible cost to the NHS during the first three years following positive NICE guidance.

8.2 What number of patients were assumed to be eligible? How was this figure derived?

According to the expected licence, rituximab will be prescribed to chronic lymphocytic leukaemia (CLL) patients requiring treatment who have not been previously treated. The CLL incidence rate in 2007 was 0.0051% (Cancer Research UK, February 2008[78]). The incidence rate of CLL is assumed to remain constant in the following years. The total population of England and Wales is estimated to be 54,895,969 in 2009 (first year of rituximab marketing authorisation), 55,319,249 in 2010 and 55,744,028 in 2010 (GAD 2008). The CLL incidence rate of 0.0051% will result in 2,800 new CLL patients in 2009, 2,821 in 2010 and 2,843 in 2011.

Approximately a third (33%) of patients with previously untreated CLL will never need treatment (Dighiero T., 2003[7]) and die with, rather than of, their disease. The rest (67%) of the total incident population will either require immediate treatment or will eventually require treatment. In the model it is assumed that two thirds (67%) will be eligible for rituximab combination therapy. The total eligible population for 2009, 2010 and 2011 is 1,257, 1,266 and 1,276 respectively. The calculations are summarised in Table 71.

Table 70. Estimated number of patients eligible to receive treatment

Assumptions	Percentage	Value 2009	Value 2010	Value 2011
Local population		54,895,969	55,319,249	55,744,028
Prevalence of CLL	0.0051%	2,800	2,821	2,843
Proportion of patients requiring treatment	67%	1,876	1,890	1,905
Proportion of new patients who receive first-line treatment who are eligible for R combination therapy (incidence population)	67%	1,257	1,266	1,276
Staggered uptake (assumed increasing from current 2008 market update of 14%)		30%	50%	100%
Total number of 1st line treated CLL patients per annum		**377**	**633**	**1,276**

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

The use of rituximab in the treatment of CLL patients will be in addition to standard chemotherapy and will be given as an add-on to current treatment regimens. Therefore rituximab is not expected to displace any treatment regimen currently prescribed to CLL patients.

8.4 What assumption(s) were made about market share (where relevant)?

Current evidence (Genactis CLL Monitor, Q2 2008[65]) suggest that rituximab is currently used off-label in 14% of new patients. Given that rituximab is currently used in the treatment of diffused large B-cell lymphoma and follicular lymphoma within the NHS, it is assumed that clinicians will be familiar with the medication's characteristics. Therefore an additional 16% uptake has been assumed in the first year of licensed use, with further increases to 100% by year 3. As shown in Table 71

the total number of patients that are expected to be treated with rituximab combination therapy is 377, 633 and 1,276 for the three years following licensed use.

8.5 What unit costs were assumed? How were these calculated?

Rituximab is given at different doses based on the cycle number. In the first cycle patients receive 375mg/m^2. In the 5 subsequent cycles patients receive 500 mg/m^2. An average patient has a body surface area (BSA) of 1.8 m^2. The weight-based calculation of a patient with this BSA will equate to 675 mg given in the first cycle and 900 mg given in all subsequent cycles.

Two vials are available currently, and the same ones will be available for the new indication:
1: Single-use vial containing rituximab 100 mg/10 ml priced at £174.63 (BNF 56)
2: Single-use vial containing rituximab 500 mg/50 ml priced at £873.15 (BNF 56)
Each ml of solution contains 10 mg of rituximab.

In order to minimise wastage, the first cycle of rituximab treatment could comprise of one 500 mg (50 ml) vial and two 100 mg (2 ×10 ml) vials, giving a total of 700 mg. The 700 mg of the first cycle will cost £1,222.41. In the subsequent cycles patients would be given 900 mg. The dosage can be prepared by using one 500 mg vial (50 ml) and four 100 mg (4 × 10 ml) vials, giving a total of 900 mg. Each subsequent cycle costs £1,572.67. Hence five cycles of this dosage will cost £7,858.35. The total cost of a full course of treatment is £9,080.76 per patient.

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

When rituximab is added to the current chemotherapy treatments will be administered during hospital day-case visits. Reference costs 2006/2007[69] were used to determine the cost of each visit. The published costs do not provide a tariff for a day-case hospital visit therefore the inpatient cost was used in the model ('Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance'; HRG code: SB15Z); this is valued at £430 per visit. This is a conservative assumption and will only be additionally incurred if the chemotherapy combination is not provided on the same day. If the chemotherapy is given on the same day, rituximab can be given at the same time thus resulting in an incremental cost of less than £430. Specifically, the additional cost incurred will be the difference between £430 and the standard administration cost incurred by the chemotherapy combination.

