NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Rituximab for the treatment of relapsed/refractory Chronic Lymphocytic Leukaemia

Roche Submission to the
National Institute for Health and Clinical Excellence
Submitted: 7th July 2009

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Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the 'Guide to the single technology appraisal process' – www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

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) in January 2009. It is anticipated that opinion from the Committee on Medicinal Products for Human Use (CHMP) will follow on **23rd July 2009**, with full European Union marketing authorisation following 44 days after this. Thus an estimated date for final authorisation is **September 7th 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 licence will allow the addition of MabThera to ***any*** chemotherapy combination deemed appropriate by the prescribing physician, with fludarabine based regimes being the most widely used. The following wording is anticipated in the summary of product characteristics (currently being evaluated by the regulatory authorities):

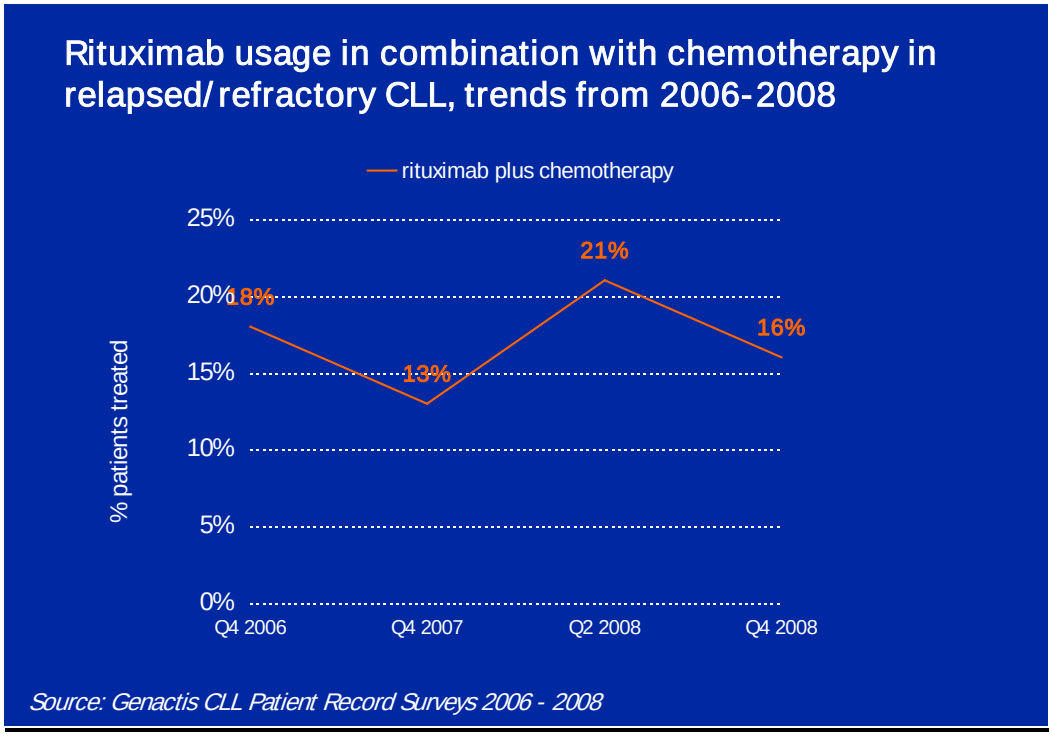
"MabThera is indicated for the treatment of patients with first line and relapsed/refractory chronic lymphocytic leukaemia (CLL) in combination with chemotherapy."

Thus, it is anticipated that the current wording in the SmPC specifying use of rituximab in first-line patients only will be broadened and the revised wording will reflect the use of rituximab at any stage of treatment (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.

Market research carried out by Roche over the last two years indicates that there is already some use of rituximab in relapsed/refractory CLL, as highlighted in Figure 1below. This data would indicate that approximately 16% of patients on average with relapsed/refractory CLL in the United Kingdom receive a rituximab-containing regime currently.

Figure 1. Rituximab Use in Relapsed/Refractory CLL, 2006-2008



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

No, the technology does not have regulatory approval anywhere 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?

The indication in this submission will also be evaluated by the Scottish Medicines Consortium in August 2009. Full guidance to NHS Scotland is expected by December 2009.

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 physician's 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 (REACH) were based on Phase II studies (Keating et al 2005[1]; Tam et al, 2008[2]; Wierda et al, 2005[3]).

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 (excluding VAT) is £174.63.

The NHS cost of a 50 ml vial of rituximab (excluding 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 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[4]) 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[5]).

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 relapsed CLL (as discussed in question 1.4), staff will 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.

Table 1. Overview of Decision Problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Patients with relapsed chronic lymphocytic leukaemia.	It is anticipated that the licence will reflect patients with both relapsed and so-called 'refractory' disease, so the full population would be correctly defined as '**patients with relapsed/ refractory lymphocytic leukaemia**'. Thus the population considered in the submission will be slightly broader than in the final scope issued by NICE, reflecting the nature of the anticipated licence.
Intervention(s)	Rituximab (in combination with chemotherapy)	The licence will allow addition of rituximab to any chemotherapy. As in the first-line submission, the available data suggests that irrespective of the chemotherapy, rituximab adds efficacy with manageable toxicity.
Comparator(s)	Chlorambucil Fludarabine combination therapy Cyclophosphamide, doxorubixin, vincristine, prednisone (CHOP) combination Stem-cell transplant	The comparators considered in this submission are fludarabine combination therapy, chlorambucil, and CHOP. The pivotal, Phase III randomised study (REACH) provides a direct comparison of the most common fludarabine combination therapy used in practice (fludarabine and cyclophosphamide – FC) versus FC combined with rituximab – R-FC. Although there are alternative treatment options for previously treated CLL patients, due to differing patient characteristics of those who receive different chemotherapies, it would be inappropriate to compare R-FC versus chemotherapies other than FC (for example, R-FC compared to chlorambucil or R-FC compared to CHOP). This is because fludarabine-based combination therapy is usually administered to younger and/or fitter CLL patients, whereas chlorambucil is often reserved for the more frail and elderly. Similarly, CHOP is often reserved for patients in whom

		fludarabine is contraindicated. Instead, for each chemotherapy comparator, the appropriate intervention arm should be rituximab in combination with the comparator chemotherapy (i.e. R-chlorambucil versus chlorambucil; R-CHOP versus CHOP). There is no data currently on the combination of rituximab with chlorambucil in relapsed/refractory CLL. One phase II trial for R-CHOP in fludarabine refractory patients is used as the basis for a simple cross trial comparision provided in section 6.8. In addition, a wealth of phase II data is included in this submission demonstrating the efficacy and tolerability of rituximab in combination with <u>any</u> base chemotherapy regime. In the final scope, NICE have noted that stem-cell transplant could be considered as a comparator. However, we do not feel that this would be appropriate. In the United Kingdom in 2008, only 47 transplants were carried out for CLL (British Society of Blood and Marrow Transplantation, BSBMT[6]).These are always done in very specific patients who are often younger and have a suitable donor for an allograft. There is no generalisable clinical decision point currently where a physician has to decide between a transplant and (rituximab based) chemotherapy. A transplant is done in very few patients (less than 0.5%), and therefore should not be considered a comparator for this submission.
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival Response rates Adverse Effects of treatment Health-related quality of life	These outcomes are covered in the submission. The Functional Assessment of Cancer Therapy – General (FACT-G), was used as a tool to capture health-related quality of life in the REACH study. This data will be presented. A further analysis to evaluate the impact of rituximab on patients' QoL, a Quality adjusted time Without disease Symptoms or treatment Toxicity (Q-TWiST) was applied to REACH data. In the economic analysis, predicted time in each health state was weighted using CLL utility scores from the literature (Hancock et al, 2002[7]) to account for patient quality of life and to estimate QALYs. An observational study estimating the health-related quality of life profiles of UK patients with CLL is underway. Interim results can be made available to NICE

		upon request.
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	A semi-Markov model with three health 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 REACH trial follow-up using the best parametric fit. Because median overall survival had not been reached in the REACH study, 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%.
Subgroups to be considered	If evidence allows, the appraisal should consider subgroups based on the following: P53 presence and p53 mutation or deletion	It is anticipated that the marketing authorisation will not exclude patients with p53 deletion/mutation. There are patients with p53 abnormalities included in the clinical trials appraised in this submission and data will be analysed accordingly.
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 treatment of relapsed/refractory chronic lymphocytic leukaemia. **Within this remit, a marketing authorisation is expected by the the 7th September 2009**. It is expected that the licence will read as follows:

"MabThera is indicated for the treatment of patients with first line and relapsed/refractory 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 (ie 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 most common therapies for previously treated patients with chronic lymphocytic leukaemia are fludarabine combination therapy (primarily fludarabine and cyclophosphamide – FC) and chlorambucil. With regards to

CHOP, although significantly less commonly used than fludarabine combinations and chlorambucil, this regime may be prescribed in the UK as an alternative second-line treatment option for CLL patients unsuitable for fludarabine. It is therefore appropriate to present specific data comparative to FC, chlorambucil, and CHOP. The key comparative randomised Phase III study (REACH) that forms the core of this submission is a direct comparison of rituximab combined with FC (R-FC) versus FC. As previously highlighted in section 2, it would be inappropriate to compare R-FC versus chemotherapies other than FC. Instead, for each chemotherapy comparator, the appropriate intervention arm should be rituximab in combination with the comparator chemotherapy. With regards to CHOP, data is presented in the form of a simple indirect study comparison. Currently, there is no phase II/III trial data available for chlorambucil in combination with rituximab in previously treated CLL, however, a wealth of phase II data is included in this submission demonstrating the efficacy and tolerability of rituximab in combination with *any* base chemotherapy regime.

Table 2. Decision Problem Overview

Disease setting	Current standards of care in England	Relevant rituximab license indication	Questions for this appraisal
Patients with relapsed/refractory CLL who are symptomatic, and require treatment.	Fludarabine combination therapy and chlorambucil. Market research carried out on behalf of Roche suggests that around 51% of patients in the relapsed setting receive one or other of these treatment regimes. In addition, approximately 16% of previously treated patients have rituximab added to their cytotoxic chemotherapy (Section 4).	The anticipated licence is likely to read as follows: "MabThera is indicated for the treatment of patients with first line and relapsed/refractory chronic lymphocytic leukaemia (CLL) in combination with chemotherapy"	Is rituximab, when given in combination with chemotherapy to patients with relapsed/refractory CLL needing treatment 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 patients with relapsed/refractory CLL consists of a phase III trial and several supporting Phase II studies.

In the Phase III trial REACH (sections 6.1-6.4), patients with symptomatic relapsed/refractory CLL who needed treatment 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, the hypotheses being tested were generally to assess the efficacy and tolerability of rituximab combination chemotherapy in patients with previously treated CLL. These studies add valuable extra information to support the anticipated broad R-chemotherapy licence and highlight that the base regime does not preclude efficacy (section 6.8.4.1) and does not cause alarming or unexpected toxicity (section 6.7). Furthermore, these data support the use of R-FC and other rituximab-based combinations in fludarabine-refractory CLL patients (section 6.8.4.2) (who were excluded from entry in REACH), demonstrating that even in this poor prognosis group of patients R-chemotherapy may be a useful therapeutic option. Finally, data from more than 200 patients (section 6.8.4.3) demonstrate that rituximab-containing regimens, specifically repeat administrations of R-FC (and variants thereof), are a viable and useful therapeutic option for patients whose initial treatment consisted of rituximab.

Key Clinical Results: REACH

REACH randomised 552 patients to FC or R-FC (276 in each arm). The efficacy results from the main analysis are summarised in Table 3 below.

Table 3: Summary of Overall Efficacy: REACH, Main Analysis

Median Follow up 25.3 months

Parameter	FC	R-FC
PFS		
median (months)	20.6	30.6
p value (Log-Rank test)	0.0002	
HR [95%CI]; p value; Wald test		
Non-stratified (unadjusted)	0.65 [0.51; 0.82]; 0.0002	
Stratified (unadjusted)	0.66 [0.51; 0.84]; 0.0008	
Overall survival		
Median (months)	51.9	-[a]
p value (Log-Rank test)	0.2874	
HR [95% CI] p value (Wald test)		
Non-stratified (unadjusted)	0.83 [0.59;1.17]; 0.2871	
Stratified (unadjusted)	0.87 [0.60;1.25]; 0.4447	
Event Free Survival		
Median (months)	19.3	28.7
p value (Log-Rank test)	0.0002	
HR [95%CI] p value (Wald test)		
Non-stratified (unadjusted)	0.64 [0.51; 0.81]; 0.0002	
Stratified (unadjusted)	0.64 [0.50;0.82]; 0.0004	
Response Rates		
Best Overall Response Rates		
Response	58.0%	69.9%
Non-response	42.0%	30.1%
p value (Chi-squared test)	0.0034	
Complete response	13.0%	24.3%
Partial response	44.9%	45.7%
Stable disease	22.1%	17.0%
Progressive disease	5.4%	2.5%
Missing	14.5%	10.5%
End of Treatment Response Rates		
Response	52.9%	63.4%
Non-response	47.1%	36.6%
p value (Chi-squared test)	0.0123	
Complete response	9.1%	13.8%
Partial response	43.8%	49.6%
Stable disease	21.7%	19.6%
Progressive disease	10.9%	6.5%
Missing	14.5%	10.5%
Duration of Response[b]		
Median (months)	27.6	39.6
p value (Log-Rank test)	0.0252	
HR [95% CI] p value (Wald test)		
Non-stratified (unadjusted)	0.69 [0.50; 0.96]; 0.026	
Stratified (unadjusted)	0.65 [0.46; 0.93]; 0.0180	
Disease Free Survival[c]		
Median (months)	42.2	39.6
p value (Log-Rank test)	0.8842	
HR [95%CI] p value (Wald test)		
Non-stratified (unadjusted)	1.06 [0.49;2.28]; 0.8850	
Stratified (unadjusted)	1.25 [0.46; 3.37]; 0.6598	
Time to New Treatment		
Median (months)	34.2	-[a]

Parameter	FC	R-FC
p value (Log-Rank test)	0.0024	
HR [95%CI] p value (Wald test)		
Non-stratified, (unadjusted)	0.65 [0.49; 0.86]; 0.0026	
Stratified (unadjusted)	0.65 [0.48; 0.88]; 0.0057	

[a] Median has not yet been reached
[b] Only in patients with Best Overall Response assessed as complete or partial response
[c] Only in patients with Best Overall Response assessed as complete response

The results of this study demonstrated a highly statistically significant and clinically meaningful benefit when rituximab was used in combination with FC chemotherapy in patients with relapsed/refractory CLL. The primary endpoint of PFS was prolonged by a median of 10 months (20.6 months for FC and 30.6 months for R-FC) and the risk of disease progression or death was reduced by 35% when rituximab was added to the FC regimen (p=0.0002, Log-Rank test). These benefits were robust and apparent in almost all of the 48 pre-specified subgroups. With regards to the secondary efficacy endpoints noted, most showed significant and relevant improvements for the R-FC arm.

Key clinical results: Supportive studies

Results from REACH are confirmed by published literature from a total of 8 supportive studies involving more than 480 previously treated patients treated with rituximab in combination with a range of chemotherapy regimens. In all these supportive studies, high response rates of $\geq$ 65% were achieved. Results from one retrospective cohort analysis comparing R-FC with FC or F alone also demonstrated an OS benefit for the cohort treated with rituximab containing therapy compared to the cohorts treated with chemotherapy alone. Furthermore, 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. These studies add valuable extra information to support the broad R-chemotherapy licence that is expected and highlight that the base regime does not preclude efficacy.

Although the REACH study did not include patients who were refractory to fludarabine, data from 2 studies by the MDACC CLL group and 10 additional publications support the view that rituximab-based combination regimens have worthwhile efficacy in these patients, reporting overall response rates generally above 50%. Data from more than 200 patients in non-randomized trials also demonstrate that rituximab-containing regimens, specifically repeat administration of R-FC (and variants thereof) are a viable and useful therapeutic option for patients whose initial treatment contained rituximab, despite these patients being excluded from the pivotal phase III study. Together, these data support the anticipated licence for R-chemotherapy in both rituximab naïve and pre-treated patients who have relapsed after or are refractory to chemotherapy.

Demonstrating the Cost Effectiveness of Rituximab

The economic evaluation utilises the key outcomes of the BO17072 (REACH) clinical trial and is designed for the purposes of estimating lifetime NHS costs and QALYs for R-FC versus FC. 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”.

Lifetime progression free survival was estimated from an extrapolation of the PFS curves from the REACH trial for the R-FC and FC arms. 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 £8,226 per patient. Over an expected lifetime, R-FC is estimated to generate an additional £8,326 of total costs per patient compared to FC alone. R-FC is predicted to extend discounted progression free survival by 0.92 years and discounted overall survival by 0.67 years compared to FC.

The reference case cost per QALY for R-FC compared to FC is estimated to be £14,240. The ICER is therefore below the lower NICE threshold of £20,000/QALY gained. 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 relapsed / refractory CLL with a high degree of certainty. A threshold analysis suggests that the incremental benefit associated with rituximab in combination with other chemotherapies would need to be 50% less than that observed for R-FC compared to FC in order to exceed an ICER of £30,000 per QALY gained.

Summary

One large well-designed randomised controlled trial demonstrates that for relapsed/refractory patients with CLL who need treatment, 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 35%. 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. These data also confirm that R-chemotherapy is efficacious in high-risk, fludarabine refractory patients as well as patients who have previously been exposed to rituximab. The economic evaluation of R-FC versus FC also illustrates that rituximab is a highly cost effective treatment for patients with relapsed/refractory 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.

4.1.1. 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.

4.1.2. 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, 2008[8]).

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, 2008[9]) is helping to further characterise this complex malignancy.

4.1.3. 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 (Hallek et al, 2008[16]).

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 may be carried out at initiation of treatment or after therapy to confirm complete response.

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 4: 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**

4.1.4. 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, 2000[10]). 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, 2004[11]).

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, 1999[12]). 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 (eg Kaufman and Rai, 2008[13]). Testing for del17p is thus advised prior to initiation of therapy for CLL.

4.1.5. 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, 2003[14]).

Standard criteria drawn up The National Cancer Institute Working Group in 1996 (Cheson et al, 1996[15]), which were updated last year (Hallek et al, 2008[16]) 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 (ie >6cm below the left costal margin) or progressive or symptomatic splenomegaly.

3. Massive nodes (ie >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, 1999[17]). 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. last 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.

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 (eg 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 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, 2002[18]; Rawstron et al, 2001[19]; Provan et al, 1996[20]). 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 (eg 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.

4.1.5.2. First-Line Treatments

The management of previously untreated disease is not relevant to the population described in the decision problem of this submission and has been covered in detail in the previously submitted STA for rituximab for the treatment of first-line CLL.

4.1.5.3. Second and Subsequent Line Treatments

The indications for second line and subsequent treatments are symptomatic and/or progressive disease, as for initial therapy. However, 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 (eg 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 CLL patients is then dependent upon a number of factors, most importantly age, performance status, associated diseases, prognostic factors, immune status, previous therapy administered, the response and duration of response to such therapy, and time from last therapy. Furthermore, the goal of therapy, whether palliative or aggressive, must also be weighed into the decision when deciding on the next line of treatment.

Currently, fludarabine-based combinations are viewed as the most efficacious regimens for patients with relapsed or refractory CLL who are sufficiently fit to tolerate this treatment (ESMO guidelines (Eichhorst et al, 2008[21])).

Current ESMO clinical recommendations state:

“The first line treatment may be repeated, if the relapse or progression occurs >12 months after initial therapy. If relapse occurs within 12 months or if the disease does not respond to the first-line therapy, the following options are recommended in accordance with the administered first-line therapy:

- Fludarabine, FC or cladribine after chlorambucil.
- Fludarabine combinations [with cyclophosphamide (FC) and/or mitoxantrone (FCM)] ± monoclonal antibodies (FR, FCR, FCM-R, FA) in fludarabine-refractory patients or relapse after fludarabine-based therapy.
- Monoclonal antibody (alemtuzumab), especially in chemotherapy-refractory patients.
- Bendamustine ± monoclonal antibodies after chlorambucil or purine analog-based therapy.

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

- Allogeneic progenitor cell transplantation is the only curative therapy so far and is indicated in high-risk [del(17p), del(11q)] and/or refractory disease."

It should also be noted that even though it is currently off-label (and the subject of this submission), approximately 16% of patients receive rituximab combination therapies for relapsed/refractory CLL (see Figure 1).

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, both 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 51%% of all prescribed chemotherapy regimes for relapsed/refractory treatment of CLL in the United Kingdom. Furthermore, the pivotal Phase III randomised study (REACH) provides a direct comparison of the most common fludarabine combination therapy used in practice (fludarabine and cyclophosphamide –FC) versus FC combined with rituximab – R-FC.

With regards to CHOP, although significantly less commonly used than fludarabine combinations and chlorambucil (representing approximately 5% of prescribed regimes), current BCSH guidelines recommend CHOP as an alternative second-line treatment option for CLL patients unsuitable for fludarabine (Oscier et al, 2004[22]). To this end, Roche also considers CHOP an appropriate comparator for this submission.

In the final scope, NICE have noted that stem-cell transplant could be considered as a comparator. However, we do not feel that this would be appropriate given that (a) so few transplants are carried out in CLL patients in the UK (47 in 2008, accounting for <0.5% of patients) and (b) only fit, high risk patients are candidates for treatment. In addition, allogeneic transplatation is generally performed as a conolidation procedure in patients who have responded to second or subsequent line therapy and not as an altermative. Given these facts, in the real world clinicians would not have to decide between offering a transplant and (R-) chemotherapy. Accordingly, we feel transplant should not be considered as a comparator for this submission.

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, 1998[4]), 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 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 (O'Brien et al, 2001[23]) 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, 2005[1]; Tam et al, 2008[2]). The dose of rituximab used was 500mg/m^2 (with a dose of 375mg/m^2 only for the first cycle). The same research group has also examined the R-FC regimen, using the same dosing schedule, in 177 previously treated CLL patients (Wierda et al, 2005[3]). This study will be analysed subsequently as part of this submission. Subsequent randomised phase III studies compared FC to R-FC in both previously untreated (CLL-8) and relapsed/refractory (REACH) CLL patients. REACH (analysed in detail in this submission) is the pivotal study that has been presented to the regulatory authorities for an extension to rituximab's marketing authorisation, using the rituximab dose pioneered in the MD Anderson Phase II studies.

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 (ie 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, 1994[24]; Demiden et al, 1997[25]; and Anderson et al, 1997[26]).

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 after relapse; rituximab in combination with chemotherapy offers the best opportunity for the longest PFS.

Therefore, it is suggested that after first-line treatment of CLL, patients receive 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 treatment options 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?

7. What are the optimum salvage treatment strategies? How should fludarabine-refractory disease be approached?

These issues (except 4 – which forms the core clinical discussion of this submission) have been extensively covered in Sections 4.1.5.1, when treatment goals in CLL were discussed and 4.1.5.3, where optimum salvage regimes were considered.

Best practice in the United Kingdom in previously untreated patients 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 (particularly in light of the recent data from CLL-8). The optimal management strategy for those in which fludarabine-based therapy is not deemed appropriate (eg 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 is 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 (eg 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.

Specifically in relation to relapsed/refractory disease, little guidance in the literature relative to evidenced based medicine exists for second-line or greater therapy in CLL. In the UK, salvage therapy choices are largely dictated by magnitude and duration of response to initial treatment. Some of the most recent clinical recommendations for second line chemotherapy were published in 2007 by the European Society for Medical Oncology (ESMO) (Eichhorst et al, 2007[21]) and largely reflect current practice in the UK ie repeat first-line treatment if relapse or progression occurs >12 months after initial therapy; if relapse occurs within 1 year of completing initial therapy or if disease does not respond to first-line therapy, patients should receive an alternative regime (described in detail in Section 4.1.5.3). Following publication of the results from UK CLL-4, more patients in the UK are being treated with fludarabine combination therapy upfront. Accordingly, more patients are presenting with fludarabine-refractory disease. The prognosis of these patients is very poor, with median survival being measured in months (Monserrat et al, 2006[27]). Current consensus is that fludarabine-based combinations are the most efficacious regimens for these patients if they are sufficiently fit to tolerate treatment (ESMO guidelines) with both FC-R, FCM, and FCM-R demonstrating promising activity in phase II studies (these trials will be discussed at length in section 6.8 of this submission). For patients with predominantly marrow disease and who are 17p deleted, alemtuzumab may be considered. Allogeneic stem cell transplantation may also be considered in younger patients with good performance status and an HLA-matched sibling or unrelated donor.

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, 2004[22]).

At the time of publication of these guidelines, the MRC UK CLL-4 study was still recruiting, where the hypothesis testing the relative efficacy and tolerability of fludarabine alone, chlorambucil alone or fludarabine and cyclophosphamide combined (FC) in previously untreated CLL patients was being analysed in a prospective randomised controlled study (Catovsky et al, 2007[28]). Accordingly, guidance for second-line and subsequent treatment focuses on patients treated with upfront chlorambucil or fludarabine monotherapy. This was an entirely reasonable approach as the superior efficacy and good tolerability of FC in first-line patients had not been formally established, with the final analysis of this study reported in 2007. These guidelines also note that "*rituximab combined with fludarabine (with or without cyclophosphamide) may be effective in refractory CLL and warrants further evaluation in this setting*". Roche is aware that these guidelines are in process of being updated and should become available 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 (Eichhorst et al, 2007[21]), which offer guidance on second-line treatments as previously outlined in Section 4.1.5.3 of this submission. These guidelines state that fludarabine/rituximab combinations may be an option in fludarabine refractory patients, together with other antibody treatments (alemtuzumab) and transplantation.

American guidelines updated last year by The National Comprehensive Cancer Network (NCCN Practice Guidelines in Oncology, 2008[29]) recommend the use of chemotherapy +/- rituximab or alemtuzumab as second line therapy in CLL patients. They also state that high dose therapy with allogeneic stem cell rescue should be considered as an option. The use of ritixuximab combination therapy for second line treatment falls under NCCN Category 2A with respect to level of evidence and consensus (by their definition Category 2A is “based on lower-level evidence in clinical experience and uniform consensus”). These recommendations are based on American led Phase II studies, which will be analysed subsequently in this submission (Section 6.8). 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 treatment of patients with relapsed/refractory chronic lymphocytic leukaemia**' narrows down the number of relevant studies. First-line trials, trials with a mixture of first line/relapsed + refractory patients, rituximab monotherapy studies, and studies incorporating 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 in previously treated CLL patients. BO17072 (The REACH study[30]) is the first study of this type available for analysis, and forms the key component of the marketing authorisation application for rituximab in previously treated CLL. The clinical study report represents the only Phase III trial data available for inclusion in this submission 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 9.2, as requested.

6.2 Study selection

6.2.1 Complete list of RCTs

1. Roche. REACH Final Clinical Study Report BO17072. January 2009.[30]

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 REACH study.

At this point it should be noted that a randomised Phase II ***non-comparative*** study involving fludarabine, cyclophosphamide, and mitoxantrone (FCM) with or without rituximab in previously treated CLL has been published (Hillmen et al, 2007[31]). However, the design of this study did not allow a statistical comparison between the rituximab-containing and –non-containing arms. The study does however add important data about efficacy and safety in the relevant population at hand and is therefore included in the list in Section 6.2.4 and is discussed fully with the 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 5. List of relevant non-randomised controlled trials supporting the efficacy and tolerability of rituximab in combination with different chemotherapy regimes

Study [Ref]	Title	Regimen	No of Patients Included	Source Document
Wierda et al., 2005[3]	Chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab for relapsed and refractory chronic lymphocytic leukemia	R-FC	177 patients with recurrent/refractory CLL	Publication
Wierda et al., 2006[32]	A retrospective comparison of three sequential groups of patients with recurrent/refractory chronic lymphocytic leukemia treated with fludarabine-based regimens	F, FC or R-FC	N=143 R-FC (out of 177 patients from above) N=251 F; N=111 FC	Publication
Hillmen et al., 2007[31]	NCRI CLL201 Trial: A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone with or without rituximab in previously treated CLL	FCM ± R	N=23 FCM; N=23 R-FCM	Conference abstract
Lamanna et al., 2006[33]	Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated CLL	R-PC	46 previously treated patients with CLL (n=32) or other low Grade B-cell neoplasms (n=14)	Publication
Lamanna et al., 2007[34]	Pentostatin, cyclophosphamide, rituximab, and mitoxantrone: A new highly active regimen for patients with CLL previously treated with PCR or FCR	R-PCM	21 previously treated patients with CLL (n=17) or other low Grade B-cell neoplasms (n=4)	Conference abstract
Robak et al., 2007[35]	Rituximab plus cladribine with or without cyclophosph. in patients with relapsed or refractory CLL	R-Cl± C	N=18 R-Cl; N=28 R-ClC	Publication
Fischer et al., 2008[36]	Bendamustine in combination with rituximab for patients with relapsed CLL: A MC, phase II trial of the GCLLSG	R-B	81 patients	Conference abstract

Study [Ref]	Title	Regimen	No of Patients Included	Source Document
Eichhorst et al., 2005[37]	CHOP plus rituximab in fludarabine refractory CLL or CLL with autoimmune hemolytic anemia or Richter's transformation: First interim analysis of a phase II trial of the German CLL Study Group	R-CHOP	34 patients refractory to F or with AIHA as well as in patients with Richter's transformation	Conference abstract
Tam et al., 2008[38]	Salvage therapy following failure or relapse after FCR chemo-immunotherapy as initial treatment for chronic lymphocytic leukemia	Various, including R alone, R+HDMP, R+A and R-FC (+/- A or L)	79 patients with CLL relapsing after first-line R-FC	Conference abstract

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 (REACH) 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. In addition the single-arm Phase II study by Weirda et al.[32] provides longer term follow-up (34 months), for patients treated with the combination of R-FC, the same rituximab combination analysed in the comparative Phase III study. The REACH trial has a follow up of a maximum of 25.3 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.

Table 6. List of relevant non-randomised controlled trials supporting the efficacy of rituximab-containing regimens in patients with fludarabine-refractory* CLL

Study (ref)	Salvage Treatment	No of Patients Included	Source Document
Wierda., et al 2005 [3]	R-FC	33 (of 177 total)	Publication
Woyach et al, 2009 [39]	R+ etanercept	18 (of 36 total)**	Publication
Castro et al, 2008 [40]	R+HDMP	14**	Publication
Faderl et al, 2003 [41] †	R + A	32	Publication
Nabhan et al, 2004 [42]	R + A	11	Publication
Wierda et al, 2006 [43]†	CFAR	32 (of 79 total)	Publication
Tsimberidou et al, 2008 [44]†	OFAR	30	Conference abstract
Lamanna et al, 2006 [33]	R-PC	8	Publication
Klepfish et al, 2008 [45]	R + FFP	5**	Publication
Winkler et al, 1999 [46]	R alone	8 (of 11 total)	Publication
Tam et al, 2007 [47]†	Intensive R-combinations	9	Publication
	Non-intensive R-combinations (including R + GMCSF, R+A, R+MP, R-FC, CFAR)	19	

*Various definitions– includes patients who were not primary refractory (failed to achieve a CR or PR lasting at least 6 months) in some cases, and patients who were also refractory or unsuitable for alemtuzumab (Tam et al, 2007)
**Including some patients pre-treated with rituximab
†Data from phase II and/or retrospective studies from the MDACC (potential for overlap with other studies)
NS: not specified; R: rituximab; HDMP: high dose methylprednisolone; A: alemtuzumab; CFAR: cyclophosphamide, fludarabine, alemtuzumab, and rituximab: OFAR: oxaliplatin, fludarabine, cytarabine, and rituximab; R-PC: rituximab, pentostatin, cyclophosphamide; FFP: fresh frozen plasma.

Justification for inclusion

These studies have been included to highlight the efficacy of rituximab-containing chemotherapy regimes in patients with fludarabine refractory CLL. To enter REACH, patients had to have achieved a response (PR or CR) to single agent fludarabine (or other nucleoside analog) that lasted at least 6 months. Thus, there were no patients in the study who were refractory to fludarabine (defined as failure to achieve a PR or CR that lasted at least 6 months) (the rationale for this exclusion criterion is explained in greater detail in section 6.8.4.2). Despite this, there is a significant level of phase II evidence to suggest that R-FC and other rituximab-containing regimes are a useful therapeutic option for these patients. These studies are outlined above in Table 6 and are key supporting data in the

variation application to the EMEA for rituximab (plus chemotherapy) in the treatment of relapsed/refractory CLL patients.

Table 7. List of relevant non-randomised controlled trials supporting the efficacy of re-treatment with rituximab-containing regimens in patients with relapsed/refractory CLL

Study (ref)	Initial Treatment	Re-Treatment	No of Patients Included	Source Document
Wierda et al., 2005 [3]	Rituximab ± chemotherapy	R-FC	22	Publication
Tam et al., 2008 [38]	R-FC	R-FC, rituximab monotherapy, R±A, CFAR,	80	Conference abstract
Lamanna et al., 2006 [33]	Rituximab + chemotherapy	R-PC	7 (of 32 CLL pts)	Publication
Herold et al., 2000 [48]	Rituximab monotherapy	Rituximab monotherapy	1 (of 2 CLL pts)	Publication
Zent et al., 2008 [49]	Rituximab + Alemtuzumab	Rituximab + Chemotherapy	9 (of 30 CLL pts)	Publication
Gupta et al., 2002 [50]†	R-CD	R-CD	5	Publication
Winkler et al., 1999 [46]	Rituximab monotherapy	Rituximab monotherapy	1	Publication
Lamanna et al., 2008 [34]	R-PC or R-FC	R-PC + Mitoxantrone	11	Conference abstract
Woyach et al., 2009 [39]	Rituximab +chemotherapy	Rituximab + Etanercept	26	Publication
Castro et al., 2008 [40]	Rituximab + chemotherapy	Rituximab + HDMP	3 (of 14 CLL pts)	Publication
Klepfish et al., 2008 [45]	Rituximab + chemotherapy	Rituximab + FFP	3	Publication

Abbreviations: R-PC: rituximab, pentostatin, cyclophosphamide; R-CD: rituximab, cyclophosphamide, dexamethasone; R-FC: rituximab, fludarabine, cyclophosphamide; FFP: fresh frozen plasma; HDMP: high dose methyprednisolone; A: alemtuzumab; CFAR: cyclophosphamide, fludarabine, alemtuzumab, and rituximab.
† CLL patients treated for autoimmune-hemolytic anemia (AIHA).

Justification for inclusion

These studies have been included to highlight the efficacy of re-treatment with rituximab-containing chemotherapy regimes in patients with relapsed/refractory CLL. Despite the REACH study excluding patients who were previously treated with rituximab or other monoclonal antibodies (rationale explained in section 6.8.4.3), data from more than 200 patients in non-randomized studies

demonstrate that rituximab-containing regimens, specifically repeat administration of R-FC (and variants thereof) are a viable and useful therapeutic option for patients whose initial treatment contained rituximab. These studies are highlighted above in Table 7 and are the key supporting data in the application for the variation to the marketing authorisation that Roche hopes will allow a licence for rituximab in relapsed/refractory CLL in both rituximab naïve and pre-treated patients.

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.

There are no relevant ongoing trials from which additional evidence will be avilable in this time period.

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

Publications identified		**Publications excluded on first screening (all randomised clinical trials including rituximab combination therapy in previously treated CLL aimed to be identified)**	**No. excluded**	**Reasons for exclusion**	**No excluded (1st /2nd stage)**
Medline, EmBase,	213	Based on title	164	Not a trial	141/0
ASH Abstracts via Biosis	85	Based on abstract	184	Duplicates	18/0
Medline in process	19	Based on publication	2	Not CLL	46/0
EmBase Alerts	13				
Cochrane Reviews	20	**Publications excluded at second stage as "irrelevant" to decision problem**		Not a randomised trial including R-chemotherapy in first-line CLL	106/0
EMEA submission	1				
Total	351	Based on abstract	3	Not a comparative RCT	0/3
		Total publications excluded	350	First-line CLL	36/0

Total included: 1 publication (REACH CSR)

Figure 3. CONSORT flow chart detailing selection process for supporting non-randomised studies highlighting the efficacy and tolerability of rituximab in combination with different chemotherapy regimes

Publications identified		**Publications excluded on first screen (all non-randomised clinical trials including rituximab combination chemotherapy for previously treated CLL aimed to be identified)**	**No. excluded**	**Reasons for exclusion**	**No excluded (1st /2nd stage)**
Medline, EmBase,	213	Based on title	96	Duplicates	18/0
ASH Abstracts via Biosys	85	Based on abstract	244	First-line CLL or mixed disease with other indolent B-cell malignancies included	58/0
Medline in process	19	Based on publication	2	Not CLL	46/0
	13				
EmBase Alerts					
Cochrane	20	**Publications excluded at second stage as "irrelevant" to decision problem**		Not a clinical trial	141/0
EMEA submission	1				
Total	351	Based on abstract	N/A	No rituximab	3/0
		Total publications excluded	342	Comparative RCT	1/0
				Trial not consistent with expected licence (eg including maintenance, monotherapy or combination with other antibodies, investigational agents)	75/0

Total included:

9 publications

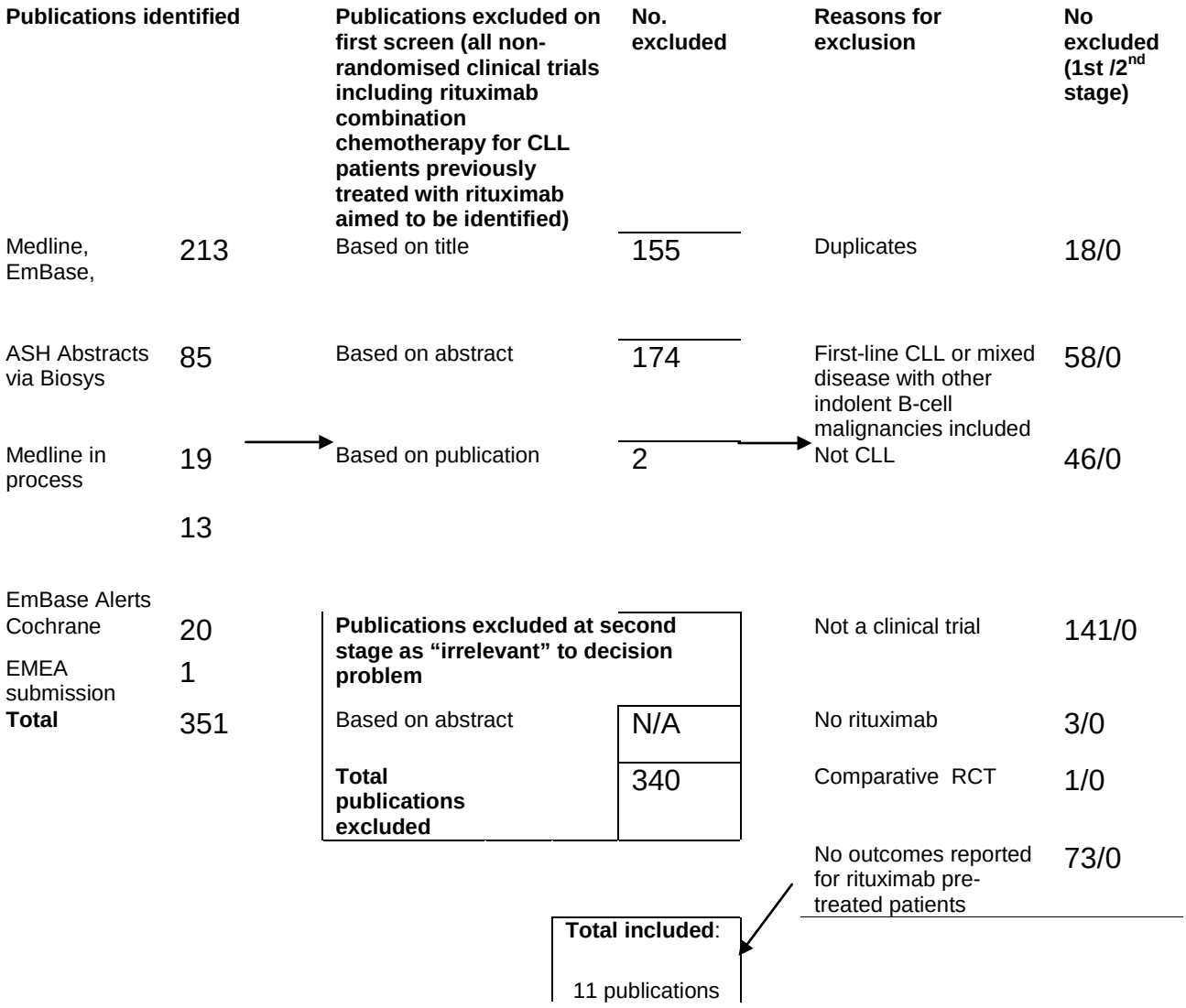
Figure 4. CONSORT flow chart detailing selection process for supporting non-randomised studies highlighing the efficacy of rituximab-containing regimens in patients with fludarabine-refractory CLL

Publications identified		Publications excluded on first screen (all non-randomised clinical trials including rituximab combination chemotherapy for fludarabine-refractory CLL aimed to be identified)	No. excluded	Reasons for exclusion	No excluded (1st /2nd stage)
Medline, EmBase,	213	Based on title	149	Duplicates	18/0
ASH Abstracts via Biosys	85	Based on abstract	176	First-line CLL or mixed disease with other indolent B-cell malignancies included	58/0
Medline in process	19	Based on publication	2	Not CLL	46/0
	13				
EmBase Alerts					
Cochrane	20	**Publications excluded at second stage as "irrelevant" to decision problem**		Not a clinical trial	141/0
EMEA submission	1				
Total	351	Based on abstract	N/A	No rituximab	3/0
		Total publications excluded	340	Comparative RCT	1/0
				No outcomes reported for fludarabine-refractory patients	73/0

Total included:

11 publications

Figure 5. CONSORT flow chart detailing selection process for supporting non-randomised studies highlighting the efficacy of re-treatment with rituximab-containing regimens in patients with relapsed/refractory CLL



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 both 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 previously treated CLL patients in a Phase III setting.

Objectives Stated by the Investigators

The primary objective of study BO17072 (REACH) was:

- To demonstrate a clinically relevant statistical superiority in progression free survival (PFS) with rituximab when used in combination with fludarabine and cyclophosphamide (R-FC) compared with fludarabine and cyclophosphamide alone (FC) for the treatment of previously treated patients with CLL.

Secondary objectives of REACH were:

- To evaluate and compare, in each study arm, event free survival (EFS), disease free survival (DFS) in CR patients, duration of response and ORR (CR, nPR, PR)
- To determine and compare OS for each study arm
- To evaluate and compare the proportion of patients with molecular remission
- To evaluate and compare the safety profile of patients treated with the combination of R-FC versus FC
- To characterize the pharmacokinetics of rituximab, fludarabine and cyclophosphamide
- To evaluate the relationship between various baseline markers and clinical outcome parameters in a subset of patients in each study arm
- To analyze pharmacoeconomics (medical resource utilization) in both treatment arms
- To assess quality of life (QoL) in the two treatment arms.

Overall Design

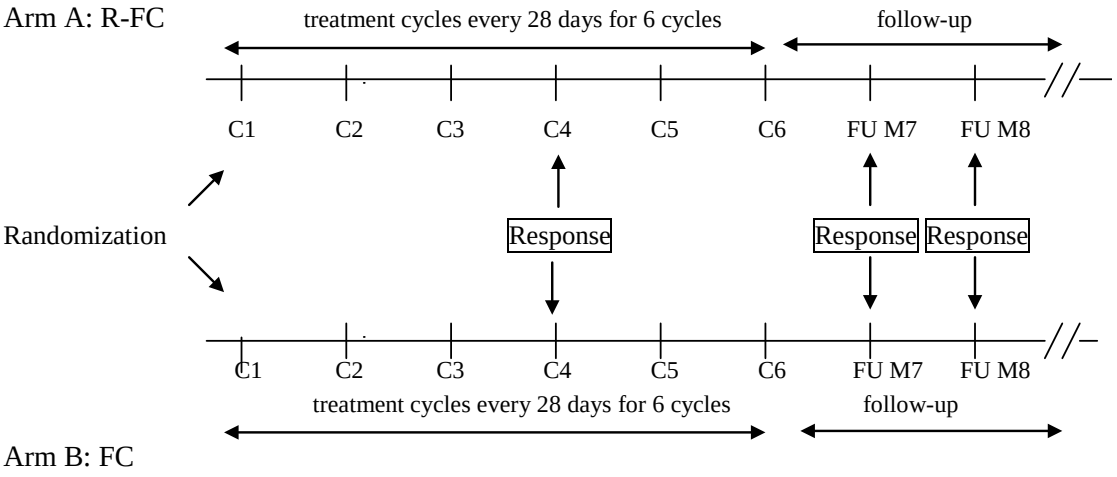
This was a randomized (1:1), multicenter, open-label, comparative, parallel group, two-arm study of R-FC versus FC in patients with previously treated CD20 positive relapsed CLL (according to National Cancer Institute [NCI] criteria). Patients were randomly assigned to treatment groups through a central randomization process, with the majority of patients stratified according to the following stratification factors:

- Country
- Previous treatments (alkylator refractory, alkylator sensitive, fludarabine [or other nucleoside analogue])
- Time from first diagnosis to randomization (< 2 years, < 5 years, < 10 years, ≥ 10 years)
- Beta-2 microglobulin (≤ upper limit of normal [ULN], > ULN).

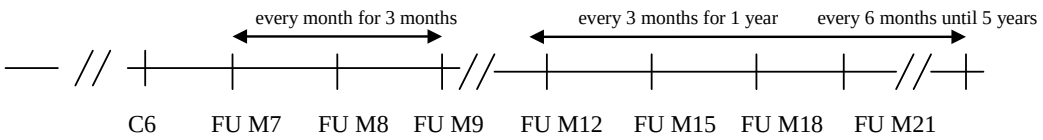
After randomization, patients were scheduled to receive 6 cycles of treatment. Subsequently, there were follow-up visits every month for three months, then every three months until 33 months, every 6 months until 5 years and then every year until 8 years (see Figure 6 below).

Figure 6. Overall Design of REACH

Treatment Phase



Follow-up phase for both arms of the study



NB. From protocol version D onwards, follow-up visits continued 3-monthly until 33 months, 6 monthly until 5 years and then annually until 8 years

Participating Research Groups

The study was sponsored by Roche.

Overall Patient Population Description

Previously treated patients with CD-20 positive CLL.

Number of patients and Recruitment Period

A total of 552 patients were randomized in 88 centres in 17 countries (Australia, Belgium, Canada, Denmark, France, Hungary, Italy, Netherlands, New Zealand, Norway, Poland, Romania, Russia, Spain, Sweden, UK, USA). Patients were recruited between July 31, 2003 and August 10, 2007.

Principal Investigator: Prof Tadeusz Robak, Poland

Blinding

Open-label.

Randomisation Technique

Patients were randomized using a dynamic allocation method (minimization with biased coin assignment) by a central interactive voice response system provided by ClinPhone (ClinPhone Ltd., Meadow Grove, Nottingham NG2 3HF, United Kingdom). The randomisation was stratified according to country, previous treatment, time from first diagnosis to randomization, and beta-2 microglobulin, with patients allocated 1:1 between R-FC and FC treatment groups.

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) q28d. Patients randomized 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.

REACH: Inclusion and Exclusion Criteria

Inclusion Criteria

- Age 18 years or older
- Established diagnosis of B-cell CLL by NCI Working Group criteria

- Patients with CD20 positive B-cell CLL (NCI criteria) who had been previously treated with one of the following chemotherapy regimens:
    - Single agent chlorambucil +/- prednisone/prednisolone,
    - Single agent fludarabine (or other nucleoside analogue),
    - Alkylator-containing combination therapy (eg, CHOP/CVP).

Note: Patients had to have achieved a response (PR or CR) to single agent fludarabine (or other nucleoside analogue) that had lasted at least 6 months (ie, patients had to be fludarabine-sensitive). Patients who had had single agent alkylator therapy or an alkylator regimen could have achieved progressive disease (PD), stable disease (SD), PR or CR as maximal response (ie, be alkylator-refractory or alkylator-sensitive). Alkylator-refractory patients had to have had a minimum exposure to alkylator therapy as detailed in Table 8. Up until the second protocol amendment (out of a total of 5), patients with sequential use of an alkylating agent followed by fludarabine were allowed to enter the study.

- Life expectancy > 6 months
- ECOG performance status 0-1
- ANC $\geq 1 \times 10^9$/L
- Platelet count $\geq 50 \times 10^9$/L
- Creatinine clearance, calculated according to the formula of Cockcroft and Gault $\geq$ 60 mL/min
- Total bilirubin $\leq 2 \times$ ULN
- Alkaline phosphatase and transaminases $\leq 2 \times$ 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.
- Written informed consent.

Patient Population Definitions

The terms fludarabine sensitive, alkylator refractory and alkylator sensitive are defined in Table 8 below.

Table 8. Patient Population Definitions

	Definition	Eligible Patients	Ineligible Patients
Fludarabine (or other nucleoside	Patients must have achieved a response (PR or CR) that lasted at least 6	F → response (PR/CR) →	F+C (concurrent)

analogue) <u>sensitive</u>	months.	relapse (PD)	F+C (sequential) F→ SD/PD F→ Response, but PR/CR <6month duration.
Alkylator <u>Sensitive</u>	Patients must have achieved a PR or CR to previous alkylator therapy	<u>CHOP/CVP</u> → Response (CR/PR) → Relapse (PD) <u>Single course or intermittent use of Chlorambucil</u> – response (PR/CR) → Relapse (PD) whilst off treatment	
Alkylator <u>Refractory</u>	Patients' best response to first line alkylator therapy is PD/SD after a minimum of 8 (PD) to 12 (SD) weeks of single-agent chlorambucil or 2 (PD) to 3 (SD) cycles of alkylator-containing combination therapy. Patients have responded (PR/CR) to initial alkylator therapy but had SD as a response to the last course of alkylator therapy. After last exposure to first line alkylator treatment, patient has: 1) PD after having been treated with a minimum of 8 weeks or 2 cycles of alkylator therapy or 2) SD after having been treated with a minimum of 12 weeks or 3 cycles of alkylator therapy.	<u>CHOP/CVP</u> → Best response is Stable Disease (SD) <u>CHOP/CVP</u> → Progress through therapy (PD) <u>Chlorambucil</u> → respond (PR/CR) to first period of treatment → followed by intermittent use of chlorambucil → no response to last period of chlorambucil ie, PD/SD whilst on therapy	

F = Fludarabine C = Cyclophosphamide

Exclusion Criteria

- Patients who had received prior combination treatment with cyclophosphamide <u>and</u> fludarabine either concurrently or sequentially.

- Patients who were refractory to fludarabine (or any nucleoside analogue). Refractory is defined as not achieving at least a PR for a minimum duration of 6 months.

- Patients who had had prior treatment with interferon, rituximab or another monoclonal antibody

- Patients who had had a prior allogeneic bone marrow transplant (BMT) or autologous BMT or peripheral blood stem cell transplant (PBSCT) or patients who were considered to be candidates for allogeneic or autologous BMT or PBSCT as assessed by his/her treating physician.

- Fertile men or women of childbearing potential not using adequate contraception (oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile)

- Severe Grade 3 or 4 non-hematological toxicity or prolonged (> 2 weeks) Grade 3 or 4 cytopenia on prior fludarabine (or other nucleoside analogue)regimen

- Patients with a history of fludarabine-induced or clinically significant autoimmune cytopenia as assessed by his/her treating physician (Coombs-positive patients without clinical signs of autoimmune hemolytic anemia (AIHA) are eligible for study entry)

- Patients with a history of other malignancies within 2 years prior to study entry, except for adequately treated carcinoma *in situ* of the cervix; basal or squamous cell skin cancer; low grade, early stage localized prostate cancer treated surgically with curative intent; good prognosis DCIS of the breast treated with lumpectomy alone with curative intent.