Therefore, the maximum potential additional cost of the attendances to allow six IV rituximab infusions is £2,580 per patient.

8.7 Were there any estimates of resource savings? If so, what were they?

The addition of rituximab to the current treatment regimens is not associated with any direct resource savings.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Even though the addition of rituximab in the current treatment chemotherapy regimens is not associated with any direct, short-term resource savings, its use will generate cost offsets in the long-term as health outcomes for patients treated with rituximab have been demonstrated to improve. In particular, given the increased time in remission reported with R-FC in the CLL-8 study, there are potential savings from delayed expenditure on second line CLL treatments.

References

Please see end of document for full reference list: pp 170-176.

Appendices

7.4 Appendix 1

Summary of Product Characteristics (Draft)


SmPC DRAFT.pdf

7.5 Appendix 2: search strategy for section 6

The following information should be provided.

7.5.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library.**

Dialog Datastar was used to search Medline (MEYY), Medline in process (MEIP), Embase (EMYY), Embase alerts (EMBA) and Biosis (BIYY - for abstracts presented at The American Society of Haematology [ASH] annual meeting). The Cochrane Library controlled trials database was searched for clinical trials of rituximab in chronic lymphocytic leukaemia.

Additionally the Roche application for a Type II variation to the MabThera marketing authorisation was reviewed for the relevant study report (CLL-8) and any other information not obtained elsewhere.

Please note the same searches were used to extract randomised and non-randomised studies.

7.5.2 The date on which the searches were conducted.

MEYY: 15/10/2008 **Cochrane Library:** 2/10/2008

EMYY: 15/10/2008

MEIP: 28/10/2008

EMBA: 28/10/2008

BIYY: 31/10/2008

7.5.3 The date span of the search.

Wherever possible databases were searched from 01/01/2000 to the present. The Cochrane library was tested in its entirety.

7.5.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search Strategy for MEYY/EMYY

No.	Database	Search term	Info added since	Results
1	MEYY	leukemia#.W..MJ.	unrestricted	56446
2	MEYY	B-Lymphocytes#.DE.	unrestricted	32467
3	MEYY	1 OR 2	unrestricted	87411
4	MEYY	rituximab.RN.	unrestricted	3237
5	MEYY	3 AND 4	unrestricted	718
6	MEYY	5 AND chronic	unrestricted	268
7	EMYY	Rituximab.W..MJ.	unrestricted	2726
8	EMYY	Chronic-Lymphatic-Leukemia.MJ.	unrestricted	4901
9	EMYY	7 AND 8	unrestricted	164
10	EMYY MEYY	combined sets 6, 9	unrestricted	432
11	EMYY MEYY	dropped duplicates from 10	unrestricted	88
12	EMYY MEYY	unique records from 10	unrestricted	344
13	MEYY	6 AND PT=CLINICAL-TRIAL#	unrestricted	48
14	EMYY	9 AND CLINICAL-TRIAL#	unrestricted	57
15	EMYY MEYY	combined sets 13, 14	unrestricted	105
16	EMYY MEYY	dropped duplicates from 15	unrestricted	18
17	EMYY MEYY	unique records from 15	unrestricted	87

Search Strategy for BIYY

No.	Database	Search term	Info added since	Results
1	BIYY	PT=MEETING-ABSTRACT OR PT=MEETING-POSTER	20000101	1321475
2	BIYY	rituximab.TI.	20000101	2853
3	BIYY	(chronic ADJ lymphocytic ADJ leukemia OR CLL).TI.	20000101	4374
4	BIYY	2 AND 3	20000101	227
5	BIYY	4 AND 1	20000101	157
6	BIYY	5 AND HUMANS# AND ABSTRACT=YES	20000101	133
7	BIYY	untreated OR first ADJ line	20000101	46626
8	BIYY	6 AND 7 AND HUMANS# AND ABSTRACT=YES	20000101	53
9	BIYY	8 NOT relapse	20000101	41

Search Strategy for EMBA

No.	Database	Search term	Info added since	Results
1	EMBA	rituximab OR rituxan	unrestricted	155
2	EMBA	chronic ADJ lymph$ ADJ leuk$	unrestricted	97
3	EMBA	1 AND 2	unrestricted	8

Search Strategy for MEIP

No.	Database	Search term	Info added since	Results
1	MEIP	rituximab OR rituxan	unrestricted	292
2	MEIP	chronic ADJ lymph$ ADJ leuk$	unrestricted	221
3	MEIP	1 AND 2	unrestricted	19

For the above searches, Boolean search terms used were “AND” and “OR”

Search Strategy for Cochrane Library

The entire Cochrane library was searched for “rituximab and Chronic lymphocytic leukaemia or Chronic lymphatic leukaemia or Chronic lymphatic leukaemia in Cochrane Central Register of Controlled Trials”

7.5.5 Details of any additional searches, for example searches of company databases (include a description of each database).