- Patients with co-morbid conditions that would require long term use (> 1 month) of systemic corticosteroids during study treatment (eg, chronic obstructive pulmonary disease [COPD]). Steroid use $\leq$ 1 month was permissible

- Patients with active bacterial, viral, or fungal infection requiring systemic therapy

- Patients with a history of severe cardiac disease; eg, NYHA Functional Class III or IV heart failure, myocardial infarction within 6 months, ventricular tachyarrhythmias requiring ongoing treatment, or unstable angina

- Seizure disorders requiring anticonvulsant therapy

- Severe COPD with hypoxemia

- Uncontrolled diabetes mellitus

- Uncontrolled hypertension

- Transformation to aggressive B-cell malignancy (eg, large B-cell lymphoma, Richter's syndrome, or prolymphocytic leukemia [PLL])

- Known infection with HIV, hepatitis B or hepatitis C. Although testing for hepatitis B was not mandatory, this was to be considered for all patients considered at high risk of hepatitis B infection and in endemic areas. Patients with *any* serological evidence of current or past hepatitis B exposure were excluded unless the serological findings were clearly due to vaccination

- Treatment with any other investigational agent, or participation in another clinical trial within 30 days prior to entering this study

- Known hypersensitivity or anaphylactic reactions to murine antibodies or proteins

- Any co-existing medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent.

Demographics and Disease Characteristics at Baseline in REACH

Patient demographic characteristics were well balanced across the two treatment arms (Table 9). The overall study population comprised more male than female patients (67% versus 33%, respectively) as would be expected in a CLL patient population, and had a median age of 63 years. The majority of patients (57%) were below the age of 65 years, 26% were $\geq$ 65 and $\leq$ 70 years old, 17% were > 70 years old. The majority of patients were Caucasian, a reflection of the countries in which the study was conducted.

Table 9. Summary of Demographic Data (ITT)

	FC N = 276	R-FC N = 276	ALL N = 552
Sex			
FEMALE	95 (34%)	89 (32%)	184 (33%)
MALE	181 (66%)	187 (68%)	368 (67%)
n	276	276	552
Race			
BLACK	-	-	-
CAUCASIAN	273 (99%)	271 (98%)	544 (99%)
ORIENTAL	-	1 (<1%)	1 (<1%)
OTHER	3 (1%)	4 (1%)	7 (1%)
n	276	276	552
Age (years)			
Mean	61.3	62.1	61.7
SD	9.11	9.17	9.14
Median	62.0	63.0	63.0
Min-Max	35 - 81	35 - 83	35 - 83
n	276	276	552
Age (years) Categories			
< 65	162 (59%)	155 (56%)	317 (57%)
>=65 - <=70	68 (25%)	74 (27%)	142 (26%)
> 70	46 (17%)	47 (17%)	93 (17%)
n	276	276	552
Weight (kg)			
Mean	76.8	76.5	76.7
SD	14.43	15.01	14.71
Median	75.0	76.0	75.0
Min-Max	47 - 126	46 - 127	46 - 127
n	276	276	552
Height (cm)			
Mean	169.6	170.2	169.9
SD	8.81	9.67	9.25
Median	170.0	170.0	170.0
Min-Max	149 - 191	145 - 197	145 - 197
n	271	273	544

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

Baseline Disease Characteristics

Both treatment arms were well balanced with respect to disease stage and ECOG status (Table 10). At baseline, 10% of patients had Binet stage A disease, the majority of patients (59%) had Binet stage B disease and 31% had Binet stage C disease. At pre-therapeutic staging, 60% of patients had an ECOG performance status of 0, 40% of patients had an ECOG of 1. Slightly more patients in the FC arm than in the R-FC arm had B symptoms at baseline (31% FC versus 26% R-FC).

Table 10. Summary of Disease Assessment at Baseline (ITT)

	FC N = 276	R-FC N = 276	ALL N = 552
Binet Stage			
A	31 (11%)	24 (9%)	55 (10%)
B	160 (58%)	166 (60%)	326 (59%)
C	85 (31%)	86 (31%)	171 (31%)
n	276	276	552
B Symptoms			
YES	85 (31%)	72 (26%)	157 (28%)
NO	191 (69%)	204 (74%)	395 (72%)
n	276	276	552
ECOG Status			
0	161 (59%)	169 (61%)	330 (60%)
1	114 (41%)	107 (39%)	221 (40%)
n	275	276	551

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

The median time from first diagnosis was nearly 4 years, as would be expected in patients with CLL, a disease that generally follows a chronic course. Time from diagnosis was similar in the two treatment arms; FC median 3.7 years (range 0.1-23.4 years) and R-FC median 3.8 years (range 0.1-25.2 years). At the time of the first diagnosis, 138 patients [50%] in the FC group and 132 patients [48%] in the R-FC group had Binet stage A disease. The median time from last progression was 1.64 months (range 0.1-46.2 months) for the FC arm and 1.61 months (range 0-28.9 months) for the R-FC arm.

Table 11. Summary Of CLL Diagnosis History (ITT)

Protocol(s): BO17072 (I17072U)
Analysis: ITT Center: ALL CENTERS
Snapshot Date: 16SEP2008 Cutoff Date: 23JUL2008

	FC N = 276	R-FC N = 276	ALL N = 552
Time From First Diagnosis* (Years)			
Mean	4.70	4.80	4.75
SD	3.782	3.984	3.881
Median	3.69	3.79	3.73
Min-Max	0.1 - 23.4	0.1 - 25.2	0.1 - 25.2
n	276	276	552
Time From First Diagnosis* (Years)			
< 2	73 (26%)	71 (26%)	144 (26%)
2- <5	98 (36%)	100 (36%)	198 (36%)
5- <10	77 (28%)	75 (27%)	152 (28%)
>=10	28 (10%)	30 (11%)	58 (11%)
n	276	276	552
Binet Stage At First Diagnosis			
A	138 (50%)	132 (48%)	270 (49%)
B	81 (29%)	90 (33%)	171 (31%)
C	17 (6%)	24 (9%)	41 (7%)
UNKNOWN	40 (14%)	30 (11%)	70 (13%)
n	276	276	552
Binet Stage At Baseline			
A	31 (11%)	24 (9%)	55 (10%)
B	160 (58%)	166 (60%)	326 (59%)
C	85 (31%)	86 (31%)	171 (31%)
n	276	276	552
Time From Last Progression* (Months)			
Mean	3.39	3.04	3.21
SD	5.378	3.991	4.733
Median	1.64	1.61	1.61
Min-Max	0.1 - 46.2	0.0 - 28.9	0.0 - 46.2
n	274	275	549
n	276	274	550

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
* - Until randomization.
Time from first diagnosis uses imputation of day (set to 15)
and month (set to 30th June) where missing.
Time from last progression uses imputation of day (set to 15) where missing.
inclusion criteria only up to protocol amendment C.

As would be expected, almost all patients that had bone marrow assessments (261/272 patients [96%] in the FC arm and 265/270 patients [98%] in the R-FC arm) had bone marrow involvement, and the percentage of patients with diffuse, nodular or diffuse and nodular involvement was similar in both arms.

Baseline Tumor Assessments

At baseline, more patients in the FC arm (83/274 [30%] versus 66/275 patients [24%] in the R-FC arm) had hepatomegaly, Table 12. At baseline, the majority of patients in both groups had splenomegaly (175/275 [64%] FC versus 191/274 [70%] R-FC). In both arms, 20/276 patients (7%) had extranodal disease and 21/276 (8%) had bulky disease. The treatment groups were well balanced with regards to baseline tumor assessments – the slight difference in hepatomegaly being counterbalanced by the slight difference in splenomegaly in the opposite direction.

Table 12. Summary Of Tumor Assessment At Baseline (Part I) (ITT)

	FC N = 276	R-FC N = 276	ALL N = 552
Hepatomegaly			
YES	83 (30%)	66 (24%)	149 (27%)
NO	191 (70%)	209 (76%)	400 (73%)
n	274	275	549
Splenomegaly			
YES	175 (64%)	191 (70%)	366 (67%)
NO	100 (36%)	83 (30%)	183 (33%)
n	275	274	549
Extranodal Lesions			
YES	20 (7%)	20 (7%)	40 (7%)
NO	256 (93%)	256 (93%)	512 (93%)
n	276	276	552
Bulky Disease*			
YES	21 (8%)	21 (8%)	42 (8%)
NO	255 (92%)	255 (92%)	510 (92%)
n	276	276	552

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
* The threshold for declaring a lesion was 7.5 cm

Baseline Laboratory Data

Baseline hematology values were well balanced between both treatment arms (Table 13). Hemoglobin was ≤ 10 g/dL in 16% of patients and platelet counts were ≤ 100 x 10^9/L in 28% of patients. Approximately half of the patients (44%) had lymphocyte counts > 50 x 10^9/L at study entry. Slightly more patients in the R-FC arm (27%) than the FC arm (21%) had lymphocyte counts in the range 50-100 x 10^9/L.

Table 13. Summary of Hematology at Baseline (Categorized, ITT)

	FC N = 276	R-FC N = 276	ALL N = 552
Hemoglobin (g/dL)			
<=10	43 (16%)	44 (16%)	87 (16%)
> 10	227 (84%)	230 (84%)	457 (84%)
n	270	274	544
Platelets (10**9/L)			
<=100	74 (27%)	79 (29%)	153 (28%)
>100	198 (73%)	195 (71%)	393 (72%)
n	272	274	546
Lymphocytes (10**9/L)			
0-25	97 (36%)	89 (33%)	186 (34%)
> 25-50	60 (22%)	58 (21%)	118 (22%)
> 50-100	57 (21%)	74 (27%)	131 (24%)
>100	57 (21%)	52 (19%)	109 (20%)
n	271	273	544

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

.

Standard laboratory tests other than hematology parameters (beta-2 microglobulin, lactate dehydrogenase [LDH] and Coombs test) were balanced between the treatment arms at baseline, Table 14.

Table 14. Summary Of Beta-2 Microglobulin, LDH And Coombs Test At Baseline (ITT)

Protocol(s): BO17072 (I17072U)
Analysis: ITT Center: ALL CENTERS
Snapshot Date: 16SEP2008 Cutoff Date: 23JUL2008

	FC N = 276	R-FC N = 276	ALL N = 552
Beta2-Microglobulin (mg/L)			
Mean	3.9	4.0	4.0
SD	2.10	2.39	2.25
Median	3.5	3.4	3.5
Min-Max	0 - 17	0 - 16	0 - 17
n	263	268	531
Beta2-Microglobulin (>ULN)			
YES	205 (78%)	203 (76%)	408 (77%)
NO	58 (22%)	65 (24%)	123 (23%)
n	263	268	531
LDH (U/L)			
Mean	371.0	360.4	365.6
SD	216.66	204.76	210.61
Median	341.0	329.0	334.0
Min-Max	96 - 2228	98 - 2463	96 - 2463
n	269	274	543
LDH (>ULN)			
YES	98 (36%)	91 (33%)	189 (35%)
NO	171 (64%)	183 (67%)	354 (65%)
n	269	274	543
Direct Or Indirect Coombs Test			
POSITIVE	27 (10%)	35 (14%)	62 (12%)
NEGATIVE	236 (90%)	224 (86%)	460 (88%)
n	263	259	522

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

Calculated creatinine clearance (Cockcroft-Gault) values at baseline were balanced in both treatment arms, and overall, the majority of patients (86% in FC, 84% R-FC) had creatinine clearance values of $\geq$ 60 mL/min (

Table 15).

Creatinine clearance was calculated locally by the investigator and during the study the protocol was amended to include patients with a lower creatinine clearance in order to improve recruitment. The creatinine clearance requirement was subsequently increased back to 60 mL/min. The intervening period accounts for many of the patients with a creatinine clearance $\geq$ 50 and $\leq$ 60 mL/min. Patients entering the study with a creatinine clearance < 50 mL/min entered in violation of the protocol.

Table 15. Summary Of Creatinine Clearance Values At Baseline (Categorized) (ITT)

Protocol(s): BO17072 (I17072U)
Analysis: ITT Center: ALL CENTERS
Snapshot Date: 16SEP2008 Cutoff Date: 23JUL2008

	FC N = 276	R-FC N = 276	ALL N = 552
Estimated creatinine clearance (ml/min)			
< 50	9 (3%)	12 (4%)	21 (4%)
>=50 - <60	29 (11%)	32 (12%)	61 (11%)
>=60 - <70	52 (19%)	60 (22%)	112 (21%)
>=70	180 (67%)	169 (62%)	349 (64%)
n	270	273	543

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

Additional Baseline Prognostic Factors

Overall, the distribution of prognostic parameters was as expected for the population and was relatively balanced between the treatment arms (Table 16). Sixty-three percent of patients had unmutated IgVH at baseline (65% on FC and 61% on R-FC) and 42% in each treatment arm were ZAP-70-positive.

Analysis of the two prognostic factors in combination did not reveal any major imbalances in subgroups between the treatment arms. This is especially true for patients with the worst prognostic combination (IgVH unmutated and ZAP-70-positive, 38% on FC versus 36% on R-FC).

Table 16. Summary of IgVH Status and ZAP-70 at Baseline (ITT)

	FC N = 276	R-FC N = 276	ALL N = 552
IgVH			
MUTATED	92 (35%)	100 (39%)	192 (37%)
UNMUTATED	170 (65%)	158 (61%)	328 (63%)
n	262	258	520
ZAP-70			
POSITIVE	84 (42%)	89 (42%)	173 (42%)
NEGATIVE	115 (58%)	122 (58%)	237 (58%)
n	199	211	410
ZAP-70/IgVH			
POSITIVE/MUTATED	8 (4%)	13 (6%)	21 (5%)
POSITIVE/UNMUTATED	76 (38%)	73 (36%)	149 (37%)
NEGATIVE/MUTATED	62 (31%)	72 (35%)	134 (33%)
NEGATIVE/UNMUTATED	53 (27%)	47 (23%)	100 (25%)
n	199	205	404

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

Overall, cytogenetic abnormalities were also relatively balanced between the treatment arms (Table 17). In the FC arm, there were slightly more patients with the more favorable chromosomal aberrations del(13q) [60% FC versus 56% R-FC] and trisomy 12 [15% FC versus 11% R-FC]. Patients with the more unfavorable del(17p) and del(11q) aberrations were relatively equally distributed between the treatment arms [9% FC versus 7% R-FC for del(17p) and 22% FC versus 21% R-FC for del(11q)].

Patients with a complex karyotype (≥ 2 cytogenetic abnormalities) were more frequent in the FC arm than in the R-FC arm (23% on FC versus 18% on R-FC) and patients with no cytogenetic abnormalities were more frequent in the R-FC arm than in the FC arm (18% on FC versus 27% on R-FC), Table 17.

Table 17. Summary of Cytogenetic Abnormalities (ITT)

	FC N = 276	R-FC N = 276	ALL N = 552
Del11q			
YES	59 (22%)	56 (21%)	115 (22%)
NO	204 (78%)	214 (79%)	418 (78%)
n	263	270	533
Del13q			
YES	159 (60%)	150 (56%)	309 (58%)
NO	105 (40%)	120 (44%)	225 (42%)
n	264	270	534
Del17p			
YES	24 (9%)	18 (7%)	42 (8%)
NO	239 (91%)	251 (93%)	490 (92%)
n	263	269	532
Trisomy 12			
YES	40 (15%)	29 (11%)	69 (13%)
NO	223 (85%)	241 (89%)	464 (87%)
n	263	270	533
Number Of Cytogenetic Abnormalities			
0	47 (18%)	72 (27%)	119 (22%)
1	157 (59%)	150 (56%)	307 (57%)
2	59 (22%)	42 (16%)	101 (19%)
3	1 (<1%)	6 (2%)	7 (1%)
4	1 (<1%)	-	1 (<1%)
n	265	270	535

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

Immunophenotyping at Baseline

Detailed baseline immunophenotyping data was requested at study entry and the study patients were considered to have fulfilled the criteria for CD20 positive CLL if they were either CD20 positive or CD5/CD20 positive (cut-offs for positivity defined as at least 20%). The great majority of patients (96% overall, Table 18) were documented to be CD20 positive at baseline.

A higher proportion of patients in the R-FC arm were CD38-positive (91/160 [57%] on R-FC versus 79/164 [48%] on FC). CD38 positivity is a marker of poor prognosis. However, evaluation of CD38 expression was optional in this study and, therefore, data is not available for all patients.

Table 18. Summary of Lymphocyte Immuno-phenotyping at Baseline (ITT)

	FC N = 276	R-FC N = 276	ALL N = 552
CD20 Positive			
YES	244 (95%)	253 (98%)	497 (96%)
NO	13 (5%)	6 (2%)	19 (4%)
n	257	259	516
CD38+			
POSITIVE	79 (48%)	91 (57%)	170 (52%)
NEGATIVE	85 (52%)	69 (43%)	154 (48%)
n	164	160	324

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Positive - either gated or total value greater than or equal to 20%.
CD20 positive - either CD20+ or CD5+/CD20 positive.

Previous or Concurrent Diseases

Most patients in each treatment group were recorded to have a previous or concurrent disease (84% FC versus 83% R-FC) in addition to CLL. The types and frequencies of diseases were similar in the two treatment arms, Table 19.

Table 19. Summary Of Previous And Concomitant Diseases By Superclass Term (ITT)

Body System/ Disease	FC N = 276 No. (%)	R-FC N = 276 No. (%)
ALL BODY SYSTEMS	231 (84)	229 (83)
VASCULAR DISORDERS	98 (36)	105 (38)
METABOLISM AND NUTRITION DISORDERS	59 (21)	70 (25)
GASTROINTESTINAL DISORDERS	60 (22)	68 (25)
INFECTIONS AND INFESTATIONS	68 (25)	57 (21)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	60 (22)	52 (19)
SURGICAL AND MEDICAL PROCEDURES	43 (16)	45 (16)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	45 (16)	40 (14)
CARDIAC DISORDERS	40 (14)	43 (16)
IMMUNE SYSTEM DISORDERS	36 (13)	37 (13)
PSYCHIATRIC DISORDERS	39 (14)	28 (10)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	29 (11)	30 (11)
NERVOUS SYSTEM DISORDERS	25 (9)	28 (10)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	23 (8)	27 (10)
RENAL AND URINARY DISORDERS	20 (7)	26 (9)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	26 (9)	20 (7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	20 (7)	21 (8)
HEPATOBILIARY DISORDERS	23 (8)	15 (5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	16 (6)	20 (7)
EYE DISORDERS	13 (5)	19 (7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	15 (5)	15 (5)
ENDOCRINE DISORDERS	17 (6)	11 (4)
INVESTIGATIONS	11 (4)	7 (3)
EAR AND LABYRINTH DISORDERS	7 (3)	9 (3)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	6 (2)	9 (3)
SOCIAL CIRCUMSTANCES	3 (1)	2 (<1)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	-	1 (<1)

Investigator text for Concurrent Diseases encoded using MedDRA version 11.0.
Percentages are based on N.

Previous and Concomitant Medications

Previous Treatments for CLL

Patients were categorized by the investigator at study entry according to their response/resistence to prior therapy and these categories were used for stratification. These data are summarized in Table 20.

Overall, the use of anti-CLL treatment prior to study entry was balanced between the treatment arms. The majority of patients (56%) were classified as alkylator-sensitive by the investigator, 26% were classified as alkylator refractory, 16% as having received prior fludarabine, and 1% as having received sequential fludarabine and alkylating agents (before the second protocol amendment).

The majority of patients (452/552 [82%]) had had prior monotherapy: 363/552 patients (66%; 178 patients [32%] R-FC, 185 patients [34%] FC) had been treated with chorambucil, cyclophosphamide or another alkylating agent (including bendamustine and prednimustine) and 87/552 patients (16%; 40 patients [7%] R-FC, 47 patients [9%] FC) had been treated with fludarabine, cladribine or both. Only 100/552 patients (18%; 58 patients [10%] R-FC, 44 patients [8%] FC) had had prior multi-agent chemotherapy, including 14/552 (2.5%) who had been treated with fludarabine/cladribine combinations and 88/552 (16%) who had been treated with “other” agents. Only one patient had been previously treated with rituximab (a single dose 2 years prior to study entry, in addition to CHOP) – this patient was granted a waiver to enter the study and was randomized to the FC arm.

Table 20. Summary Of Previous Chemotherapy Category (ITT)

	FC N = 276	R-FC N = 276	ALL N = 552
Previous Chemotherapy			
ALKYLATOR REFRACTORY	71 (26%)	74 (27%)	145 (26%)
ALKYLATOR SENSITIVE	155 (56%)	152 (55%)	307 (56%)
FLUDARABINE	47 (17%)	43 (16%)	90 (16%)
SEQUENTIAL ALKYLATING AGENTS AND FLUDARABINE	3 (1%)	5 (2%)	8 (1%)
n	276	274*	550
Single Agent Chemotherapy			
YES	231 (84%)	221 (80%)	452 (82%)
NO	45 (16%)	55 (20%)	100 (18%)
n	276	276	552

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

*2 patients had blank entries for this data field on the CRF;
Patient 36931/3313 previous chemotherapy = alkylator sensitive
Patient 36929/3105 previous chemotherapy = sequential

Previous Treatments Not Associated with CLL

The types of previous treatments not associated with CLL and the numbers of patients treated were similar across treatment arms. Overall, the previous treatments are a reflection of the previous diseases seen in the study population and expected in a population of this age.

Concomitant Treatments

All patients who received study medication also received other concomitant treatments. Overall, the most common medications were antibacterial agents (94% FC versus 93% R-FC), antiviral agents (82% FC versus 86% R-FC), uricosuric/uricostatic (prophylaxis for tumour lysis syndrom) agents (76% FC versus 82% R-FC) and 5-HT3 antagonists (76% FC versus 74% R-FC). The profile of concomitant medications was similar for both treatment arms, apart from corticosteroids, antihistamines and analgesics, which were used as premedication for patients receiving rituximab and colony stimulating factors which were used more frequently in the R-FC arm. During Cycles 1-6, 1%-7% more patients in the R-FC arm received colony stimulating factors compared to the FC arm (Table 21), and overall, 9% more patients in the R-FC arm received colony stimulating factors (49% in FC, 58% in R-FC).

Table 21. Number Of Patients Receiving Treatments Of 'Class Colony Stimulating Factors' By Cycle

	FC N=272 No. (%)	R-FC N=274 No. (%)	ALL N=546 No. (%)
Cycle 1:			
Yes	49 (18%)	51 (19%)	100 (18%)
No	223 (82%)	223 (81%)	446 (82%)
Total	272 (100%)	274 (100%)	546 (100%)
Cycle 2:			
Yes	57 (21%)	67 (24%)	124 (23%)
No	194 (71%)	195 (71%)	389 (71%)
Total	251 (92%)	262 (96%)	513 (94%)
Cycle 3:			
Yes	70 (26%)	81 (30%)	151 (28%)
No	166 (61%)	169 (62%)	335 (61%)
Total	236 (87%)	250 (91%)	486 (89%)
Cycle 4:			
Yes	59 (22%)	79 (29%)	138 (25%)
No	150 (55%)	149 (54%)	299 (55%)
Total	209 (77%)	228 (83%)	437 (80%)
Cycle 5:			
Yes	57 (21%)	74 (27%)	131 (24%)
No	140 (51%)	138 (50%)	278 (51%)
Total	197 (72%)	212 (77%)	409 (75%)
Cycle 6:			
Yes	43 (16%)	52 (19%)	95 (17%)
No	124 (46%)	133 (49%)	257 (47%)
Total	167 (61%)	185 (68%)	352 (64%)

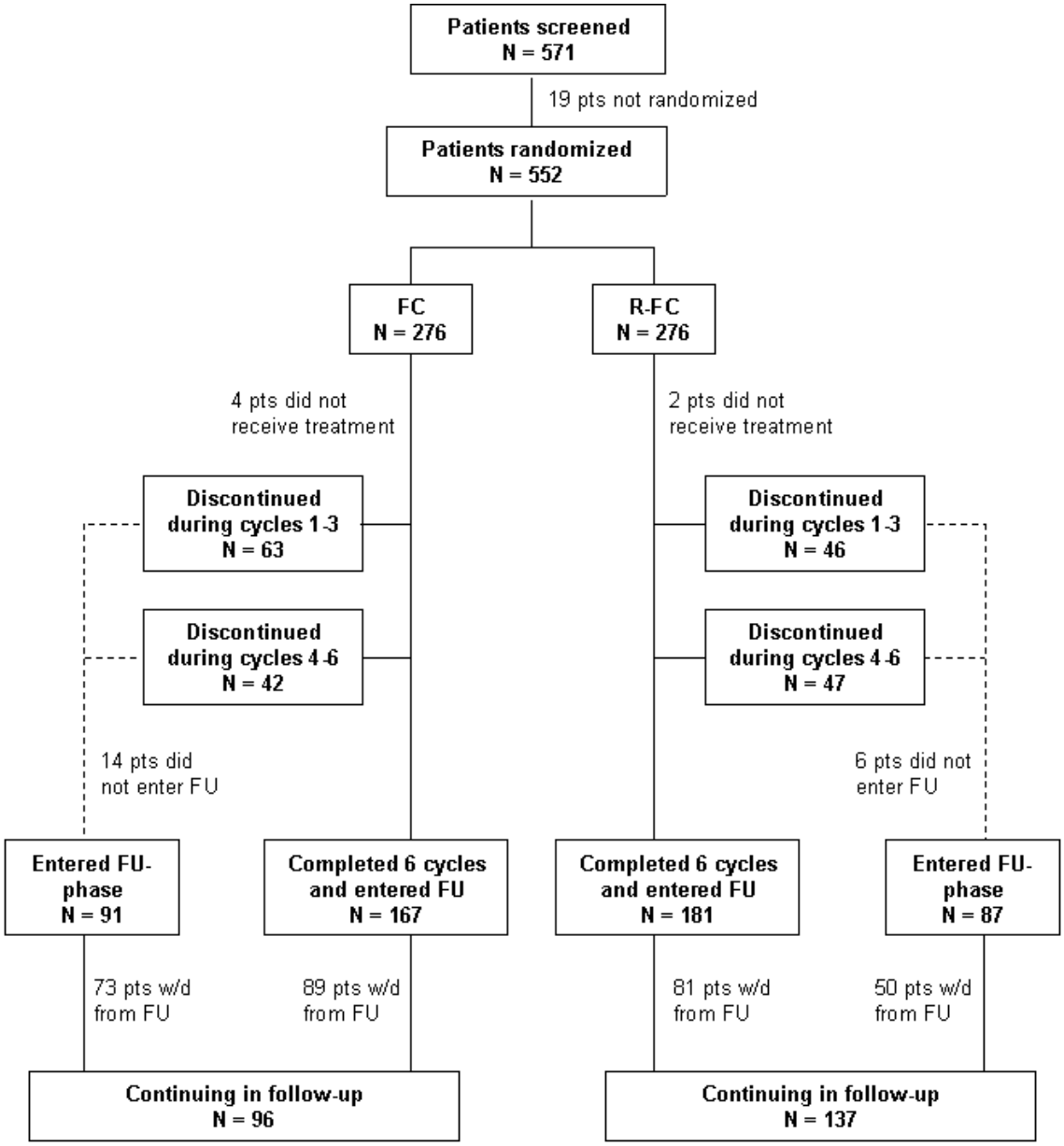
- This summary table contains only patients who were treated with study medication
- This summary table considers only the start date of the treatment with colony stimulating factors. If the treatment continues over two or more cycles a patient will appear only in the summary statistic of the cycle where the treatment started
- includes Granulocyte Colony Stimulating Factors and EPO

The high usage of antibacterial and antiviral agents was as expected based on protocol requirements for prophylactic antibiotics / antivirals in all patients, and prophylactic treatment for tumour lysis syndrome, which was initially discretionary but became mandatory for all patients after protocol version F (Dec 5 2006). Otherwise the concomitant treatments given in REACH reflect the concurrent diseases in the study population and were as expected in a population of this age.

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 7. Patient Disposition



Abbreviations: pts, patients; FU, follow-up; w/d, withdrawn

From a total of 571 patients screened, 552 patients were enrolled and randomized in this two-arm study: 276 patients per arm. Only 19 patients did not meet screening criteria and this was due mainly to their first line treatment which

made them ineligible for the study. Patients were recruited at 88 centers in 17 countries: Australia, Belgium, Canada, Denmark, France, Hungary, Italy, Netherlands, New Zealand, Norway, Poland, Romania, Russia, Spain, Sweden, UK, USA. The majority of the patients were enrolled in France (87 patients, 16% of the total), Russia (78 patients, 14%), Poland (74 patients, 13%) and Canada (56 patients, 10%). All other countries recruited between 16 and 36 patients (3%-7% of the total) apart from Sweden, the US and Norway, where 6 (1%), 2 (< 1%) and one (< 1%), patient were recruited, respectively. The first patient was randomized on July 31, 2003 and the last on August 10, 2007.

A total of 6 randomized patients (4 patients FC, 2 patients R-FC) did not receive any study treatment. In the FC arm, 3 patients refused treatment and 1 patient did not meet one of the entry criteria (had more than one previous line of chemotherapy). In the R-FC arm, one patient became ill before receiving any treatment (AIHA) and the other patient had violations of entry criteria (creatinine clearance and neutrophil count).

A slightly lower number of patients in the FC arm than in the R-FC arm completed 6 cycles of treatment, 167 FC versus 181 R-FC, and fewer patients in the FC arm than in the R-FC arm are still being followed for progression and survival (overall 96 patients in FC versus 137 patients in R-FC), Figure 7. The reasons for and the timings of premature withdrawals are discussed below.

Patients Withdrawn Prematurely from the Study

Patients Prematurely Discontinuing Trial Treatment

Overall, more patients in the FC arm than the R-FC arm prematurely discontinued trial treatment (109 patients [39%] on FC versus 95 patients [34%] on R-FC). Treatment discontinuations due to safety reasons were balanced between the treatment arms (29% in each arm). Ten and 7 patients on FC and R-FC, respectively, died during the treatment phase.

Study treatment discontinuations due to non-safety reasons were more frequent in the FC arm than in the R-FC arm (29 patients [11%] versus 16 patients [6%]). This was mostly due to more patients in the FC arm withdrawing due to insufficient therapeutic response (13 patients on FC versus 4 patients on R-FC), and more patients in the FC arm who refused study treatment (11 patients on FC versus 2 patients on R-FC).

Of the patients who refused treatment, both patients in the R-FC arm had completed 3 cycles of treatment at the time of refusal; one had SD and the other had achieved a PR. In comparison, three patients who refused treatment on the FC arm did so immediately after randomization, with another patient refusing treatment after 2 cycles in order to have rituximab-containing therapy. Six patients refused after 1 cycle for unspecified reasons. A single patient refused after 2 cycles (no details available) with another refusing after 4 cycles having achieved a CR (after 3 cycles of treatment).

Of the 5 patients who withdrew from R-FC for “other reasons”, one patient was withdrawn at the investigator’s discretion due to myelosuppression, another had study treatment delayed for > 2 weeks despite having only Grade 2 neutropenia, another was withdrawn due to a misunderstanding of how many cycles of

treatment he had had, another chose to withdraw and another withdrew at the investigator's discretion at Cycle 3 having achieved a CR.

Table 22. Summary of Premature Discontinuation of Trial Treatment (ITT)

Reason for Withdrawal	FC N = 276 No. (%)	R-FC N = 276 No. (%)
Safety	80 (29)	79 (29)
Adverse Event(a)	70	72
Death	10	7
Non-Safety	29 (11)	16 (6)
Insufficient Therapeutic Response	13	4
Early Improvement	2	0
Violation of Selection Criteria at Entry	3	3
Other Protocol Violation	0	1
Refused Treatment(b)	11	2
Failure to Return	0	1
Other	0	5
Total	109 (39)	95 (34)

(a)=Including intercurrent illness (b)=Including 'did not co-operate', 'withdrew consent'
Percentages are based on N.
Patients who never received trial treatment are included.

An analysis of withdrawals at each cycle did not reveal any unexpected trends. Withdrawals during Cycle 1 were higher in the FC arm than in the R-FC arm (8% versus 4%) and, the main reasons for withdrawal in both arms was AE/intercurrent illness (4% versus 3%). Withdrawals from the FC arm fell to 5% during Cycle 2 and continued at 4% in the R-FC arm. Withdrawals during Cycle 3 were higher in both the FC arm (10%) and the R-FC arm (8%) (this was the time patients with stable disease could stop treatment according to protocol) and dropped again during Cycle 4 to 4% in FC and 6% in R-FC. During Cycle 5, withdrawals increased again in both treatment arms to 11% in FC and 10% in R-FC. The only withdrawals during Cycle 6 were from the R-FC arm (3 patients for AEs and 1 death).

During the first 3 cycles of treatment, 42/276 patients (15%) withdrew from the FC arm and 37/276 (13%) patients withdrew from the R-FC arm for safety reasons, ie, AEs and deaths. A higher proportion of patients withdrew from the FC arm due for non-safety reasons, 21/276 (8%) compared to 9/276 patients (3%) in the R-FC arm. The withdrawal rate during Cycles 1-3, was higher than during Cycles 4-6. Withdrawals for safety and non-safety reasons during Cycles 4-6 were balanced in both treatment arms.

Patients Withdrawn Prematurely from the Follow-up Phase

For this and most other analyses, the follow-up phase was defined as starting 28 days after the last dose of study medication (ie, end of last cycle). Of the total of 526 patients (258 in FC and 268 in R-FC) who entered the follow-up phase, more patients in the FC arm than in the R-FC arm were withdrawn early (162/258 [63%] FC versus 131/268 [49%] in R-FC) (Table 23). The main cause of withdrawal from follow-up was, as expected, insufficient therapeutic response (ie, PD) (118/258 [46%] patients in the FC arm versus 96/268 [36%] in the R-FC arm) or death (20/258 [8%] FC versus 27/268 [10%] R-FC). Nine patients in the FC arm and 6 patients in the R-FC arm were withdrawn from follow-up for

withdrawing consent. Only 2 patients in the FC arm and 1 patient in the R-FC arm withdrew due to non-fatal AEs.

Table 23. Summary Withdrawals from the Follow-up Phase Patients Entering FU Phase Only (ITT)

Reason for Withdrawal	FC N = 258 No. (%)	R-FC N = 268 No. (%)
Safety	22 (9)	28 (10)
Adverse Event(a)	2	1
Death	20	27
Non-Safety	140 (54)	103 (38)
Insufficient Therapeutic Response	118	96
Refused Treatment(b)	9	6
Failure to Return	5	1
Other	8	0
Total	162 (63)	131 (49)

(a)=Including intercurrent illness (b)=Including 'did not co-operate', 'withdrew consent'
Percentages are based on N.
Patients with a last date alive greater than 28 days after the last dose are considered to have entered the follow-up phase.
(Last date alive is the last date at which the patient was documented to be alive on the CRF based on all assessments including survival follow-up).

Of the 8 patients in the FC arm who withdrew from follow-up for “other” reasons, one patient was withdrawn after progressing and receiving a new treatment for CLL, another was withdrawn after the sponsor requested study treatment discontinuation after 1 cycle (the patient had Coomb’s-positive symptomatic hemolytic anemia at baseline and should not have entered the study. The hemolytic anemia rapidly worsened after FC), another was relocated to another country, another was diagnosed with PLL upon study entry and was excluded from the study, another received another treatment, another received a subsequent treatment for Richter’s syndrome, another was too ill to follow the study procedures, and another was withdrawn at the investigator’s discretion.

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 prespecified 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 REACH: Primary and Secondary Endpoints (as stated in Clinical Study Report)

Primary Parameter - Progression-Free Survival

The primary efficacy parameter was PFS, as assessed by the study investigator. Progression-free survival was measured from the date of randomization to the date of first documented disease progression, relapse after response, or death from any cause (ie, PFS event). Patients without a PFS event were censored at their last tumor assessment date. Start of a new CLL treatment after the randomized study treatment was not counted as an event or as a reason for censoring. In all patients (even if on new CLL treatment), response had to be assessed at each visit until progression was documented. Patients with stable disease were not considered as having had an event.

Secondary Parameters

Overall Survival

Overall survival was determined from the date of randomization to the date of death irrespective of cause. Patients who had not died at the time of the final analysis (clinical data cut-off) were censored at the date of the last contact.

Event Free Survival

Event free survival was measured from the day of randomization to the date of first documented PD, relapse after response, start of a new treatment or death from any cause (ie, EFS event). Patients without an EFS event were censored at their last tumor assessment date.

Disease Free Survival

Disease free survival was defined for all patients with a best overall response (BOR) of CR and measured the time from first documented CR in a sequence of consecutive CRs until documented disease progression, relapse or death from any cause (ie, a DFS event). Patients without a DFS event at the time of the analysis (clinical data cut-off) were censored at their last tumor assessment date.

Duration of Response

Duration of response is defined for all patients with a BOR (see paragraph below on Response Rates) of CR, nPR, PR and measures the time from the very first CR, nPR or PR to the time of documented disease relapse, progression or death from any cause (ie, DOR event). Patients without a DOR event at the time of the analysis (clinical data cut-off) were censored at their last tumor assessment date.

Time to New Treatment

Time to new treatment was measured from the date of randomization to the date of first start of a new treatment or death by any cause (ie, time to new treatment event). Patients without a DOR event at the time of the analysis (clinical data cut-off) were censored at the date of last contact.

Response rates

Response was assessed by the investigator and by an independent central review committee according to the NCI Working Group guidelines.

Tumor assessments were to be made at screening, after Cycle 3 and Cycle 6, at confirmation of response (~month 9), and then every 3 months until 33 months, every 6 months until 5 years (with an additional visit at 60 months), and at least yearly thereafter until progression or death. CT scans were to be performed at regular intervals but not at every disease assessment. The response assessments assigned by the investigator at each time point were used to calculate for each patient:

A best overall response (BOR)

An end of treatment response (ETR)

The reason for having two categories of response was to allow for the sometimes slow recovery of cytopenias after fludarabine-based therapy.

Best overall response (BOR) was defined as the patient's best response at any time during the study prior to first PD or subsequent CLL treatment. A patient was defined as a responder if he/she had a complete or partial response on two consecutive occasions at least 49 days apart. However, only one normal bone marrow was required to confirm the CR. Patients fulfilling all the criteria for a confirmed CR but with histologically identified nodules in the bone marrow were classified as nodular PRs (nPRs) and included with the PRs.

End of treatment response (ETR) was defined as the patient's response after completion of treatment, using a time window of up to 7 months after the end of treatment. A patient was defined as a responder if he/she had a complete or partial response on two consecutive occasions at least 49 days apart, with at least one of the two required consecutive response assessments occurring before the end of this period and prior to first PD or subsequent CLL treatment. Disease assessments during treatment (notably the post-Cycle 3 assessment) were also taken into consideration in patients with less than 2 response assessments during the 7 month period after the end of treatment. Only one normal bone marrow was required for a confirmed CR. Patients fulfilling all the criteria for a confirmed CR but with histologically identified nodules in the bone marrow were classified as nodular PRs (nPRs) and included with the PRs.

For both ETR and BOR, any assessments after initiation of alternative treatment for CLL were ignored. Patients with a single assessment of CR or PR (ie, an unconfirmed CR or PR) were considered non-evaluable for BOR and/or ETR.

For both endpoints, all patients with a response of CR or PR were regarded as responders, and patients with a response of SD or PD were considered non-responders. Patients without any response assessments (due to any reason) and patients who were non-evaluable for response (single assessment of CR or PR) were considered non-responders.

Molecular Response was only assessed in patients with clinical CR. A patient was defined as a molecular responder (ie, no detectable minimal residual disease

[MRD-negative]) if there was no evidence of IgVH gene rearrangement in peripheral blood or bone marrow after treatment.

Further secondary ***objectives*** included:

- To evaluate and compare the safety profile of patients treated with the combination of R-FC versus FC
- To characterize the pharmacokinetics of rituximab, fludarabine and cyclophosphamide
- To evaluate the relationship between various baseline markers and clinical outcome parameters in a subset of patients in each study arm
- To analyze pharmacoeconomics (medical resource utilization) in both treatment arms (see Section 7)
- To assess quality of life (QoL) in the two treatment arms.

Pharmacokinetic Assessment

Pharmacokinetic (PK) sampling was optional and was performed at selected sites only. It was planned to obtain plasma for the PK analysis of cyclophosphamide and fludarabine from the same subset of approximately 40 patients being sampled for rituximab PK during Cycle 3 of the study. Blood samples would be taken at the following timepoints: Cycle 3 pre-dose**,** immediately prior to the end of infusion, and at 0.5, 1, 1.5, 2, 4, 8 and 12 hours timed from the end of the infusion. It was also planned to obtain plasma for PK analyses of cyclophosphamide and fludarabine from a subset of 40 patients from the FC arm of the study: 20 with high tumor burden (defined as lymphocyte count $\geq 25 \times 10^9$/L) and 20 with low tumor burden (defined as lymphocyte count $< 25 \times 10^9$/L) during Cycle 3 of the study. Blood samples were taken on day 3.

It was also planned to obtain serum for PK analysis of rituximab from a sub-set of 40 patients in the R-FC arm: 20 each with high tumor burden (lymphocyte count $\geq 25 \times 10^9$/L) and low tumor burden (lymphocyte count $< 25 \times 10^9$/L) during Cycles 1, 3 and 6 of the study. During Cycles 1, 3 and 6, blood samples were obtained predose, and at 8 (immediately prior to end of infusion), 11, and 24 hours, and on Days 3, 5, 7, 14, 21 and 28 (samples could be taken at any time during the day but the exact time was recorded in the CRF). Samples scheduled on Days 7, 14 and 21 could be taken on Days 8, 15 and 22, if preferred. Following the final infusion (Cycle 6), additional blood samples were taken at months 7, 8, 9 and 12.

Patients from participating centers were assigned to PK sampling after randomization to treatment arms.

Quality of Life Assessments

The Functional Assessment of Cancer Therapy – General (FACT-G), version 4.0, translated into over 40 languages, is a patient reported questionnaire that measures general aspects of Quality of Life (QoL) among cancer patients. It comprises 27 items assessing four subscales; physical well-being, social and

family well-being, emotional well-being and functional well-being. Scoring guidelines for each subscale as well as handling of missing data was in accordance with described methodology put forth in the Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System version 4 (Nov 1997).

Quality of life assessments were made at the end of Cycles 3, 6 and at 1 year. On each occasion, the assessment was made before evaluation of disease response or progression.

Safety Assessment

Adverse Events:

All AEs occurring after the initiation of trial treatment were recorded until 28 days after completion of study treatment.

Serious Adverse Events:

All SAEs occurring after initiation of trial treatment were reported until 1 year post-treatment or initiation of new CLL treatment. All SAEs considered related to study treatment were reported indefinitely.

Response Assessments

Assessment of response was performed according to the NCI revised guidelines for the diagnosis and treatment of CLL (Hallek et al, 2008[16]) with additional CT scan evaluation of lymphadenopathy during the treatment period and at time points indicated in follow-up section below. Response assessments included clinical examination and assessment of B symptoms, evaluation of peripheral blood counts and, when scheduled, CT scan of the neck (if clinically involved), chest, abdomen and pelvis. An abnormal (or new) lymph node was defined as one $\geq$ 1.5 cm in diameter. Bone marrow biopsy was necessary only for the confirmation of CR.

Response was assessed after 3 and 6 treatment cycles and at a minimum of 8 weeks later (month 9) for confirmation of response. Unless there was unequivocal progression based on peripheral blood lymphocyte counts according to the NCI Working Group Guidelines for CLL ($\geq$ 50% increase in the absolute number of lymphocytes to at least 5×10^9/L), lymphadenopathy was assessed by CT scan post Cycle 3, post Cycle 6 and (for patients with a CR or PR at the post Cycle 6 assessment) at confirmation of response (month 9). In case of treatment discontinuation before completing 6 treatment cycles for reasons other than PD, a full tumor assessment including CT scans to evaluate lymphadenopathy was performed approximately 4 weeks after the end of treatment. For patients achieving a PR or CR at this time, a full confirmatory assessment, including CT scans and bone marrow (for CR) was completed 8 weeks later. For patients achieving stable disease at the end of treatment assessment, CT scans were not mandatory 8 weeks later.

Patients with CR or PR after 3 cycles continued treatment to 6 cycles. Patients with PD after 3 cycles discontinued treatment. Patients with stable disease (SD) after 3 cycles could continue treatment at the investigator's discretion.

The definition of CR required that a patient satisfy all of the following criteria for a period of at least 8 weeks:

- Absence of lymphadenopathy by physical examination and on CT scan (ie, all lymph nodes < 1.5 cm in diameter)
- No hepatomegaly or splenomegaly by physical examination or on CT scan
- Absence of B symptoms
- Normal CBC as exhibited by
    - Polymorphonuclear leukocytes $\geq 1.5 \times 10^9$/L
    - Platelets > 100×10^9/L
    - Hemoglobin > 11.0 g/dL (untransfused). Although anemia due to autoimmune hemolysis is an exception to this rule in updated versions of the response criteria, normal hemoglobin is required for CR in all cases.
- Bone marrow biopsy and aspirate was performed 8 weeks after clinical, radiological and laboratory evaluations had demonstrated that the requirements for a CR have been achieved. The bone marrow sample had to be normocellular for age with less than 30% of the cells being lymphocytes. Lymphoid nodules should be absent. If the bone marrow was hypocellular, a repeat biopsy was taken 4 weeks later and samples were re-reviewed in conjunction with prior pathology.

The definition of a PR required that a patient satisfy all of the following criteria:

- ≥50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value
- ≥50% reduction in lymphadenopathy by CT scan examination
- ≥50% reduction in the size of the liver and /or spleen by physical examination or on CT scan (if abnormal at baseline)

and at least one of the following for a minimum of 8 weeks:

- Polymorphonuclear leukocytes $\geq 1.5 \times 10^9$/L or 50% improvement over baseline
- Platelets > 100×10^9/L or 50% improvement over baseline
- Hemoglobin > 11.0 g/dL or 50% improvement over baseline without transfusion

A subset of patients who were otherwise in complete remission but had bone marrow nodules that could be identified histologically are referred to as nodular PR (nPR) and were included in the PRs.

Patients who fulfilled the criteria for a CR but had persistent anemia or thrombocytopenia apparently unrelated to disease, but possibly related to drug toxicity were considered PRs.

The definition of PD required at least one of the following criteria:

- ≥50% increase in the sum of the products of at least two lymph nodes compared to their smallest size (at least one lymph node must be ≥ 2 cm) or appearance of new lymph nodes (at least one must be ≥ 1.5 cm in diameter) or any new extranodal lesion (regardless of size)

- ≥50% increase in the size of hepatosplenomegaly as determined by measurement below the relevant costal margin or by 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 (eg, Richter's syndrome or PLL with > 55% prolymphocytes)

In the absence of progression, the presence of a ≤ 2 g/dL decrease in Hb, or ≤ 50% decrease in platelet count and/or granulocyte count did not exclude a patient from continuing the study.

Progression and relapse are defined as per the NCI criteria. Minimal disease detected by molecular methods or flow cytometry with a peripheral lymphocyte count of less than 5×10^9/L did not count as PD.

Patients who had not achieved a CR, PR or had not exhibited PD were considered to have stable disease (SD).

Consistency of assessment techniques was recommended for all patients, with the same assessment technique being used throughout the treatment period for evaluating all lesions (eg, CT scan, physical examination). According to protocol, the same investigator was to make the measurements for all assessments for each individual patient.

Length of Follow-up

All patients were followed up every month for the first 3 months after their last dose of trial treatment (ie, months 7, 8 and 9 for patients receiving 6 cycles), then every 3 months until 33 months (ie, months 12, 15, 18, 21, 24, 27, 30 and 33), every 6 months until 5 years (ie, months 39, 45, 51, 57 with an additional visit at month 60), and then at least annually until 8 years after entering the study. At each visit until 5 years (or disease progression if it occurred before 5 years), assessments included physical examination, standard hematology and biochemistry tests, vital signs, weight, liver and spleen size, B symptoms and ECOG performance status. After 5 years, patients were only followed for survival and progression (if it had not already occurred). After disease progression, patients were followed for survival only.

During follow-up, quality of life was assessed at month 12 only. Lymphadenopathy was assessed by CT scan at baseline and unless there was unequivocal progression based on peripheral blood lymphocyte counts according to the NCI Working Group Guidelines for CLL (≥ 50% increase in the absolute number of lymphocytes to at least 5×10^9/L), CT scan of the neck (if clinically involved), chest, abdomen and pelvis were performed after Cycle 3, after Cycle 6, and two months later (month 9) for patients with a CR or PR, to confirm response. During follow-up, for patients who received 6 cycles of therapy, CT scans were performed at 12, 18, 24 and 30 months from start of treatment or until progression. In addition, if nodal or extranodal progression occurred without detectable disease progression in the peripheral blood at any other time point including after month 30, a CT scan was performed to accurately verify the disease progression.

In case of treatment discontinuation before completing 6 treatment cycles for reasons other than PD, a full disease assessment, including CT scans to evaluate lymphadenopathy, was performed approximately 4 weeks later followed by a confirmatory disease assessment, including a bone marrow (for patients achieving a CR) and CT scans (for patients who achieved a PR or CR) at this time. For patients who discontinued study treatment prior to receiving 6 cycles of therapy, follow-up CT scans were performed at 6, 12, 18 and 24 months after the end of treatment (ie, 4 weeks after the last dose) or until progression. In addition, if nodal or extranodal progression occurred without detectable disease progression in the peripheral blood at any other time point, including after month 30, a CT scan was performed to accurately verify the disease progression. Other disease assessments (physical examination, B symptoms and peripheral blood count) were performed every 3 months until 27 months, and every 6 months until 51 months after the end of treatment.

The type and date of the first CLL treatment subsequent to the study treatment was recorded.

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.

Statistical Hypothesis

A two-sided non-stratified log-rank test was used in the primary analysis for testing the difference in PFS between the two treatment groups. After accounting for the actual numbers of PFS events available at clinical cut-off of the interim analysis, the significance level for the final analysis was 4.50% (the overall alpha level is 5%).

The hypothesis was:

$$H_0: \text{PFS (R-FC)} = \text{PFS (FC alone)}$$

versus

$$H_A: \text{PFS (R-FC)} \neq \text{PFS (FC alone)}$$

where PFS denotes the survival distribution of the parameter time to PFS.

The primary analysis of PFS used the investigator assessment and was based on the intent-to-treat population (ITT).

For the secondary efficacy parameters further tests between the two treatment groups were performed. All tests were two-sided and were based on an alpha level of 5%. Since the tests are only of exploratory nature, no power calculations were performed.

Planned Sample Size

The primary endpoint of PFS was used to determine sample size. However, no robust reference data for second-line treatment of CLL patients was available at the time the study was designed. Taking into consideration that the patient population included patients that relapsed after alkylator and/or fludarabine (or other nucleoside analog) treatment, an estimate of 20 months for median PFS was considered reasonable for the FC arm by expert CLL physicians. Table 24 provides an overview of the required number of events depending on the overall alpha level and hazard ratio (HR). The following assumptions were made for the calculation for the number of events:

- two-sided Log-Rank test was used for the comparison
- an interim analysis was to be performed at two thirds of the number of events
- the power is 80%
- exponential distribution of the parameter PFS
- randomization was 1:1 between the two treatment groups

Table 24. Required Number of Events

Overall alpha level	Hazard Ratio	Treatment effect (%)	Median PFS (months)		2 Year PFS Rate (%)		Number of Events
			FC	R-FC	FC	R-FC	
0.05	0.800	25	18	22.5	39.7	47.7	639
			20	25.0	43.5	51.4	
			22	27.5	46.9	54.6	
	0.769	30	18	23.4	39.7	49.1	463
			20	26.0	43.5	52.7	
			22	28.6	46.9	55.9	
	0.741	35	18	24.3	39.7	50.4	356
			20	27.0	43.5	54.0	
			22	29.7	46.9	57.1	
	0.714	40	18	25.2	39.7	51.7	284
			20	28.0	43.5	55.2	
			22	30.8	46.9	58.3	
0.01	0.800	25	18	22.5	39.7	47.7	944
			20	25.0	43.5	51.4	
			22	27.5	46.9	54.6	
	0.769	30	18	23.4	39.7	49.1	682
			20	26.0	43.5	52.7	
			22	28.6	46.9	55.9	
	0.741	35	18	24.3	39.7	50.4	522
			20	27.0	43.5	54.0	
			22	29.7	46.9	57.1	
	0.714	40	18	25.2	39.7	51.7	417
			20	28.0	43.5	55.2	
			22	30.8	46.9	58.3	

An 8-month difference (40% increase) in the median PFS from 20 months to 28 months, assuming an exponential distribution, translates into a 2 year progression-free rate in patients receiving FC of 43.5% and R-FC of 55.2%. This corresponds to an approximate 29% risk reduction (ie, HR = 0.714). This 40% increase in rituximab plus FC over FC alone is a reasonable assumption from recent publications (Wierda et al, 2005[3]; Wierda et al, 2006[32]) suggesting that the addition of rituximab was effective in lowering the HR in this patient population.