None done and therefore not applicable.

7.5.6 The inclusion and exclusion criteria.

As discussed in section 6, no randomised controlled studies relevant to the decision problem were excluded.

7.5.7 The data abstraction strategy.

As detailed above.

7.6 Appendix 3: search strategy for section 7

7.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **Health Economic Evaluation Database**
- **NHS Economic Evaluation Database (NHS EED).**

Dialog Datastar was used to search Medline (MEYY), Medline in process (MEIP), Embase (EMYY).

NHS EED

ISPOR Research Digest

7.6.2 The date on which the search was conducted.

All searches were conducted on the 10th of November 2008

7.6.3 The date span of the search.

Wherever possible databases were searched from 01/01/2000 to the present. The Cochrane library was tested in its entirety.

7.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search Strategy for EMYY and MEYY

Search Strategy

No.	Database	Search term	Info added since	Results
1	EMYY	rituximab	unrestricted	10753
2	EMYY	RITUXIMAB.W..MJ.	unrestricted	2766
3	EMYY	economic-evaluation#.DE.	unrestricted	92067
4	EMYY	cost-benefit-analysis#.DE. OR cost-effectiveness-analysis#.DE. OR (cost ADJ Minimization-analysis#).DE.	unrestricted	75340
5	EMYY	Chronic ADJ lymphatic ADJ leukemia	unrestricted	8061
6	EMYY	CHRONIC-LYMPHATIC-LEUKEMIA.MJ.	unrestricted	4931
7	EMYY	2 AND 6	unrestricted	167
8	EMYY	3 AND 4	unrestricted	75340
9	EMYY	3 OR 4	unrestricted	92067
10	EMYY	9 AND 7	unrestricted	6
11	EMYY	3 OR 4	unrestricted	92067
12	EMYY	2 AND 6	unrestricted	167
13	EMYY	11 AND 12	unrestricted	6
14	MEYY	antibodies-monoclona#.DE.	unrestricted	0
15	MEYY	antibodies-monoclonal#.DE.	unrestricted	81538
16	MEYY	Cost-benefit-analysis#.DE. OR cost-benefit-analysis.DE.	unrestricted	34487
17	MEYY	economics#.W..DE.	unrestricted	244004
18	MEYY	Chronic ADJ lymphatic ADJ leukemia OR chronic ADJ lymphocytic ADJ leukemia	unrestricted	6764
19	MEYY	15 AND rituximab	unrestricted	3558
20	MEYY	16 OR 17	unrestricted	244006
21	MEYY	19 AND 18	unrestricted	269
22	MEYY	20 AND 21	unrestricted	1
23	EMYY MEYY	combined sets 13, 22	unrestricted	7
24	EMYY MEYY	dropped duplicates from 23	unrestricted	2
25	EMYY MEYY	unique records from 23	unrestricted	5

The five records found and the reason for their exclusion are summarised below.

- Keating M J. Managing CLL: A new level of sophistication. ONCOLOGY 2007; 21(14): 1659-1662

Excluded on the basis that the study is not a health economic evaluation

- Scott W G, Scott H M. Economic evaluation of third-line treatment with alemtuzumab for chronic lymphocytic leukaemia. Clinical Drug Investigation 2007; 27(11): 755-764

Excluded on the basis that the study was performed from a New Zealand perspective.

- Smolej L. Fludarabine-induced autoimmune hemolytic anemia in a CLL patient: Rituximab as the treatment of choice? . Leukemia Research; 2006 , 31(2): 267-267

Excluded on the basis that the study was not a UK study

- Plosker G L, Figgitt D P. Rituximab: A review of its use in non−Hodgkin's lymphoma and chronic lymphocytic leukaemia. Drugs 2003; 63(8): 803-43

Excluded on the basis that the study is not an economic evaluation

- Reuben B D. American Society of Hematology: Latest clinical findings from 99 nations

Excluded on the basis that the study is not an economic evaluation

Search Strategy for ISPOR Research Digest

Disorder: Cancer, Topic: Cost studies, Keyword: rituximab AND cll

No results found

Search Strategy for NHS EED

Rituximab AND CLL : 1 result

Scott W G, Scott H M. Economic evaluation of third-line treatment with alemtuzumab for chronic lymphocytic leukaemia. Clinical Drug Investigation 2007; 27(11): 755-764

Excluded on the basis that the study was performed from a New Zealand perspective.

7.6.5 Details of any additional searches, for example searches of company databases (include a description of each database).

No additional searches were performed.

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