The number of patients required and the duration of recruitment and follow-up to observe 284 events is displayed in Table 25.

Table 25. Required Number of Patients for Different Recruitment and Follow-up Assumptions

Recruitment (months)	Maximum Study Duration (months)	Expected Study Duration Under H1 (months)	Number of Patients per Months	Overall Number of Patients
56 60	61 60	55 55	9 9	500 535 *
50 **55**	57 **56**	52 **51**	10 **10**	500 **550**
46 50	54 53	49 48	11 11	500 550

Assumption for the numbers in the table: The required number of events is 284 and a constant recruitment rate.

* Since the calculated maximum duration of the study is equal to the recruitment period no more than 535 patients needed to be recruited for this scenario.

Based on the above considerations, recruitment of 550 patients was planned. An 8 month difference (40% increase) in the median time to PFS between FC and R-FC ensured 80% power to establish superiority of R-FC at an overall alpha level of 5%. Formal clinical cut-off for the statistical analysis was triggered when 284 events were observed in the population of all randomized patients.

With this number of events (N = 284), it was possible to detect a treatment difference in terms of median PFS of about 50.5% (HR = 0.664) with a power of 80% at an overall alpha level of 1%.

Analysis Populations

Intent-to-Treat Population (ITT):

According to the protocol the primary analysis population was defined as all patients who were formally randomized. Patients were included in the primary analysis population regardless of whether they received treatment or not. Patients were analyzed according to the therapy that they were randomized to receive.

All efficacy analyses will be based on the ITT population.

Full Analysis Set (FAS; following an intent-to-treat principle):

In this study the FAS is identical to a strict definition of an ITT population (see paragraph above on the ITT population).

Per Protocol Set (PPS; evaluable patient set):

All randomized patients who received at least 3 cycles of randomized treatment and patients who terminated treatment before 3 cycles because of progression or death and adhered to the protocol were considered in the per protocol patient set. Patients included in this analysis population had at least one disease/tumor assessment during or after treatment and no major protocol violation from the following list:

- Not formally randomized or randomized after clinical cut-off date
- Withdrawal of consent
- No follow-up
- Less than 3 cycles of randomized treatment received (except for progression or death within the first 84 days after randomization). Note that 'randomized treatment' implies that the patient received a dose of each randomized component of immunochemotherapy in all 3 cycles in order to be included in the PPS.
- Unconfirmed diagnosis of CD20 positive B-cell CLL by NCI Working Group criteria
- Baseline ECOG performance status ≥ 2
- Prior treatment with interferon, rituximab or another monoclonal antibody
- Prior treatment with alkylating agents and fludarabine (other nucleoside analogue) [sequential or concurrent] Note that patients with prior sequential treatment with alkylating agents and fludarabine (or other nucleoside analogue) are not protocol violators if they were randomized prior to protocol amendment C. Nevertheless, they will be excluded from the per protocol set.
- Prior BM or PBSC transplant prior to study entry
- Inadequate tumor assessment at baseline. – An adequate tumor assessment at baseline consists at least of the following assessments:
    - Absolute lymphocyte count, platelets and hemoglobin
    - Screening CT scans of chest, abdomen and pelvis performed
    - Liver and spleen size assessed
- Inadequate disease assessment after start of treatment (except for unequivocal progression based on peripheral blood lymphocyte counts or death within the first 84 days after randomization). Note that CT scans will not be performed at all disease assessments (ie, not all follow-up visits include a mandatory CT scan). Nevertheless, at least one post-baseline tumor assessment including CT scans of chest, abdomen and pelvis (and all other assessments as listed above for baseline) is required for inclusion of a patient in the PPS.

Efficacy analyses for the primary parameter and the secondary endpoint, OS, were repeated for the PPS in order to assess the robustness of the results and to quantify more precisely the magnitude of the potential clinical benefit of the treatment.

Sensitivity Analysis Population

The primary efficacy analysis of PFS is based on the ITT population as defined above. A sensitivity analysis which excludes all patients in the previous treatment stratification category “alkylating agents and fludarabine” from the ITT was performed as these patients were no longer eligible subsequent to protocol amendment C. This sensitivity analysis was performed for the primary efficacy parameter and the secondary efficacy parameter, OS, using both a non-stratified and a stratified log-rank test.

Analysis Populations for Secondary Endpoints

Other secondary efficacy parameters were analyzed only on the ITT population.

Safety Analysis Population (SAP)

All patients who received at least one dose of trial treatment and had at least one safety follow-up, whether withdrawn prematurely or not, will be included in the safety analysis. The safety parameters will be presented according to the therapy the patient received.

Interim Analysis

Amendment F to the protocol required that the final analysis be performed when 284 events (progressions or deaths) had occurred. The interim analysis was planned when 66.7% of the total events (190 events) had been observed. The interim analysis was prepared by an independent statistical center, Bremen Institute for Prevention Research and Social Medicine (BIPS) under the lead of the DSMB statistician, and the interim analysis meeting of the DSMB took place February 6th, 2008, in a closed session.

For the interim analysis, the primary parameter, PFS (investigator assessed), and a 2-sided log-rank test were to be used to compare the FC arm with the R-FC arm. If the statistical test was significant either in favor of the FC arm or the R-FC arm and all results (OS and IRC reviewed PFS) were persuasive, robust and internally consistent, the DSMB could have recommend that the study be fully evaluated, ie, all secondary parameters to be analyzed. Regardless of the DSMB’s recommendation, patients continued to be followed up for PD and OS according to the protocol. If the statistical test was not significant, the study was to continue as planned and no results were to be available for anybody involved in the conduct of the study.

The interim analysis followed a group sequential design according to O’Brien and Fleming as implemented by Lan and DeMets using an α-spending function. This method allows for interim analyses at unequal increments and the DSMB could change the frequency of the analysis if necessary without destroying the integrity by increasing the overall probability of the type I error. To maintain a two-sided type I error of 5%, this approach results in the two-sided boundary of approximately 2.5093 (nominal p = 0.0121) for the interim analysis and 1.9929 (nominal p = 0.0463) for the final analysis**.** As a conservative measure to encourage stopping only for particularly persuasive results, the actual boundary that was used for the interim analysis was no lower than 2.652 (nominal p = 0.008).

At the time of the interim analysis (clinical cut-off June 26, 2007), there were 205 PFS events available. To account for the additional information (205 PFS events instead of the 190 required by the protocol) and in order to maintain the overall 2-sided type I error of 5%. The 2-sided boundary for the final analysis was calculated to be approximately 2.0094 (nominal p = 0.0450).

The minutes from the DSMB interim analysis, received by the sponsor in December, 2008. The key points from the minutes are as follows:

The DSMB agreed that the primary end point (investigator assessed PFS) had met the required statistical hurdle for significance.However it was also clear that the IRC-PFS had not met its hurdle and this was considered to be an essential part of the interim analysis as it was the critical end point for regulatory submission in the US.

PFS	*p* value Log rank	Hazard ratio	95% confidence intervals
Investigator	<0.001	0.57	[0.43, 0.75]
IRC	0.012	0.73	[0.57, 0.93]

Efficacy Analysis

Primary Efficacy Analysis

The treatment arms were compared for PFS by using a two-sided non-stratified log-rank test. Estimates of the treatment effect are expressed as hazard ratios including two-sided 95% confidence limits. In addition Kaplan-Meier estimates, median time of PFS as well as PFS rates for one, two and three years after randomization with 95% confidence intervals are reported. A stratified log-rank test with the stratification factors, previous treatment, time from first diagnosis and beta-2 microglobulin was done to confirm the primary statistical analysis. The data reporting and analysis manual (DRAM), describes how underrepresented strata were pooled for the stratified analysis. In particular, patients who were stratified to the previous treatment stratification category “alkylating agents and fludarabine” prior to protocol amendment C are included in the “fludarabine” stratum. (Note that patients who had received prior alkylating agents **and** fludarabine were no longer eligible as of protocol amendment C).

The main model considered treatment only (referred to as “unadjusted”). Progression free survival was also analyzed using a Cox regression model adjusted for treatment and the following baseline prognostic factors: age, gender, Binet stage, ECOG performance status (PS), Ig VH mutational status, ZAP-70, high tumor burden (baseline lymphocyte count > 10^9/L), time from first diagnosis, beta-2 microglobulin and previous treatment. Interaction effects of each of the covariates with treatment were also examined in order to assess whether the treatment effect is different across different values of the covariates.

Furthermore, a Cox regression analysis for PFS was performed applying a model that contained treatment and the collected baseline cytogenetic abnormalities (del[13q], trisomy 12, del[11q] and del[17p]). Cox regression analyses was performed only in those patients that had information available for all the covariates included in each of the models.

Hazard ratios for PFS with the corresponding 95% CI are also presented by subgroup defined by the factors used in the Cox models and additionally by race, B symptoms at baseline, bone marrow involvement, IgVH/ZAP-70 and creatinine clearance.

Secondary Efficacy Parameters

The time to event endpoints OS, EFS, DFS, duration of response and time to new treatment, were analyzed using the non-stratified and stratified log-rank test (two-sided). Estimates of the treatment effect are expressed as HRs including two-sided 95% confidence limits. In addition Kaplan-Meier plots and estimates including an estimate of the median and event free rates for one, two and three years after randomization with 95% confidence intervals are reported. Subgroup analyses are presented for OS.

Best overall and end of treatment response rates in the treatment groups were compared using a chi-square test. In addition, 95% confidence limits for the difference using the Anderson-Hauck approach were calculated. Rates and 95% confidence limits according to Pearson-Clopper are given for each treatment group. The effect of prognostic factors, as mentioned above, was assessed in an exploratory analysis using logistic regression. The results are presented in terms of odds ratios including 95% confidence limits and associated p-values.

For molecular response rate and other molecular and genetic markers only a descriptive analysis was performed: the absolute number of responders and the percentage is presented in each treatment group.

Quality of Life Analysis

The following quality of life analyses were performed for the clinical study report: the FACT-G Total Score (as described in the FACIT Manual) at the end of Cycle 6 was analyzed using an analysis of covariance with treatment as main factor and baseline FACT-G Total Score as a covariate. If the FACT-G Total Score at the end of Cycle 6 was missing it was replaced by the FACT-G Total Score at the end of Cycle 3. All FACT-G subscores (eg, physical, social/family, emotional and functional well-being) and the total score were summarized descriptively by change from baseline tables over time.

6.3.6 Critical appraisal of relevant RCTs

Table 26. Critical Appraisal

Criterion	REACH (BO17072)
How was allocation concealed?	REACH was an open-label study. Placebo control for a study involving IV rituximab administration and pre-medication would have been very difficult and probably considered unethical. All Phase III rituximab studies to date have been open-label. End-points measured were objective and any potential effect obtained by infusing a placebo rituximab would have

	been unable to significantly confound the results.
What randomisation technique was used?	Patients were randomized using a dynamic allocation method, 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 At the time of final analysis (data cut-off July 23 2008), with a median observation time of 25.3 months, the study demonstrated a highly statistically significant improvement in PFS with the addition of rituximab to FC. This PFS benefit was robust and apparent in almost all pre-specified subgroups. It is appreciated that the the OS data are immature and did not demonstrate a statistically significant advantage when rituximab was added to FC. This is maybe unsurprising given median OS in CLL is 5-10 years plus OS benefits may be masked by subsequent treatment options. Nonetheless, OS data will continue to be collected with further results with a longer period of follow-up becoming available in 2010.
Assessors aware of treatment allocation?	It is likely that assessors were aware of treatment allocation in this study, however, the assessment of CLL post treatment is very objective and it is very unlikely that this will have biased results. In addition, an independent assessment of the data was performed at the interim and final analysis, where patients were in a blinded manner assessed for response and progression based on peripheral blood counts, bone marrow biopsy results, CT scans and reports of physical examination. These data, however, have not yet become available.
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?	REACH was an international study including the UK. There are no obvious differences between the study population and non-trial patients requiring treatment for

and

chronic lymphocytic leukaemia in the UK, except, perhaps that the study patients are slightly younger (median age of 63 compared to median age at diagnosis of 65-70 for non-trial patients).

How does the population compare with patients who are likely to receive R-FC in The United Kingdom

The vast majority (99%) of patients in the trial were caucasian, which would compare very favourably with a British population. Indeed the highest recruiting countries (France, Russia, Poland, and Canada), all provide a demographic of patients that would be very similar in general to The United Kingdom.

Disproportionate recruitment of younger patients is a general problem in oncology clinical trials – the study had no upper age limit for participation, and the oldest patient recruited was 83.

Was the dosage regimen acceptable and justifiable?

Currently, the licensed, approved dose for rituximab in lymphoma (whether monotherapy or given in combination with chemotherapy) is 375mg/m^2. It had become apparent from monotherapy dose finding studies in CLL (O'Brien et al, 2001[51]), 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. [1] and Wierda et al. [3] at The MD Anderson Cancer Center in The United States) felt that the lymphoma dose was not appropriate for CLL and a higher dose would be required. 500mg/m^2 was decided upon as an acceptable higher dose for CLL patients to use in combination with FC.

The dosing chosen in REACH was based on the MDAAC Phase II studies. A dose reduction of 375mg/m^2 in cycle 1 was decided on to minimise any potential cytokine release/ tumour lysis that may have been triggered by the known large circulating tumour burden in CLL. This is also the licensed dosing regimen in previously unterated CLL pateints as recently approved by the EMEA on the basis of compelling data from the phase III CLL-8 trial.

Thus the dosing of rituximab in this study was entirely appropriate and consistent with Phase II R-FC studies in CLL. The dosing used in these Phase II studies was also rationalised and based upon a published dose-finding study as highlighted above.

The dosing of fludarabine and cyclophosphamide was the same in both arms. The approved standard dose of fludarabine as monotherapy in patients with relapsed CLL is 25 mg/m^2/day for the first 5 days of each 28-day cycle (usually 6 cycles). O'Brien and colleagues evaluated the safety and efficacy of combined fludarabine (30 mg/m^2) and

cyclophosphamide (300-500 mg/m^2) therapy given daily for three days over 6 cycles (4-6 week cycle duration) (O'Brien et al, 2001[51]). A dose reduction in cyclophosphamide from 500 mg/m^2 to 300 mg/m^2 appeared effective in reducing the severity of myelosuppression. Therefore, to improve the safety profile further in the REACH study, an even lower dose of fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2/day) was used. This is the same regimen as used in the MDACC phase II studies (Keating et al, 2005[1]; Wierda et al, 2005[3]).

The dosing of R-FC used in this study will be the approved dose in the SmPC.

Were the inclusion and exclusion criteria appropriate?

The inclusion and exclusion criteria were entirely appropriate and consistent with accepted and validated criteria for running CLL trials.

Please note that patients who were previously treated with rituximab were excluded from the study as, at the time of study planning in 2001 and 2002, patients who had recieved rituximab therapy in the first-line setting were considered rare. At the time (and for most of the recruitment period) no monoclonal antibodies were approved for the first-line treatment of CLL patients. Data on the use of rituximab-containing regimens after failure of first-line rituximab-containing therapy has, however, been reported in more than 200 pateints in a variety of small series and case reports. These data will be discussed at length in Section 6.8 in support of guidance that will not exclude CLL patients who have previously recieved rituximab-containing therapy from treatment with rituximab-containing combinations at relapse, as per the anticipated licence.

Patients who were refractory to fludarabine were also excluded from entry into REACH. Exclusion of these patients was based on the view that such patients are relatively uncommon (Johnson et al, 1996[52]; Leporrier et al, 1991[53]; Rai et al, 2000[54]), have a poor prognosis, and are unlikely to benefit from further fludarabine-based therapy. This view was based mainly on a retrospective analysis of 147 patients with fludarabine-refractory CLL from the MDACC, available at the time (Keating et al, 2002[55]). Since then, additional efficacy data on patients with fludarabine refractory CLL has become available from the MDACC demonstrating that R-FC is a useful therapeutic option for patients whose disease is refractory to prior fludarabine-containing therapy (Wierda et al, 2005[3]; Wierda et al, 2006[32]). These data are supported by data on other rituximab-containing regimens in fludarabine-refractory CLL and are discussed together in Section 6.8 in support of guidance that will reflect the anticipated licence, allowing

	"relapsed/refractory" patients to be eligible for treatment with rituximab in combination with chemotherapy.
Were both arms of the study group comparable?	Yes – as detailed in section 6.3.2, patient characteristics in both arms were well balanced at baseline.
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 subsequent treatment options will limit the ability to show an overall survival benefit in favour of R-FC, an issue that has been seen in a number of Phase III CLL studies.

6.3.6.1 Summary

The critical appraisal reveals that REACH 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 treatment of relapsed/refractory CLL.

6.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

6.4.1 Introduction: REACH Results

A pre-planned interim efficacy analysis of the REACH study was performed with a clinical cut-off of June 26, 2007, after two-thirds (190/284 planned, 205 actual) of the events (progression or deaths) had been reported. But because the Independent Review Committee (IRC) assessed PFS did not cross the pre-specified threshold at that time (actual result: p=0.012) and because all patients

had completed therapy, the DSMB recommended that the study should be continued until the final analysis. As a consequence, only results from the final analysis (data cut-off July 23 2008) are submitted.

At the time of the clinical cut-off (July 23, 2008), the median observation time in the overall group was 25.3 months. Patients were followed for a median observation time of 24.1 months (range: 1 day-56 months) in the FC arm and 27.2 months (range: 8 days-56.5 months) in the R-FC arm. Eighty-four percent of patients in the FC arm and 86% in the R-FC arm have been observed for at least 12 months. More than 50% of patients in each treatment arm have observation periods of more than 2 years (51% in FC, 56% in R-FC).

6.4.2 Efficacy Results

The overall efficacy results are summarised for the intention to treat (ITT) population below in Table 27.

The addition of rituximab to fludarabine plus cyclophosphamide resulted in a clinically relevant and statistically significant improvement in PFS in previously treated CLL patients. These data are supported by results of the secondary efficacy parameters. Under a nominal significance level $\alpha = 0.05$ (2-sided), significant improvements were observed in most of the secondary endpoints including EFS, duration of response, time to new CLL treatment or death and response rates.

Table 27. Summary of Overall Efficacy (ITT/FAS)

Parameter	FC	R-FC
PFS		
median (months)	20.6	30.6
p value (Log-Rank test)	0.0002	
HR [95%CI]; p value; Wald test		
Non-stratified (unadjusted)	0.65 [0.51; 0.82]; 0.0002	
Stratified (unadjusted)	0.66 [0.51; 0.84]; 0.0008	
Overall survival		
Median (months)	51.9	-[a]
p value (Log-Rank test)	0.2874	
HR [95% CI] p value (Wald test)		
Non-stratified (unadjusted)	0.83 [0.59;1.17]; 0.2871	
Stratified (unadjusted)	0.87 [0.60;1.25]; 0.4447	
Event Free Survival		
Median (months)	19.3	28.7
p value (Log-Rank test)	0.0002	
HR [95%CI] p value (Wald test)		
Non-stratified (unadjusted)	0.64 [0.51; 0.81]; 0.0002	
Stratified (unadjusted)	0.64 [0.50;0.82]; 0.0004	
Response Rates		
Best Overall Response Rates		
Response	58.0%	69.9%
Non-response	42.0%	30.1%
p value (Chi-squared test)	0.0034	
Complete response	13.0%	24.3%
Partial response	44.9%	45.7%
Stable disease	22.1%	17.0%
Progressive disease	5.4%	2.5%
Missing	14.5%	10.5%
End of Treatment Response Rates		
Response	52.9%	63.4%
Non-response	47.1%	36.6%
p value (Chi-squared test)	0.0123	
Complete response	9.1%	13.8%
Partial response	43.8%	49.6%
Stable disease	21.7%	19.6%
Progressive disease	10.9%	6.5%
Missing	14.5%	10.5%
Duration of Response[b]		
Median (months)	27.6	39.6
p value (Log-Rank test)	0.0252	
HR [95% CI] p value (Wald test)		
Non-stratified (unadjusted)	0.69 [0.50; 0.96]; 0.026	
Stratified (unadjusted)	0.65 [0.46; 0.93]; 0.0180	
Disease Free Survival[c]		
Median (months)	42.2	39.6
p value (Log-Rank test)	0.8842	
HR [95%CI] p value (Wald test)		
Non-stratified (unadjusted)	1.06 [0.49;2.28]; 0.8850	
Stratified (unadjusted)	1.25 [0.46; 3.37]; 0.6598	
Time to New Treatment		
Median (months)	34.2	-[a]

Parameter	FC	R-FC
p value (Log-Rank test)	0.0024	
HR [95%CI] p value (Wald test)		
Non-stratified, (unadjusted)	0.65 [0.49; 0.86]; 0.0026	
Stratified (unadjusted)	0.65 [0.48; 0.88]; 0.0057	

[a] Median has not yet been reached
[b] Only in patients with Best Overall Response assessed as complete or partial response
[c] Only in patients with Best Overall Response assessed as complete response

Primary Efficacy Parameter: Progression-Free Survival

The primary efficacy analysis was based on a non-stratified, two-sided Log-Rank test of investigator assessed PFS, as described in Section 6.3.5. Progression free survival was determined for the ITT population and for the PPS population.

Progression-Free Survival (Investigator Assessment)

At the time of the analysis (clinical cut-off date of July 23, 2008), approximately 9% more patients in the FC arm than in the R-FC arm had experienced an event (progression or death; 158 patients [57%] on FC versus 132 patients [48%] on R-FC) (Table 28). More patients in the FC arm than in the R-FC arm had progressed (48% FC versus 37% R-FC), whereas slightly more patients in the rituximab containing arm had died (9% FC versus 11% R-FC).

Table 28. Summary of Composition of Progression-free Survival Events (ITT, Investigator Assessment)

	FC N=276 No. (%)	R-FC N=276 No. (%)
Total number of events	158 (57.2%)	132 (47.8%)
Death	25 (9.1%)	30 (10.9%)
Progression	133 (48.2%)	102 (37.0%)

PFS - day of randomization until first documented disease progression, or death from any cause - investigator assessment

The addition of rituximab to the FC regimen significantly prolonged the median PFS when compared to the FC regimen alone (p = 0.0002, Log-Rank test) (Table 29). The Kaplan-Meier estimated median PFS was 20.6 months (627 days) with FC and 30.6 months (932 days) with R-FC. The risk of having a PFS event (progression or death, whichever occurred first) was statistically significantly decreased, by 35% (unadjusted Hazard Ratio [HR] 0.65; 95% CI [0.51; 0.82]; p = 0.0002, Wald test), for patients in the rituximab arm compared to the FC arm. Forty-four percent of the patients in the FC arm, and 60% of those in the R-FC arm, were progression-free at 2 years using Kaplan-Meier estimates.

Table 29. Summary of Progression-Free Survival (ITT, Investigator Assessment, Non-stratified Analysis)

	FC (N=276)		R-FC (N=276)
Patients with event	158 (57.2 %)		132 (47.8 %)
Patients without events*	118 (42.8 %)		144 (52.2 %)
Time to event (days)			
Median#	627.0		932.0
95% CI for Median#	[550;731]		[792;1161]
25% and 75%-ile	360;1283		460;.
Range##	1 to 1599		1 to 1720
p-Value (Log-Rank Test)		0.0002	
Hazard Ratio		0.65	
95% CI		[0.51;0.82]	
p-Value (Wald Test)		0.0002	
2 years duration			
Number left	77		119
Event Free Rate#	0.44		0.60
95% CI for Rate#	[0.37;0.51]		[0.54;0.67]

Days From Randomization To Event/Censoring (PFS) (TTPFS) - Censoring: Event (PFS) (CSPFS)
* censored
# Kaplan-Meier estimate
including censored observations

PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.
2 years duration is defined as 728 days.
Censoring occurs at last response assessment

Results of the analysis of PFS stratified by previous chemotherapy (pooled), time from first diagnosis (years) and beta-2 microglobulin (>ULN) were similar to the non-stratified analysis (Table 30).

Table 30. Log-rank Test and Risk Ratios for Progression-Free Survival (ITT, Investigator Assessment, Non-stratified and Stratified Analysis)

		Cox Regression		
R-FC versus. FC	Log-rank test (p-value)	Hazard Ratio	95% CI	p-value
No Stratification	0.0002	0.65	[0.51;0.82]	0.0002
With Stratification*	0.0007	0.66	[0.51;0.84]	0.0008

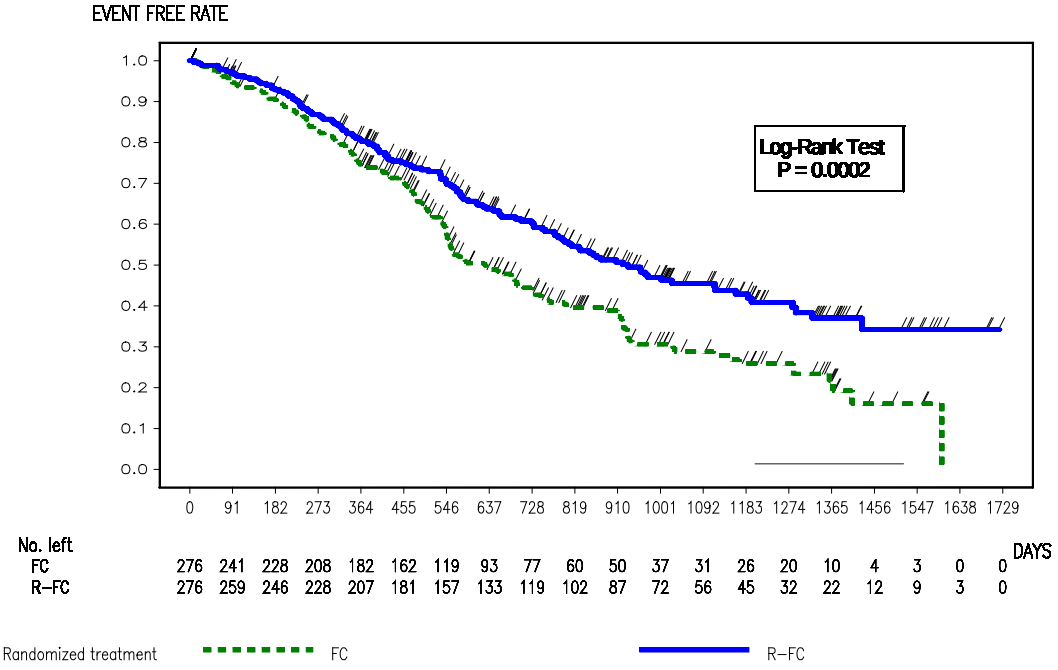
Days From Randomization To Event/Censoring (PFS) (TTPFS) - Censoring: Event (PFS) (CSPFS)
* stratified by Previous Chemotherapy (Pooled) and Beta2-Microglobulin > ULN (Yes/No) and Time From First Diag (Years) - Categ.

PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.
Censoring occurs at last response assessment

The Kaplan-Meier curves for duration of PFS show a separation of the curves approximately 3 months after study start (Figure 8) ie, at time of first scheduled response assessment.

Figure 8. Kaplan-Meier Plot of Progression-Free Survival (ITT, Investigator Assessment)

eg_pfskm_I Kaplan-Meier Plot of Progression Free Survival (ITT)
Protocol(s): BO17072 (I17072U)
Analysis Population: ITT (N=552)
Snapshot Date: 16SEP2008 Cutoff Date: 23JUL2008



PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.
2 years duration is defined as 728 days.
Censoring occurs at last response assessment

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Progression-Free Survival in the Per Protocol Population

Progression free survival was assessed in the PPS to further quantify the magnitude of the potential benefit of the treatment in the clinical population.

The PPS analysis population included all randomized patients who received at least 3 cycles of randomized treatment and patients who terminated treatment before 3 cycles because of progression or death. Patients included in this analysis population had at least one post-baseline tumor/disease assessment and no major protocol deviation.

The results of the analysis of PFS based on the PPS was consistent with the ITT analysis and demonstrated that the risk of progression was reduced by 38% (unadjusted HR [95% CI] 0.62 [0.48; 0.81], p = 0.0003) compared to the FC arm.

Results of the analysis of PFS based on the PPS population and stratified by previous chemotherapy (pooled), time from first diagnosis (years) and beta-2 microglobulin (>ULN) were similar to the non-stratified analysis.

Secondary Efficacy Parameters

Overall Survival

At the time of the analysis (clinical cut-off July 23, 2008), a total of 130 randomized patients had died: 68 patients (25%) in the FC arm and 62 patients (23%) in the R-FC arm (Table 31).

The median survival time was 1580 days (51.9 months) for patients in the FC arm and could not be estimated for patients in the R-FC arm due to limited follow-up. Treatment with R-FC reduced the risk of death by 17% when compared to FC alone, a difference which was not statistically significant (unadjusted HR 0.83; 95% CI [0.59; 1.17], p = 0.2874, Log-Rank test). At clinical cut-off, the data were still relatively immature, with the great majority of patients still alive in both treatment arms (75% FC and 78% R-FC).

Table 31. Summary of Overall Survival (ITT, Non-stratified Analysis)

	FC (N=276)		R-FC (N=276)
Patients with event	68 (24.6 %)		62 (22.5 %)
Patients without events*	208 (75.4 %)		214 (77.5 %)
Time to event (days)			
Median#	1580.0		.
95% CI for Median#	[1408;.]		[1552;.]
25% and 75%-ile	921;.		1117;.
Range##	1 to 1703		8 to 1720
p-Value (Log-Rank Test)		0.2874	
Hazard Ratio		0.83	
95% CI		[0.59;1.17]	
p-Value (Wald Test)		0.2871	
2 years duration			
Number left	141		154
Event Free Rate#	0.82		0.82
95% CI for Rate#	[0.77;0.87]		[0.77;0.87]

Days From Randomization To Event/Censoring (OS) (TTOS) - Censoring: Event (OS) (CSOS)
* censored
# Kaplan-Meier estimate
including censored observations

OS - day of randomization until death from any cause. Censoring occurs at date of last contact
2 years duration is defined as 728 days.

Results of the analysis of OS stratified by previous chemotherapy (pooled), time from first diagnosis (years) and beta-2 microglobulin (>ULN) confirmed the results of the non-stratified analysis (Table 32).

Table 32. Log-rank Test and Risk Ratios for Overall Survival (ITT) -– non-stratified and stratified

FCR versus. FC	Log-rank test (p-value)	Cox Regression Hazard Ratio	95% CI	p-value
No Stratification	0.2874	0.83	[0.59;1.17]	0.2871
With Stratification*	0.4449	0.87	[0.60;1.25]	0.4447

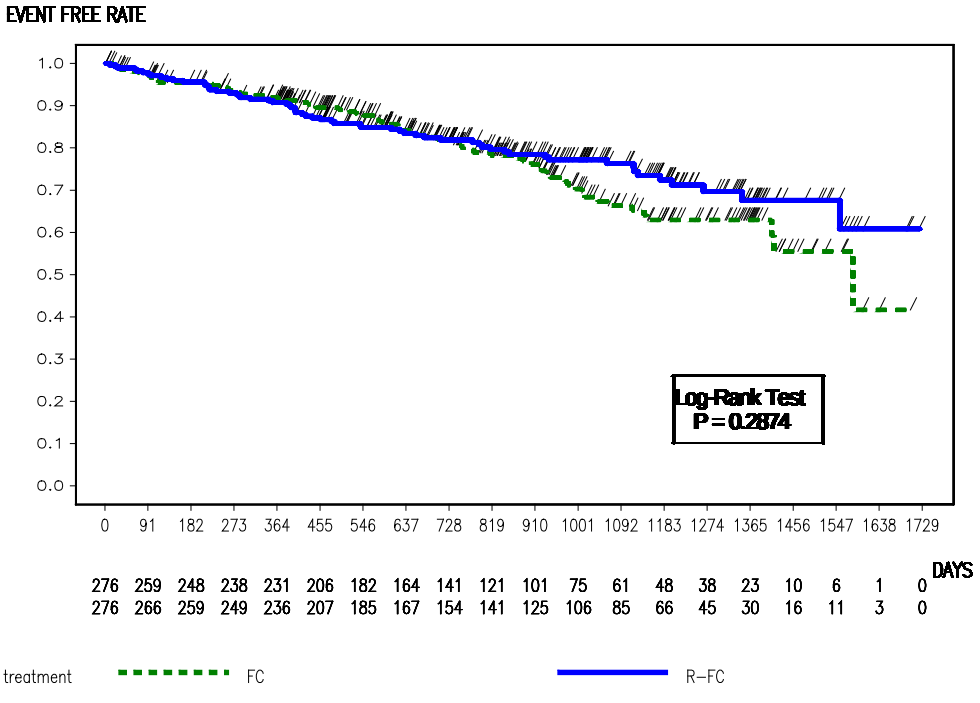
Days From Randomization To Event/Censoring (OS) (TTOS) - Censoring: Event (OS) (CSOS)
* stratified by Previous Chemotherapy (Pooled) and Beta2-Microglobulin > ULN (Yes/No) and Time From First Diag (Years) - Categ.

OS - day of randomization until death from any cause. Censoring occurs at date of last contact

The Kaplan-Meier curves for FC and R-FC overlap for a period of about 30 months (900 days), after which the curves start to separate with better survival for patients in the R-FC arm than in the FC arm (Figure 9).

Figure 9. Kaplan-Meier Plot of Overall Survival (ITT)

eg_oskm_I Kaplan-Meier Plot of Overall Survival (ITT)
Protocol(s): BO17072 (I17072U)
Analysis Population: ITT (N=552)
Snapshot Date: 16SEP2008 Cutoff Date: 23JUL2008



2 years duration is defined as 728 days.
OS - day of randomization until death from any cause. Censoring occurs at date of last contact
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Overall survival was also analyzed in the PPS. In this group, treatment with R-FC reduced the risk of death by 27% when compared to FC alone. This difference was not statistically significant (unadjusted HR 0.73; 95% CI [0.50; 1.06], p = 0.0986, Wald test). The Kaplan-Meier curves overlap for a period of about 18

months (546 days) after which they begin to separate with better OS in the R-FC arm than in the FC arm.

Event Free Survival

In the FC arm, 59% of patients experienced an EFS event (disease progression, relapse, death, or start of a new CLL treatment) compared to 49% in the R-FC arm (Table 33). Most of the events reported were disease progressions (119 events in FC, 96 events in R-FC). A total of 20 patients (7%) in the FC arm and 9 patients (3%) in the R-FC arm received a new treatment for CLL before PD was reported.

Table 33. Summary of Composition of Event Free Survival Events (ITT, Investigator Assessments)

	FC N=276 No. (%)	R-FC N=276 No. (%)
Total number of events	162 (58.7%)	134 (48.6%)
Death	23 (8.3%)	29 (10.5%)
Progression	119 (43.1%)	96 (34.8%)
Subsequent Treatment	20 (7.2%)	9 (3.3%)

EFS - day of randomization until first documented disease progression, death from any cause or start of new CLL treatment (chemotherapy, radiotherapy or other) - investigator assessment

The median EFS was significantly increased by 9.4 months from 19.3 months (586 days) in the FC arm to 28.7 months (874 days) in the R-FC arm (p = 0.0002, Log-Rank test) (Table 34). The reduction in risk of an event for patients in the R-FC arm compared to the FC arm was 36% (unadjusted HR 0.64; 95% CI [0.51; 0.81]; p = 0.0002, Wald test). The Kaplan Meier estimate of EFS at 2 years was 44% of the patients in the FC arm and 58% of the patients in the R-FC arm.

Table 34. Summary of Event Free Survival (ITT, Investigator Assessment, Non-stratified Analysis)

	FC (N=276)		R-FC (N=276)
Patients with event	162 (58.7 %)		134 (48.6 %)
Patients without events*	114 (41.3 %)		142 (51.4 %)
Time to event (days)			
Median#	586.0		874.0
95% CI for Median#	[545;731]		[756;1187]
25% and 75%-ile	309;1283		422;.
Range##	1 to 1599		1 to 1720
p-Value (Log-Rank Test)		0.0002	
Hazard Ratio		0.64	
95% CI		[0.51;0.81]	
p-Value (Wald Test)		0.0002	
2 years duration			
Number left	77		116
Event Free Rate#	0.44		0.58
95% CI for Rate#	[0.37;0.50]		[0.52;0.65]

Days From Randomization To Event/Censoring (EFS) (TTEFS) - Censoring: Event (EFS) (CSEFS)
* censored
# Kaplan-Meier estimate
including censored observations

EFS - day of randomization until 1st documented disease progression, death from any cause or
start of new CLL treatment (chemotherapy, radiotherapy or other) - investigator assessment.
2 years duration is defined as 728 days.
Censoring occurs for at last response assessment

Results of the analysis of EFS stratified by previous chemotherapy (pooled), time from first diagnosis (years) and beta-2 microglobulin (>ULN) were similar to the non-stratified analysis (Table 35).

Table 35. Log-rank Test and Risk Ratios for Event Free Survival (ITT, Investigator Assessments) -– Non-stratified and Stratified

		Cox Regression		
R-FC versus. FC	Log-rank test (p-value)	Hazard Ratio	95% CI	p-value
No Stratification	0.0002	0.64	[0.51;0.81]	0.0002
With Stratification*	0.0003	0.64	[0.50;0.82]	0.0004

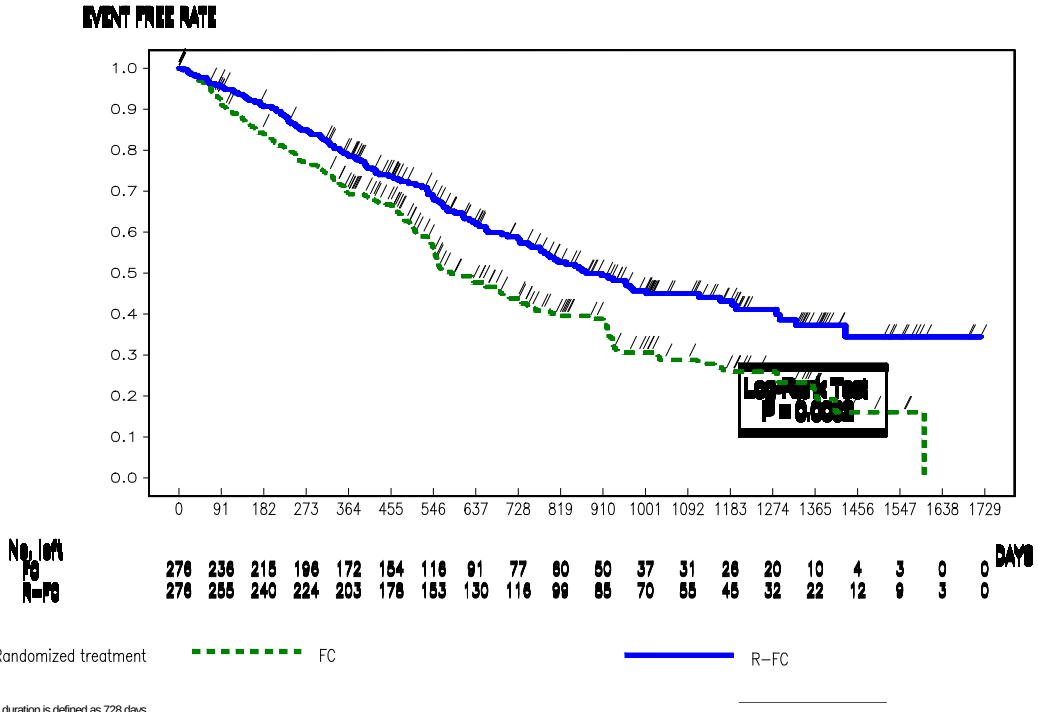
Days From Randomization To Event/Censoring (EFS) (TTEFS) - Censoring: Event (EFS) (CSEFS)
* stratified by Previous Chemotherapy (Pooled) and Beta2-Microglobulin > ULN (Yes/No) and Time From First Diag (Years) - Categ.

EFS - day of randomization until 1st documented disease progression, death from any cause or start of new CLL treatment (chemotherapy, radiotherapy or other) - investigator assessment.
Censoring occurs at last response assessment

The Kaplan-Meier curves for EFS are shown in Figure 10 below:

Figure 10. Kaplan-Meier Plot of Event Free Survival (ITT, Investigator Assessment)

eg_efskm_I Kaplan-Meier Plot of Event Free Survival (ITT)
Protocol(s): BO17072 (I17072U)
Analysis Population: ITT (N=552)
Snapshot Date: 16SEP2008 Cutoff Date: 23JUL2008



2 years duration is defined as 728 days.
EFS - day of randomization until 1st documented disease progression, death from any cause or start of new CLL treatment (chemotherapy, radiotherapy or other) - investigator assessment.
Censoring occurs at last response assessment

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Response Rates

Best Overall Response

The proportion of patients with a BOR of CR, nPR or PR was significantly higher in the R-FC arm (69.9%) compared to the FC arm (58.0%, p = 0.0034, Chi-squared test), and this was mostly due to a significantly higher CR rate (13.0% FC versus 24.3% R-FC, p = 0.0007, Chi-square test) (Table 36). The rate of patients with a PR was similar in both arms. More patients in the FC arm than in the R-FC arm had PD as their best response (5.4% versus 2.5%).

Table 36. Summary of Best Overall Response (ITT, Investigator Assessment)

	FC (N=276)		R-FC (N=276)
Responders$	160 (58.0 %)		193 (69.9 %)
Non-Responders	116 (42.0 %)		83 (30.1 %)
95% CI for Response Rates*	[51.9; 63.9]		[64.1; 75.3]
Difference in Response Rates		11.96	
95% CI for Difference in Response Rates#		[3.8; 20.1]	
p-Value (Chi-squared Test)		0.0034	
Odds Ratio		1.69	
95% CI for Odds Ratio		[1.19;2.40]	
Complete Response (CR)	36 (13.0 %)		67 (24.3 %)
95% CI for CR Rates*	[9.3; 17.6]		[19.3; 29.8]
Difference in CR Rates		11.23	
95% CI for Difference in CR Rates#		[4.6; 17.9]	
p-Value (Chi-squared Test)		0.0007	
Odds Ratio		2.14	
95% CI for Odds Ratio		[1.37;3.34]	
Partial Response (PR and nPR)	124 (44.9 %)		126 (45.7 %)
95% CI for PR and nPR Rates*	[39.0; 51.0]		[39.7; 51.7]
Difference in PR and nPR Rates		0.72	
95% CI for Difference in PR and nPR Rates#		[-7.8; 9.2]	
p-Value (Chi-squared Test)		0.8642	
Odds Ratio		1.03	
95% CI for Odds Ratio		[0.74;1.44]	
Stable Disease (SD)	61 (22.1 %)		47 (17.0 %)
95% CI for SD Rates*	[17.3; 27.5]		[12.8; 22.0]
Progressive Disease (PD)	15 (5.4 %)		7 (2.5 %)
95% CI for PD Rates*	[3.1; 8.8]		[1.0; 5.2]
Missing/not evaluable	40 (14.5 %)		29 (10.5 %)

Value Of RSBOR But nPR Recoded To PR (RSBOR2)

BOR - best overall response based on investigator response assessment.
* 95% CI for one sample binomial using Pearson-Clopper
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with best overall response of CR, PR or nPR

End of Treatment Response

As expected, the ETR rate was lower than the BOR rate in both treatment arms and this was mainly due to a lower CR rate. The proportion of patients with a response (CR/(n)PR) at the end of treatment was significantly higher in the R-FC arm (63.4%) compared to the FC arm (52.9%, p=0.0123, Chi-square test) (Table 37). Both CR and PR rates were approximately 5% higher in the R-FC arm than in the FC arm. More patients in the FC arm than in the R-FC arm had PD at the end of treatment (10.9% versus 6.5%).

Table 37. Summary of End of Treatment Response (ITT/FAS, Investigator Assessment)

	FC (N=276)		R-FC (N=276)
Responders$	146 (52.9 %)		175 (63.4 %)
Non-Responders	130 (47.1 %)		101 (36.6 %)
95% CI for Response Rates*	[46.8; 58.9]		[57.4; 69.1]
Difference in Response Rates		10.51	
95% CI for Difference in Response Rates#		[2.1; 18.9]	
p-Value (Chi-squared Test)		0.0123	
Odds Ratio		1.54	
95% CI for Odds Ratio		[1.10;2.17]	
Complete Response (CR)	25 (9.1 %)		38 (13.8 %)
95% CI for CR Rates*	[5.9; 13.1]		[9.9; 18.4]
Difference in CR Rates		4.71	
95% CI for Difference in CR Rates#		[-0.8; 10.2]	
p-Value (Chi-squared Test)		0.0818	
Odds Ratio		1.60	
95% CI for Odds Ratio		[0.94;2.74]	
Partial Response (PR and nPR)	121 (43.8 %)		137 (49.6 %)
95% CI for PR and nPR Rates*	[37.9; 49.9]		[43.6; 55.7]
Difference in PR and nPR Rates		5.80	
95% CI for Difference in PR and nPR Rates#		[-2.7; 14.3]	
p-Value (Chi-squared Test)		0.1723	
Odds Ratio		1.26	
95% CI for Odds Ratio		[0.90;1.76]	
Stable Disease (SD)	60 (21.7 %)		54 (19.6 %)
95% CI for SD Rates*	[17.0; 27.1]		[15.1; 24.7]
Progressive Disease (PD)	30 (10.9 %)		18 (6.5 %)
95% CI for PD Rates*	[7.5; 15.2]		[3.9; 10.1]
Missing/not evaluable	40 (14.5 %)		29 (10.5 %)

Value Of RSETR But nPR Recoded To PR (RSETR2)

ETR - End of Treatment Response based on investigator response assessment.
* 95% CI for one sample binomial using Pearson-Clopper
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with end of treatment response of CR,PR or nPR

Molecular Response

Minimal residual disease (MRD) assessment was only scheduled in patients achieving a CR in this study, ie, 36/276 in the FC arm and 67/276 in the R-FC arm. As a result, information on molecular response in blood is available for only a limited number of patients (32/276 [12%] patients in FC and 37/276 [13%] patients in R-FC based on MRD assessment in blood). Using the available information, the percentage of patients who achieved a high quality (MRD-negative) response was higher in patients who had received R-FC compared with patients who had received FC (16/37 [43%] R-FC versus 10/32 [31%] FC). Only 2 patients in each arm were MRD-negative at the second assessment (2/32 FC, 2/37 R-FC).

Similarly, information on molecular response in bone marrow was assessed in very few patients (FC 13/276 [5%]; R-FC 24/276 [9%]), due to the relatively low CR rate. In addition, fewer bone marrows were assessed than blood samples in

patients achieving a CR because of patient reluctance, hypocellular marrows or other factors, making it difficult to draw any conclusions. However, at the first MRD assessment a similar proportion of patients in each treatment group achieved a MRD-negative CR (4/13 [31%] FC versus 8/24 [33%] R-FC). Very few patients had a second bone marrow MRD assessment (4 FC versus 7 R-FC) and only one patient in each arm was MRD-negative (1/4 FC, 1/7 R-FC).

Duration of Response

The duration of response was assessed in patients with a best response of CR or (n)PR. Duration of response was measured the time from first response to the time of documented disease relapse, progression or death from any cause.

The median duration of response was significantly longer in the R-FC arm (39.6 months, 1204 days) than in the FC arm (27.6 months, 841 days) (p = 0.0252, Log-Rank test). The unadjusted HR was 0.69 (95% CI: 0.50; 0.96; p = 0.0260, Wald test). Fifty-eight percent of the patients in the FC arm, and 65% of those in the R-FC arm, were event free at two years. The number of deaths was similar in each treatment arm (FC 8/158 [5.1%] versus R-FC 9/188 [4.8%]) but there was a higher incidence of disease progression in the FC arm (FC 63/158 [39.9%] versus R-FC 58/188 [30.9%]). The Kaplan-Meier curves of duration of response start to separate after approximately a year. A stratified analysis factoring in previous (pooled) chemotherapy, beta-2 microglobulin > ULN and time from first diagnosis (years) was similar to the non-stratified analysis, with a HR 0.65 (95%CI 0.46; 0.93, p-value 0.0180 Wald test).

Disease Free Survival

Disease free survival (DFS) was defined as the interval from first documented CR to disease progression or death, in patients with a BOR of CR.

Of 103 patients included in the DFS analyses, two thirds came from the R-FC arm (36 FC, 67 R-FC). Of all the patients who achieved a BOR of CR, 10 patients on FC (27.8%) and 19 patients on R-FC (28.4%) progressed or died. The median time to progression or death for these patients was 42.2 months (1285 days) and 39.6 months (1204 days) for patients on FC and R-FC, respectively. A stratified analysis of DFS, factoring in previous (pooled) chemotherapy, beta-2 microglobulin > ULN and time from first diagnosis, was similar to the non-stratified analysis, with unadjusted HR 1.25 (95% CI 0.46; 3.37, p-value = 0.6598 Wald test).

Time to New Treatment for Chronic Lymphocytic Leukemia

At the time of the analysis, a total of 198 patients (40% in FC; 32% in R-FC) had started a new treatment for CLL or died. The median time from randomization to new CLL treatment or death was significantly longer for patients in the R-FC arm (median not yet reached) than for those in the FC arm (median 1042 days [34.2 months]) (p = 0.0024, Log-Rank test). The risk for new treatment or death was significantly reduced by 35% for patients in the R-FC arm compared to patients in the FC arm (unadjusted HR 0.65; p = 0.0026, Wald test). The Kaplan-Meier curves begin to separate at approximately 3 months after randomization in favour of the R-FC treatment arm. Results were similar in the stratified analysis (factoring in previous chemotherapy, beta-2 microglobulin > ULN and time from

first diagnosis) of time to new treatment or death (unadjusted HR 0.65 95% CI [0.48; 0.88], p-value 0.0057).

Subsequent Treatments for Chronic Lymphocytic Leukemia

More patients in the FC arm than in the R-FC arm started a new treatment for CLL subsequent to study treatment (25% on FC versus 17% on R-FC). The most common new treatments included:

- Monoclonal antibodies (15% FC versus 7% R-FC) including rituximab (9% FC versus 4% R-FC), alemtuzumab (7% FC versus 3% R-FC)
- Alkylating agents (12% FC versus 8% R-FC) including cyclophosphamide (10% FC versus 6% R-FC), chlorambucil (2% patients in each treatment arm)
- Corticosteroids (7% FC versus 6% R-FC) including prednisone (3% in each treatment arm) and dexamethasone (2% FC versus 1% R-FC)
- Antimetabolites (7% FC versus 5% R FC) including fludarabine (5% FC versus 4% R-FC) and cytarabine (< 1% in each treatment arm)
- Antineoplastic agents (6% FC versus 4% R-FC) including CHOP (3% FC versus 1% R-FC), CHOP plus rituximab (1% FC versus < 1% R-FC)
- Vinca alkaloids (4% patients in each treatment arm) mainly vincristine (3% FC versus 4% R-FC).

Out of 69 patients in the FC arm who relapsed and received subsequent therapy, 49% received rituximab as part of the subsequent treatment. Out of 47 patients in the R-FC arm who relapsed and received subsequent therapy, 30% received rituximab as part of the subsequent treatment. At least 2 patients in the FC arm also received subsequent rituximab as a treatment for autoimmune complications. Since only the first subsequent treatment for CLL was collected it is not known how many patients received rituximab at a later date.

Subgroup and Exploratory Analyses

Progression-Free Survival Subgroup Analyses

The impact of potential prognostic factors on the treatment effect was assessed by analyzing baseline characteristics, as outlined in Section 6.3. Risk ratios for PFS with 95% CI (R-FC versus FC) for patient subgroups based on baseline factors are presented in Figure 11 and based on putative prognostic markers in Figure 12. Overall, the results of the PFS subgroup analyses were consistent with the PFS 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 almost all of the 48 subgroups analyzed, with unadjusted HR ranging from 0.2 (subgroup positive ZAP-70/mutated IgVH) to 1.04 (CD38-negative). Figure 11, Figure 12.

Of note, the risk of progression or death was reduced in patients with and without 17p deletions (17p deletion is a poor prognostic marker and associated with treatment resistance).

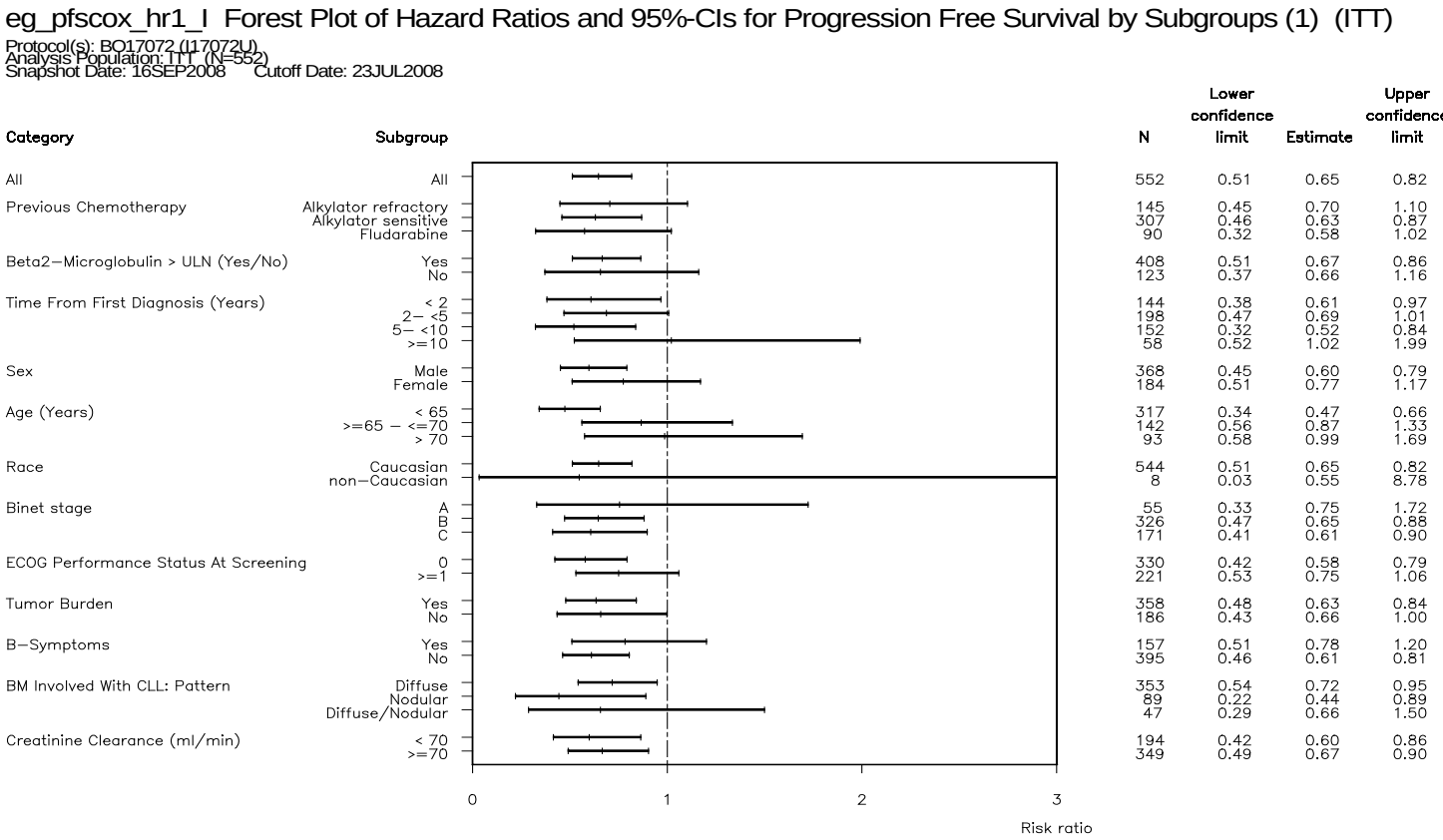
In addition, the risk of disease progression or death was meaningfully reduced by the addition of rituximab to FC for all subgroups of patients according to Binet stage (Figure 11). Compared with the FC regimen, R-FC reduced the risk of disease progression or death by 25% in 55 patients with Binet stage A disease, by 35% in 326 patients with Binet stage B disease, and by 39% in 171 patients with Binet stage C disease. This is somewhat different to the PFS subgroup analysis in the pivotal CLL-8 study in previously untreated patients with CLL (Table 38). In this study, the effect of rituximab was most pronounced in the subgroup of patients with Binet stage A disease (unadjusted HR 0.13, 95% CI [0.03;0.61]) and Binet stage B disease (unadjusted HR 0.45, 95% CI [0.32; 0.63]), whereas the risk reduction in patients with Binet stage C disease was less pronounced (unadjusted HR 0.88, 95% CI [0.58; 1.33]).

In the CLL-8 study, the less pronounced treatment effect of rituximab in the previously untreated patients with Binet stage C CLL was possibly related to an imbalance in baseline prognostic markers (unmutated IgVH and ZAP-70) favoring the FC arm. Overall, the findings in the REACH study support the administration of rituximab in combination with chemotherapy to patients with low, intermediate, and high risk CLL.

Table 38. Hazard Ratios for Progression-free Survival for Patient Subgroups According to Binet Staging (REACH and CLL-8 studies)

	REACH N=552	CLL-8 N=810
Binet Stage A		
N	55	40
HR (95% CI)	0.75 (0.33, 1.72)	0.13 (0.03, 0.61)
Binet Stage B		
N	326	516
HR (95% CI)	0.65 (0.47, 0.88)	0.45 (0.32, 0.63)
Binet Stage C		
N	171	251
HR (95% CI)	0.61 (0.41, 0.90)	0.88 (0.58, 1.33)

Figure 11. Hazard Ratios and 95% Confidence Intervals for Progression-Free Survival by Subgroup – Part I (ITT, Investigator Assessments)



PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.
Censoring occurs at last response assessment

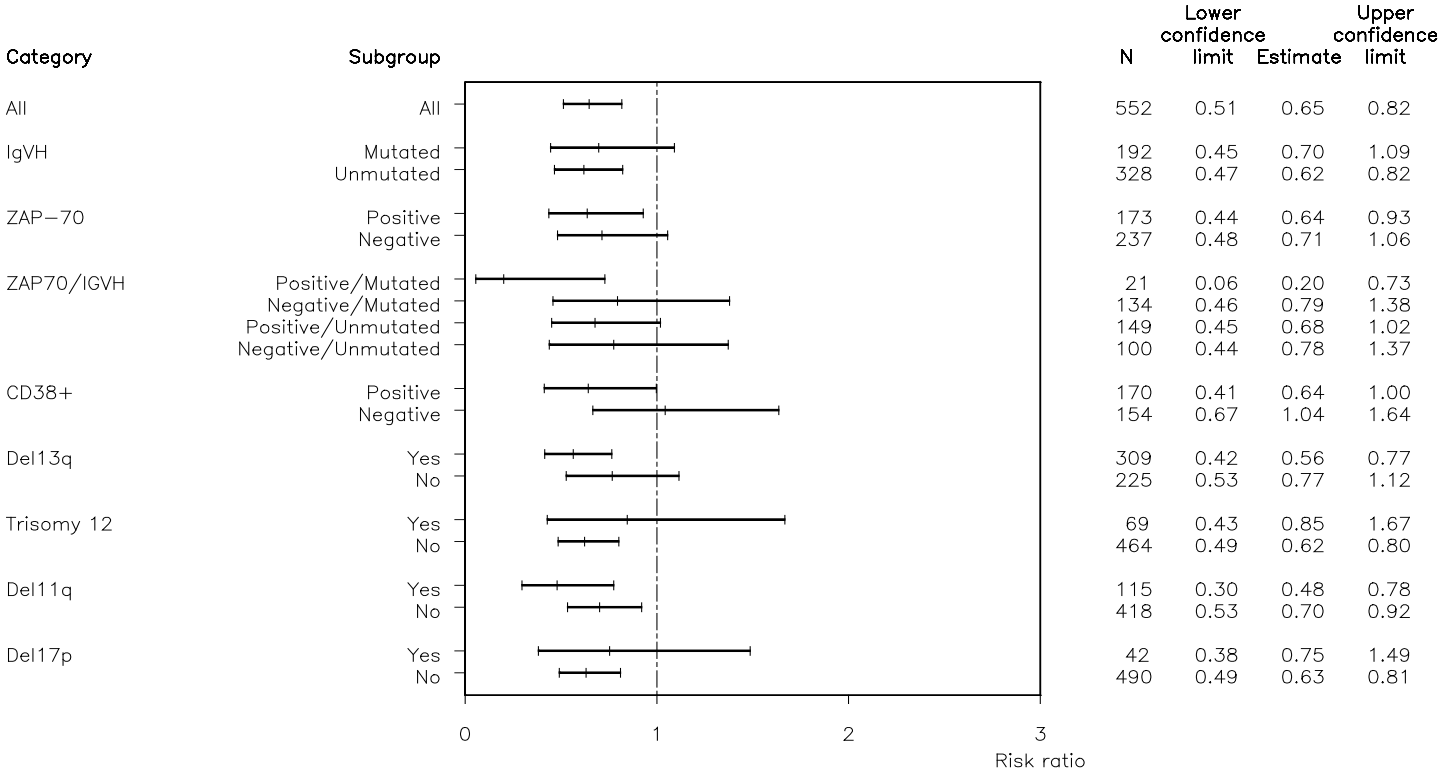
Program : $PROD/cd11899a/i17072a/eg_pfscox_hr1.sas / Output : $PROD/cd11899a/i17072u/reports/eg_pfscox_hr1_I.cgm
23SEP2008 17:08

Note: tumor burden is based on lymphocyte counts

Figure 12. Hazard Ratios and 95% Confidence Intervals for Progression-Free Survival by Subgroup – Part II (ITT, Investigator Assessments)

eg_pfscox_hr2_I Forest Plot of Hazard Ratios and 95%-CIs for Progression Free Survival by Subgroups (2) (ITT)

Protocol(s): BO17072 (I17072U)
Analysis Population: ITT (N=552)
Snapshot Date: 16SEP2008 Cutoff Date: 23JUL2008



PFS - day of randomization until 1st documented disease progression, relapse after response or death from any cause - investigator assessment.
Censoring occurs at last response assessment

Program : $PROD/cd11899a/i17072a/eg_pfscox_hr2.sas / Output : $PROD/cd11899a/i17072u/reports/eg_pfscox_hr2_I.cgm
23SEP2008 17:09

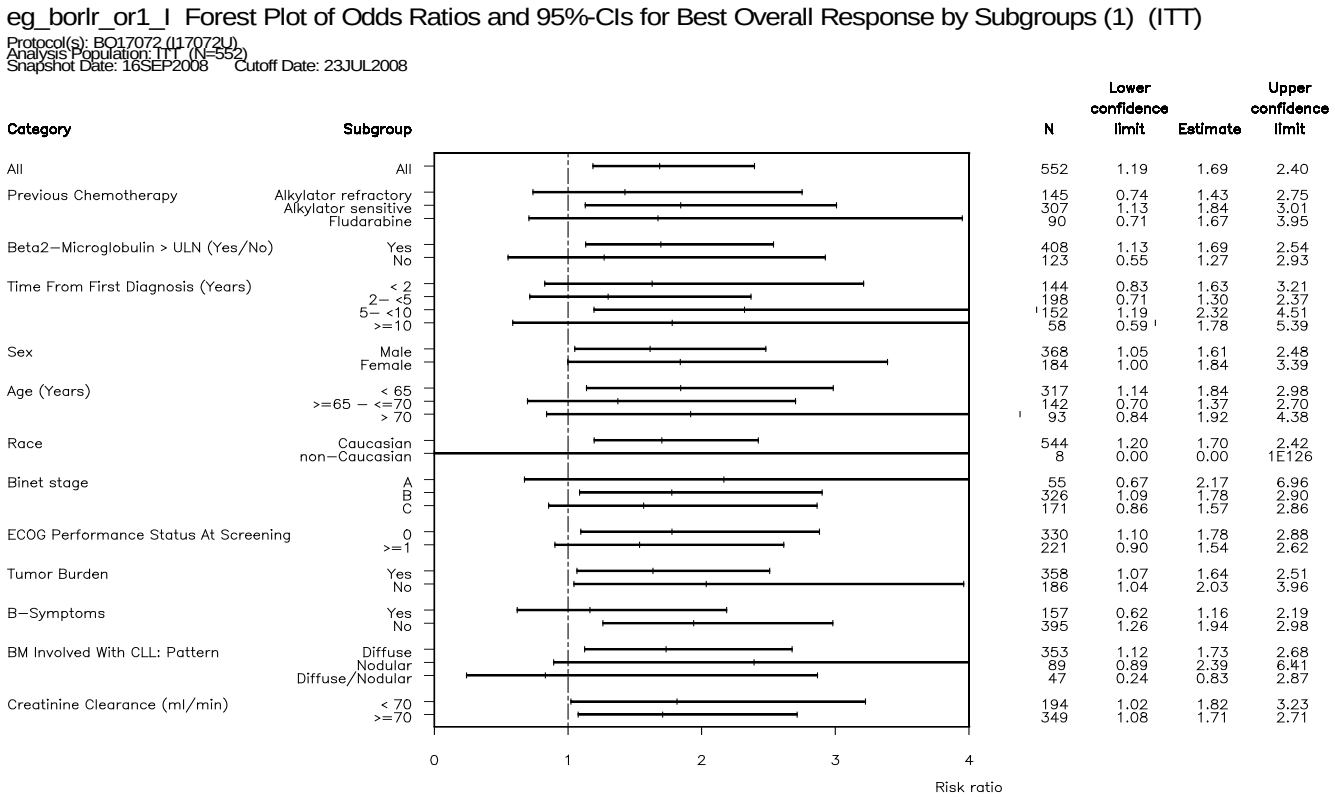
Overall Survival Subgroup Analyses

Subgroup analyses for OS demonstrated a tendency towards a reduced risk of death with R-FC compared to FC for most of the subgroups analyzed. However, due to the small number of events, further follow-up is needed to confirm the results. Therefore, the current findings should be interpreted with caution.

Best Overall Response Subgroup Analysis

A subgroup analysis defined by potential prognostic baseline factors, Figure 13**,** and putative prognostic markers, Figure 14, on the BOR revealed that the addition of rituximab was beneficial in all subgroups (ranged from odds ratio = 1.27 in patients with beta-2 microglobulin < ULN to odds ratio = 2.50 in Del17p-positive patients) apart from the subgroup of patients with diffuse nodular bone marrow. In this small subgroup of patients with diffuse/nodular bone marrow involment (N = 47) the odds ratio was 0.83. For non-Caucasian patients (N = 8) no estimate of odds ratio could be calculated because there were no non-responders.

Figure 13. Forest Plot of Odds Ratios and 95% CIs for Best Overall Response by Subgroups (1) ITT



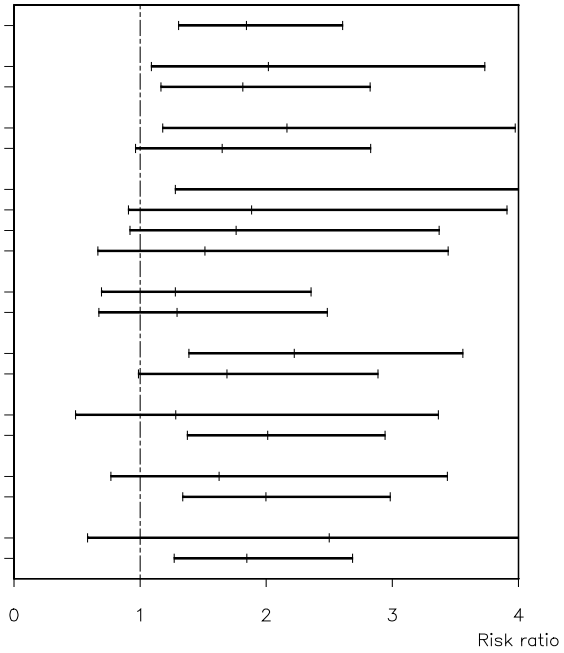
BOR - best overall response based on investigator response assessment.

Program : $PROD/cd11899a/i17072a/eg_borlr_or1.sas / Output : $PROD/cd11899a/i17072u/reports/eg_borlr_or1_l.cgm
03OCT2008 13:08

Figure 14. Forest Plot of Odds Ratios and 95% CIs for Best Overall Response by Subgroups (2) (ITT)

eg_borlr_or2_I Forest Plot of Odds Ratios and 95%-CIs for Best Overall Response by Subgroups (2) (ITT)

Protocol(s): BO17072 (I17072U)
Analysis Population: ITT (N=552)
Snapshot Date: 16SEP2008 Cutoff Date: 23JUL2008



Category	Subgroup	N	Lower confidence limit	Estimate	Upper confidence limit
All	All	552	1.30	1.84	2.61
IgVH	Mutated	192	1.09	2.02	3.73
	Unmutated	328	1.17	1.81	2.82
ZAP−70	Positive	173	1.18	2.17	3.97
	Negative	237	0.96	1.65	2.83
ZAP70/IGVH	Positive/Mutated	21	1.28	10.00	78.12
	Negative/Mutated	134	0.91	1.88	3.91
	Positive/Unmutated	149	0.92	1.76	3.37
	Negative/Unmutated	100	0.67	1.51	3.44
CD38+	Positive	170	0.69	1.28	2.35
	Negative	154	0.67	1.29	2.48
Del13q	Yes	309	1.39	2.22	3.56
	No	225	0.99	1.69	2.89
Trisomy 12	Yes	69	0.49	1.28	3.36
	No	464	1.37	2.01	2.94
Del11q	Yes	115	0.77	1.63	3.44
	No	418	1.34	2.00	2.98
Del17p	Yes	42	0.58	2.50	10.70
	No	490	1.27	1.85	2.68

BOR - best overall response based on investigator response assessment.

Program : $PROD/cd11899a/i17072a/eg_borlr_or2.sas / Output : $PROD/cd11899a/i17072u/reports/eg_borlr_or2_I.cgm
03OCT2008 13:09

Quality of Life

A QoL assessment using FACT-G was made over a one year period with assessments at screening, 3 months, 6 months, and 6 months after the end of treatment (ie, 1 year after study entry). If a patient went into the survival follow-up phase prior to the 1 year assessment for any reason, no further QoL assessments were performed. This means that patients with PD and patients withdrawn from the study for AEs or other reasons were lost at or before the 1 year time point. However, patients with stable disease who started an alternative CLL treatment should have continued to provide QoL data until PD or 1 year.

The FACT-G is a questionnaire which assesses physical well-being, social and family well-being, emotional well-being, and functional well-being. The maximum score on FACT-G is 112. In the REACH study, the initial scores at screening (median 79.5 and 80.0 in the FC and R-FC arms respectively) were high and these did not change substantially over the study period (Table 39). The differences between the study arms were very small at every time point.

Table 39. Summary Of FACT-G Total Score And Sub-Scores Over Time (ITT)

FACT-G Parameter/ Timepoint		FC N=276	R-FC N=276
Total Score			
SCREENING	Mean	78.50	79.61
	SD	14.57	14.48
	Median	79.50	80.00
	Min	36.00	21.00
	Max	108.00	108.00
	n	263	265
AFTER CYCLE 3	Mean	79.33	79.92
	SD	14.47	14.47
	Median	80.87	81.92
	Min	46.50	31.00
	Max	108.00	108.00
	n	206	218
AFTER CYCLE 6	Mean	81.99	81.92
	SD	15.58	14.70
	Median	84.00	84.00
	Min	22.50	23.00
	Max	108.00	108.00
	n	166	187
FU MONTH 12	Mean	82.16	82.86
	SD	15.97	15.94
	Median	83.10	85.00
	Min	32.60	25.00
	Max	107.00	108.00
	n	162	182

Analysis of the FACT-G score change from baseline over time also showed no meaningful difference in QoL between the two treatment arms.

Summary and Conclusions - Efficacy

The results of this study demonstrated a highly statistically significant and clinically meaningful benefit when rituximab was used in combination with FC chemotherapy in patients with relapsed/refractory CLL. The primary endpoint of PFS was prolonged by a median of 10 months (20.6 months for FC and 30.6 months for R-FC) and the risk of disease progression or death was reduced by

35% when rituximab was added to the FC regimen (p=0.0002, Log-Rank test). These benefits were robust and apparent in almost all of the 48 pre-specified subgroups. The (unadjusted) hazard ratios for these subgroups ranged from 0.20 (subgroup of patients with positive ZAP-70/mutated IgVH) to 1.04 (CD38-negative patients). As the study was not powered to detect differences in subgroups no firm conclusions can be drawn about the benefit of adding rituximab to FC chemotherapy in these subgroups.

At time of analysis, with a median observation time of 25.3 months, the OS data were immature and did not demonstrate a statistically significant advantage in OS when rituximab was added to FC. The median for OS in the FC arm was 51.9 months and had not yet been reached for the R-FC arm (p = 0.2874, Log-Rank test, risk reduction of 17%).

Significantly more patients in the R-FC arm than in the FC arm had a best overall response of PR or CR (ORR = 58.0% FC versus 69.9% R-FC, p = 0.0034, Chi-square test), and this was mostly due to a significantly higher CR rate (13.0% FC versus 24.3% R-FC, p = 0.0007, Chi-square test). As expected, some patients with a PR at the end of treatment improved to a CR at a later time point, after their bone marrows recovered from treatment.

A higher proportion of patients in the FC arm (59%) experienced an EFS event (disease progression, death or new treatment for CLL) in comparison with the R-FC arm (49%). This was mainly due to more patients in the FC arm with PD. The median EFS was significantly increased by 9.5 months from 19.2 months in the FC arm to 28.7 months in the R-FC arm (p = 0.0002, Log-Rank test, risk reduction of 36%). More patients received a new treatment for CLL before documentation of PD in the FC arm than in the R-FC arm (7% FC versus 3% R-FC).

At the time of the analysis, a total of 198 patients (40% in FC; 32% in R-FC) had started a new treatment for CLL or died. The risk for new treatment or death was significantly reduced by 35% for patients in the R-FC arm compared to patients in the FC arm (p = 0.0024, Log-Rank test).

The median duration of response, assessed in patients with a BOR of CR or PR, was significantly longer in the R-FC arm, (median 39.6 months) than in the FC arm (median 27.6 months), a difference of 12 months (p = 0.0252, Log-Rank test).

Of the 103 patients (36 FC, 67 R-FC) who achieved a BOR of CR, 10 patients on FC (27.8%) and 19 patients on R-FC (28.4%) had progressed or died. The median time to progression or death for these patients was similar in the two arms (p = 0.8842, Log-Rank test, HR 1.06). In this study the lack of difference in DFS between the treatment arms suggests that patients with relapsed/refractory CLL who achieve a CR have a similar outcome regardless of how CR is achieved. A QoL assessment using FACT-G over the period of one year did not reveal any differences between the treatment groups. The initial QoL scores were similar and high in both treatment arms and continued as such over the 1 year assessment period. Since QoL was not captured in patients with disease progression and was captured in patients who started a new CLL treatment before progression, these findings need to be interpreted with caution.

Overall the investigator based PFS benefit was shown to be robust and internally consistent.

6.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 0 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

Not applicable – only one randomised Phase III study available

6.6 Indirect/mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. An 'indirect comparison' refers to the synthesis of data from trials in which the technologies of interest have not been compared in head-to-head trials, but have been compared indirectly using data from a network of trials that compare the technologies with other interventions.

When head-to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. A 'mixed treatment comparison' refers to an analysis that includes trials that compare the interventions of interest head-to-head and trials that compare them indirectly. This mixed treatment comparison must be fully described and presented as additional to the reference-case analysis (a 'mixed treatment comparison' includes trials that compare the interventions head-to-head and indirectly).

When multiple technologies are being appraised that have not been compared within a single RCT, data from a series of pairwise head-to-head RCTs should be presented. Consideration should also be given to presenting a combined analysis using a mixed treatment comparison framework if it is considered to add information that is not available from the head-to-head comparison.

The principles of good practice for standard meta-analyses should also be followed in mixed and indirect treatment comparisons.

Not applicable.

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 (previously treated patients) is based on data from the phase III study REACH, together with a combination of safety data reported in seven Phase II studies with different base chemotherapy regimes. In REACH a total of 546 (out of 552) 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 189 extra patients.

6.7.2 Safety Data from REACH

Extent of Exposure to Trial Medication

A total of 546/552 patients received at least one dose of study medication and were therefore included in the SAP. Six patients were excluded from the SAP because they did not receive study medication. Patients were analyzed according to the treatment they actually received.

More patients in the R-FC arm received 6 cycles of therapy compared to the FC arm (67.5% [185/274] in R-FC versus 61.4% [167/272] in FC; Table 40). Most patients who stopped treatment early did so for safety reasons, and the number was balanced between the two arms. More patients in the FC arm withdrew from study treatment due to PD or patient refusal (see Section 6.3.3). More patients in the FC arm had stable disease after 3 cycles and proportionally more of these stopped treatment for this reason compared with the R-FC arm: 92 patients in the FC arm had stable disease after 3 cycles: 79% continued study therapy (73 patients) and 21% did not (19 patients), compared with 73 patients in the R-FC arm who had SD after 3 cycles: 88% continued study therapy (64 patients) and 12% did not (9 patients).

Table 40. Summary of Number of Treatment Cycles Received (SAP)

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

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

6.7.2.1 Adverse Events

Overview of Adverse Events

An overview of the safety data reported in this study with a clinical cut-off date of July 23, 2008 is shown in Table 41. Safety analyses of the REACH study are based on the safety population (SAP).

In summary:

- Almost all patients in both arms experienced at least one AE. However, the majority of events were Grade 1/2 in severity
- Seventy-four percent of patients in FC and 80% of patients in R-FC experienced at least one Grade 3/4 AE. The most common Grade 3/4 AEs reported were blood and lymphatic system disorders, and infections and infestations.
- The incidence of SAEs and fatal AEs was also higher in the R-FC arm.
- More patients had their treatment modified or interrupted for safety reasons in the R-FC arm.
- There were slightly more treatment-related deaths in the R-FC arm. However, overall there were slightly more deaths in the FC arm than in the R-FC arm.
- There were no clear and consistent trends for an increased incidence of AEs, Grade 3/4 AEs or SAEs with increasing baseline lymphocyte count or Binet stage (in either arm).
- Overall, the safety profile of rituximab in CLL was consistent with its expected safety profile.

Table 41. Overview of Adverse Event Incidence – Safety Population

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

Common Adverse Events

All Grade Adverse Events

Almost all patients experienced at least one adverse event (96% in FC, 99% in R-FC). However, the majority of events (70% in FC; 71% in R-FC) were Grade 1/2 in severity. Overall, patients in the R-FC arm experienced more AEs than patients in the FC arm (1468 AEs in FC, 1797 AEs in R-FC), mostly due to AEs in the following system organ classes (SOCs):

- vascular disorders (4% patients in FC vs 17% of patients in R-FC experienced at least one AE)
- general disorders (46% patients in FC vs 54% in R-FC experienced at least one AE),
- respiratory, thoracic and mediastinal disorders (21% patients in FC vs 28% in R-FC experienced at least one AE)
- skin and subcutaneous tissue disorders (25% patients in FC vs 31% in R-FC experienced at least one AE)
- metabolism and nutrition disorders (9% patients in FC vs 15% in R-FC experienced at least one AE)

Adverse events in the following SOCs also had a slightly higher incidence in the R-FC than in the FC arm:

- musculoskeletal and connective tissue disorders (18% FC vs 22% R-FC)
- gastrointestinal disorders (55% FC vs 58% R-FC)
- blood and lymphatic system disorders (67% FC vs 70% R-FC)
- ear and labyrinth disorders (<1% FC vs 3% R-FC)

The incidence of all Grade AEs according to other SOCs (including infections and infestations) were balanced between the treatment arms.

All Grade AEs which occurred with an at least 2% higher incidence in the R-FC arm than in the FC arm are summarized in Table 42. Overall, the slightly higher frequencies and the types of events (all Grades) observed in the R-FC arm are consistent with the known safety profile of rituximab and do not pose any new safety concerns.

Table 42. Summary of Adverse Events with ≥ 2% Higher Incidence in the R-FC Arm Compared to the FC Arm

Body System/ Adverse Event	FC N=272 No. (%)	R-FC N=274 No. (%)
GASTROINTESTINAL DISORDERS		
NAUSEA	96 (35.3)	109 (39.8)
VOMITING	51 (18.8)	57 (20.8)
CONSTIPATION	29 (10.7)	40 (14.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	114 (41.9)	122 (44.5)
FEBRILE NEUTROPENIA	34 (12.5)	43 (15.7)
GRANULOCYTOPENIA	12 (4.4)	18 (6.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
PYREXIA	42 (15.4)	68 (24.8)
CHILLS	6 (2.2)	42 (15.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
COUGH	24 (8.8)	34 (12.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
PRURITUS	13 (4.8)	20 (7.3)
URTICARIA	3 (1.1)	15 (5.5)
VASCULAR DISORDERS		
HYPOTENSION	2 (0.7)	22 (8.0)
HYPERTENSION	2 (0.7)	8 (2.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
MYALGIA	2 (0.7)	9 (3.3)

Multiple occurrences of the same adverse event in one individual counted only once.
Only AEs with a missing onset date or an onset date on or after the date of first trial medication are considered.

Grade 3 or 4 Adverse Events

The severity of AEs was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Overall, the proportion of patients reporting at least one Grade 3/4 AE was slightly higher in the R-FC arm than in the FC arm (80% versus 74%), mostly due to an imbalance (≥ 2% difference) in the following SOCs:

- blood and lymphatic system disorders (60% patients in FC versus 65% in R-FC with at least one Grade 3/4 event)
- general disorders (6% patients in FC versus 8% patients in R-FC with at least one Grade 3/4 event)
- benign and malignant neoplasms (3% patients in FC versus 7% R-FC with at least one Grade 3/4 event)

- vascular disorders (1% patients in FC versus 4% patients in R-FC with at least one Grade 3/4 event)
- investigations (1% patients in FC versus 4% patients in R-FC with at least one Grade 3/4 event)
- metabolism ad nutrition disorders (<1% patients in FC versus 3% patients in R-FC with at least one Grade 3/4 event)

The incidence of Grade 3/4 AEs in other SOCs (including infections and infestations) was balanced between the treatment arms.

Grade 3/4 AEs which occurred with a 2% or higher incidence in the R-FC arm compared with the FC arm are summarized in Table 43, and include (febrile) neutropenia, granulocytopenia and hepatitis B infections.

Table 43. Summary of Grade 3/4 Adverse Events with ≥ 2% Higher Incidence in the R-FC Arm Compared to the FC Arm (SAP)

Body System/ Adverse Event	FC N=272 No. (%)	R-FC N=274 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	108 (39.7)	116 (42.3)
FEBRILE NEUTROPENIA	32 (11.8)	40 (14.6)
GRANULOCYTOPENIA	12 (4.4)	18 (6.6)
INFECTIONS AND INFESTATIONS		
HEPATITIS B	-	6 (2.2)

Multiple occurrences of the same adverse event in one individual counted only once.
Only AEs with a missing onset date or an onset date on or after the date of first trial medication are considered.

The proportion of Grade 3/4 AEs considered by the investigators to be related to treatment was slightly higher in the R-FC arm (83% in FC vs 86% in R-FC). The higher incidence occurred within the blood and lymphatic system disorders SOC (36% FC vs 41% R-FC) and within the infections and infestations SOC (8% FC vs 11% R-FC).

Overall, with the exception of hepatitis B, the slightly higher frequencies and the types of Grade 3/4 adverse events observed in the R-FC arm are consistent with the known safety profile of rituximab and do not pose any new safety concerns.

Deaths, Serious Adverse Events and Events Leading to Treatment Withdrawals, Dose Modifications or Interruptions

Deaths

At the time of clinical cut-off (July 23, 2008), a total of 130 patients had died. There was a slightly higher number of deaths in the FC arm than in the R-FC arm (68 patients (25%) and 62 patients (23%), respectively).

General disorders and administration site conditions, including progressive disease, were the major cause of death in both treatment arms (18 patients (7%) in FC vs 17 patients (6%) in R-FC). Nineteen patients (8 patients (3%) in FC and

11 patients (4%) in R-FC) died due to benign, malignant or unspecified neoplasms. Infections and infestations (including pneumonia, septic shock and sepsis) were responsible for the deaths of 19 patients (7%) in the FC arm and 14 patients (5%) in the R-FC arm. Fourteen patients died due to cardiac disorders (6 patients (2%) in FC, 8 patients (3%) in R-FC).

The investigator considered 14 deaths (5%) in the FC arm and 19 deaths (7%; including one death due to Stevens-Johnson syndrome [probably related to cefotaxime] and one death from Hodgkin's disease/CLL transformation) in the R-FC arm related to treatment. Of the 33 patients who died from infections and infestations, 16 deaths were considered to be related to study treatment (3% [7/272] in FC vs 3% [9/274] in R-FC).

Serious Adverse Events

Overall, a slightly higher incidence of SAEs was observed in the R-FC arm (130 patients [48%] in FC; 137 patients [50%] in R-FC with at least one SAE).

A slight increase in incidence of febrile neutropenia was observed in the R-FC arm (11%) compared to the FC arm (8%), while there was a higher incidence of anemia (reported as an SAE) in the FC arm (4% in FC vs 1% in R-FC). An equal number of patients in each arm (54 patients [20%]) experienced an SAE categorized under infections and infestations, although SAEs of hepatitis B infection occurred uniquely in the R-FC arm (5 patients).

Thirty-six percent (36%) of the patients in the FC arm experienced at least one treatment-related SAE compared to 39% of patients in the R-FC arm. This slight difference was driven by a higher incidence of general disorders in the R-FC arm: 14 events versus 6 events in the FC arm (mainly pyrexia).

A slight increase in incidence of serious febrile neutropenia was observed in the R-FC arm (8% FC vs 11% R-FC). Most of these cases (8% FC vs 9% R-FC) were considered related to treatment. A higher incidence of serious anemia was noted in the FC arm (4% FC vs 1% R-FC). All of these cases were considered related to treatment.

Twenty-six patients in the FC arm experienced a fatal SAE, 14 of which were considered related to treatment, compared to 36 patients in the R-FC arm, 19 of which were considered related to treatment.

Adverse Events Leading to Treatment Discontinuation, Dose Modifications or Interruptions

The proportion of patients who discontinued treatment due to AEs was similar between the treatment arms (69 pts [25%] in FC, 72 pts [26%] in R-FC). The most common AEs that led to treatment discontinuation were blood and lymphatic system disorders (19% in FC, 17% in R-FC), such as neutropenia (7% in FC, 5% in R-FC) and thrombocytopenia (4% in each arm), and infections and infestations (5% in each arm).

Adverse events leading to dose modifications or interruptions were reported more often in the R-FC arm than the FC arm (39% patients in FC, 51% patients in R-FC). The most common reasons for dose modifications or interruptions in the

two arms were blood and lymphatic system disorders (26% in FC, 23% in R-FC), and infections and infestations (10% in each arm).

More patients in the R-FC arm had the dose modified or interrupted because of general disorders and administration site conditions (4% in FC, 14% in R-FC), gastrointestinal disorders (1% in FC, 7% in R-FC), vascular disorders (none in FC, 6% in R-FC), skin and subcutaneous tissue disorders (< 1% in FC, 5% in R-FC), cardiac disorders (none in FC, 3% in R-FC) and immune system disorders (none in FC, 3% in R-FC).

Overall, these findings are consistent with known manifestations of rituximab-related infusion-related reactions and the hematological effects of rituximab when used in combination with chemotherapy.

Adverse Events by Organ System or Syndrome

Infusion-related Reactions

Sixty-one percent of the patients in the R-FC arm reported at least one AE that started during or within 24 hours of finishing a rituximab infusion, most frequently events of the SOCs “general disorders and administration sites” and “GI disorders”. Eleven percent of the patients reported at least one Grade 3/4 and 4% experienced an SAE during or within 24 hours of finishing a rituximab infusion. No AE that started during or within 24 h of a rituximab infusion had a fatal outcome.

An analysis of AEs occurring on the first day of a treatment cycle or the next day was performed to enable a comparison with FC. The incidence of AEs occurring on the first day or the next day of a treatment cycle was higher in the R-FC arm than in the FC arm (48% of patients in FC vs 64% of patients in R-FC with at least one event). There was an increased incidence of typical rituximab infusion-related reactions (pyrexia, chills, pruritus, urticaria, etc) in the R-FC arm. The highest rate of Grade 3/4 AEs reported on the day of, or the day after the start of therapy occurred in the first treatment cycle (Cycle 1) in both arms (4% in FC, 6% in R-FC). In both arms, the number of patients with Grade 3/4 AEs gradually decreased over subsequent cycles with only 1% of patients experiencing a Grade 3/4 AE on the day of or the day after the start of therapy in Cycle 6.

Tumor Lysis Syndrome

Nine patients (3%) in the FC arm versus 6 patients (2%) in the R-FC arm had probable or definite tumor lysis syndrome (TLS). In 7 of these patients (5 in FC, 2 in R-FC), the events were serious and in 4 patients, the SAE resulted in or substantially contributed to the patient’s death (2 in FC, 2 in R-FC).

These data are in line with those observed in patients with previously untreated CLL. In the pivotal phase III CLL-8 trial, a higher incidence of TLS was observed in the FC arm compared to the R-FC arm (9 patients [2%] in FC vs 3 patients [1%] in R-FC). Almost all of these events were of Grade 3/4 severity, 5 events in the FC arm and 2 events in the R-FC arm were serious, but none of them were fatal.

These results in first- and second-line patients are fairly reassuring since the superior efficacy of R-FC might be expected to result in a higher incidence of TLS

due to a more rapid or dramatic onset of cell lysis with the initiation of therapy. Although the incidence of TLS was no higher in the R-FC arm than the FC arm in both studies, there were still 4 deaths in the REACH study (2 in each arm), highlighting the need for continued vigilance and a low threshold for prophylactic treatment. REACH required prophylactic allopurinol or rasburicase prior to treatment in all patients (after protocol amendment F) and there was a recommendation to investigators to slowly infuse rituximab and/or to split the dose over two days if peripheral lymphocyte counts were above 25 x 10^9/L.

Blood and Lymphatic System Disorders

Overall, as expected in a leukemia study, there was a high incidence of (all Grade) blood and lymphatic system disorders in both arms (67% in FC, 70% in R-FC). This high incidence of AEs was mainly driven by events of anemia, thrombocytopenia and white blood cell disorders. A higher proportion of patients in the R-FC arm experienced Grade 3/4 AEs (179 patients (65%) in R-FC vs 164 patients (60%) in FC), mainly due to slightly more events (2%-3% difference) of Grade 3/4 neutropenia, thrombocytopenia, febrile neutropenia and granulocytopenia in the R-FC arm compared to the FC arm. No patient in the R-FC arm experienced an event leading to death.

These data are similar to those obtained in previously untreated patients in the CLL-8 phase III trial (Table 44). In this study, as expected, the overall incidence of Grade 3/4 and SAEs of the blood and lymphatic system was lower than in REACH, but the difference between the treatment arms was higher.

Table 44. Summary of Blood and Lymphatic System Disorders (AEs) in Patients with CLL (REACH and CLL8 studies)

	REACH study		CLL-8 study	
	FC N=272	R-FC N=274	FC N=407	R-FC N=403
All Grade	181 (67%)	193 (70%)	n.a.	n.a.
Grade 3/4	164 (60%)	179 (65%)	161 (41%)	228 (57%)
Serious	53 (19%)	58 (21%)	44 (11%)	66 (17%)
Fatal	2 (< 1%)	–	2 (<1%)	1 (<1%)

Autoimmune Hemolytic Anemia

Overall, the incidence of autoimmune hemolytic anemia (AIHA) (all Grades) was similar in the two treatment arms (13 patients [5%] in FC, 12 patients [4%] in R-FC). However, more patients experienced a Grade 3/4 event in the FC arm (12 patients in FC vs 5 patients in R-FC). All except one (in the FC arm) of these Grade 3/4 events were considered serious by the investigator. There was no fatal event in either arm.

This observation is interesting in light of the fact that more patients were Coomb's positive at study entry in the R-FC arm (14%) than the FC arm (10%) and rituximab is used (off-label) to treat AIHA. This suggests that rituximab might have an additional protective effect against AIHA, which is a relatively frequent complication of CLL and also associated with fludarabine treatment. However, numbers are too small to draw any firm conclusions.

These data are in line with those observed in previously untreated patients in CLL-8. In this study, more patients in the FC arm than in the R-FC arm experienced a hemolytic event (2% FC versus 1% R-FC). Most of these were of Grade 3/4 intensity, none of which were fatal. Overall, however, these data are still too limited to say whether rituximab has an additional protective effect against AIHA in patients with CLL receiving FC chemotherapy. However, it does support the view that at least there is no detrimental effect.

Neutropenia

As expected, the most common Grade 3/4 hematological toxicities were neutropenia, thrombocytopenia and granulocytopenia.

The incidence of Grade 3/4 neutropenia and granulocytopenia was higher in the R-FC arm (91% and 87%, respectively) compared to the FC arm (85% and 71%, respectively). This was consistent with the higher incidence of Grade 3/4 neutropenia, febrile neutropenia and granulocytopenia, reported as AEs in the R-FC arm (42%, 15% and 7%, respectively) compared to the FC arm (40%, 12% and 4%, respectively, Table 45). Colony stimulating factors were also used more frequently in the R-FC arm (58% in the R-FC arm versus 49% in the FC arm).

Table 45. Incidence of Grade 3/4 Hematological Abnormalities (Laboratory Data, SAP)

	FC N = 272	R-FC N = 270*
Hemoglobin	50 (18%)	47 (17%)
White Blood Cells	193 (71%)	234 (87%)
Platelets	66 (24%)	75 (28%)
Neutrophils	230 (85%)	246 (91%)

* Laboratory data of 4 patients in the R-FC arm were not available

Thrombocytopenia

Thrombocytopenia is a common side effect of fludarabine and is known to occur in patients receiving rituximab-based therapy for NHL. However, in clinical trials of rituximab monotherapy (given for 4 weeks), thrombocytopenia only occurred in 1.7% of patients. When rituximab was given as maintenance treatment for up to 2 years to patients with NHL, the incidence of thrombocytopenia was low (< 1%) and no higher than in patients on observation alone. In the CLL-8 trial in patients with previously untreated CLL, the incidence of thrombocytopenia was lower in the R-FC arm than in the FC arm (10% in FC vs 7% in R-FC).

The incidence of thrombocytopenia in the R-FC arm of the REACH study was slightly higher than in the FC arm (11% versus 9% for Grade 3/4 AEs; 29% vs 26% for Grade 3/4 laboratory data).

Infections

The incidence of infections and infestations was similar in both treatment groups (51% [139/272] patients in FC versus 49% [135/274] in R-FC). Apart from a slightly higher incidence of bacterial infections in the FC arm (4%) compared to the R-FC arm (2%), the number of incidents recorded and the type of infections and infestations were comparable in the two treatment groups. Likewise, the

incidence of Grade 3/4 infections (including opportunistic infections) was comparable in the two treatment arms (19% FC vs 17% R-FC). However, the incidence of Grade 3/4 hepatitis B was higher in the R-FC arm than in the FC arm (0 patients in FC vs 5 patients in R-FC) and there were 2 deaths (both from fulminant primary hepatitis B infections).

Seven patients in the FC arm and 9 patients in the R-FC arm died due to infections and infestations that were considered related to treatment.

Apart from hepatitis B infections, these data are in line with those obtained in first-line patients in the CLL-8 study (Table 46). In this study, the incidence of all Grade, Grade 3/4 and serious infections was balanced between the treatment arms.

Table 46. Summary of Infections and Infestations in Patients with CLL (REACH and CLL8 studies)

	REACH study		CLL-8 study	
	FC N=272	R-FC N=274	FC N=407	R-FC N=403
All Grade Infections	139 (51%)	135 (49%)	n.a.	n.a.
Grade 3/4 Infections	51 (19%)	48 (18%)	67 (17%)	73 (18%)
Serious Infections	54 (20%)	54 (20%)	59 (15%)	71 (18%)
Fatal Infections	7 (2%)	9 (2%)	19 (5%)	12 (3%)

Overall, these results are reassuring since they indicate that despite a higher incidence in all Grade and Grade 3/4 AEs of the blood and lymphatic system (notably neutropenia) in patients treated with R-FC, this did not translate into a substantially higher incidence of infections or fatal infections.

Hepatitis B

As previously noted, there were more cases of hepatitis B in the R-FC arm than in the FC arm in the REACH study (7 patients in the R-FC arm versus 2 patients in the FC arm). The 7 cases of hepatitis B infection reported in R-FC arm (all Grades) included 3 primary infections, 2 reactivations, 1 chronic infection, and 1 case described as a primary infection followed by reactivation 3 weeks later. Two of the primary infections resulted in the patients' death. In comparison, there was 1 primary infection and 1 chronic infection in the FC arm (both Grade 1/2 and not considered serious).

In 5 of the 7 patients in the R-FC arm the event was Grade 3/4 in severity (versus none in the FC arm) and was considered serious by the investigator (versus none in the FC arm). In 2 of these patients, the hepatitis resulted in the patient's death (versus none in the FC arm).

It is important to note that in at least four cases (3 in R-FC and 1 in FC), the infection appears to have been a new primary infection rather than reactivation of latent hepatitis B. Furthermore, 4 of the patients who developed hepatitis were from Russia and 3 of these were from the same centre. All 3 patients from the same Russian center had a primary hepatitis B infection. These findings suggest that the relatively high incidence of hepatitis B in the REACH study may be related to recruitment of patients from regions or centers with a high risk of hepatitis B infection. Patients with CLL commonly need blood transfusions, and

this is one possible route of infection in such patients. The 3 patients from the Russian centre all had blood transfusions during the study. In previous rituximab trials in NHL or CLL (previously untreated patients), the incidence was lower and no clear imbalances were observed in hepatitis B infection (primary or reactivation). No cases of hepatitis B were reported in any of the supportive studies included in this submission.

Secondary Malignancies

Overall, 40 patients experienced 44 AEs classified as neoplasms (17/272 [6%] in FC; 23/274 [8%] in R-FC. Furthermore, 36 patients experienced SAEs classified as neoplasms (15 patients in FC and 21 patients in R-FC) and 12 patients had fatal AEs classified as neoplasms (2 patients in FC [3 events] and 10 patients [11 events] in R-FC).

The observed imbalance between the arms prompted a review of neoplasms and fatal neoplasms in the study.

As part of the review, all SAEs were checked for any additional 'hidden' cases to be included. Any AEs that were not malignant neoplasms (notably pemphigus and TLS, which are both included in the neoplasms SOC), benign disorders, malignancies representing progressive CLL (Hodgkin's disease which was classified as CLL transformation in this study), and malignancies that were most probably present before study entry (diagnosed within 28 days of study entry or with a clear history antedating study entry) were excluded.

Out of the 17 (FC) and 23 (R-FC) patients with an AE initially classified as neoplasm, 12 patients in each treatment arm remained after the review and were considered possible second malignancies. These cases included:

- Similar numbers of hematological disorders in the two arms (2 myelodysplastic syndromes [MDS] and 1 chronic myelomonocytic leukemia [CMML] in FC versus 1 MDS and 2 myelomas in R-FC)
- More solid tumors in the R-FC arm (10 in R-FC versus 3 in FC)
- More skin cancers in the FC arm (6 in FC versus 1 in R-FC)

No consistent pattern was observed in the solid tumors.

For fatal neoplasms, if cases unrelated to second malignancies (as described above) are excluded, 2 patients in the FC arm experienced fatal second malignancies versus 5 patients in the R-FC arm.

In the CLL-8 study in patients with previously untreated CLL, Grade 3/4 second malignancies were reported in <1% of patients. The incidence of fatal neoplasms was also low and similar in the two arms (4 patients [1%] FC, 3 patients [<1%] R-FC).

The REACH study was not designed to capture all malignant neoplasms since AEs were only collected until 28 days after last study drug administration, unrelated SAEs were only collected for 1 year post-treatment and only related SAEs were collected indefinitely. Bearing this caveat in mind, the incidence of

second malignancies in REACH falls within the expected range for patients with CLL - a relatively elderly population with a known increased risk of second malignancy. In a recent abstract, Tsimberidou et al. reported on malignancies among 2083 evaluable patients with CLL and SLL treated at the MDACC from 1985 to 2005 (Tsimberidou et al, 2007[56]). Among the 572 patients who had an additional malignancy diagnosed, 39.5% were diagnosed with another cancer before CLL/SLL, 52% after CLL/SLL, 5% prior to and after CLL/SLL, and 3.5% at the same time as CLL/SLL. Malignancies occurred in 303 of 1069 patients (28.3%, median follow-up of 7.7 years) who required therapy for CLL/SLL and in 268 of 1014 patients who did not require therapy (26.4%, median follow-up 4.7 years). When second malignancies were analyzed by therapy combinations the highest frequency in a rituximab containing regimen was much lower than the overall frequency (11%; median follow-up, 5.9 yrs). These results suggested that rituximab is unlikely to play a contributory role to the secondary malignancies reported in CLL patients.

Phase II Safety Data

These studies are fully analysed in section 6.8.4.1 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; (Wierda et al[3])

Patients with relapsed and refractory CLL received rituximab combined with fludarabine and cyclophosphamide in this open-label phase II study. One hundred and seventy seven patients with symptomatic or progressive disease as defined by NCI working group criteria were enrolled. Their median age was 59 years (range 36-81) and 26% were female. Median number of prior treatments was 2 (range 1-10). Toxicity analyses showed that the treatment regimen was well tolerated with toxicities for R-FC typical and expected for such a group of previously treated patients. All 6 courses of treatment were administered to 46% (n=81) of patients with 68 of these patients receiving full dose treatment. Myelosuppression was the most common reason for discontinuing treatment before six courses and occurred in 46 patients (26%). One hundred and eleven (63%) patients had AEs associated with the first infusion of rituximab, most of which were grade 1 or 2 and self-limited. The most common toxicity with R-FC was neutropenia, with grade 3 and 4 neutropenia noted in 21% and 41% of 529 assessable courses. Thrombocytopenia occurred in 17% of assessable courses (grade 3 in 10% and grade 4 in 7%). Anaemia (grade 3 and 4) was observed in 24% of patients. Despite the relatively high incidence of neutropenia, major infections (described as sepsis, pneumonia, or infection requiring hospitalization) occurred in only 34 (5%) of assessable courses. Fever of unknown origin occurred in 78 (10%) of 745 assessable courses and minor infections (defined as upper respiratory tract infections, bronchitis, cellulitis and so on, occurred in 59 (8%) of assessable courses. Herpes simplex and zoster were associated with four (1%) and six (1%) of 745 assessable courses respectively. Late neutropenia occurred in five of 45 CR patients. It was transient in all cases, and bone marrow biopsy at the time of neutropenia showed no disease in any of these patients. To date, one patient developed acute myelogeneous leukaemia 2 months after his first course of R-FC. Fours patients have developed myelodysplastic syndrome (1.5 years, 1 year, 9 months, and 3 months after five or six courses of R-FC).

Conclusions: The toxicities for R-FC were typical and expected for such a group of previously treated patients. Infusion-related toxicities with rituximab were similar in frequency and severity to the toxicities seen in other studies. The incidence of neutropenia, thrombocytopenia, and infection were similar for patients who received R-FC compared with previously treated patients in a previous trial who received FC, indicating that the addition of rituximab did not significantly increase toxicity. Late neutropenia was transient and rare in the absence of relapsed or residual disease in the bone marrow.

Treatment: R-FCM; (Hillmen et al[31])

The combination of rituximab +/- FCM chemotherapy as treatment for relpased/refractory patients with CLL was presented by Hillmen et al at the American Society for Hematology (ASH) 2007 meeting. Fifty-two patients entered into the trial, with 26 in each arm. The median age was 65 years (range 32-79) with 79% men. The median number of prior therapies was 2 (range 1-6). SAEs were reported in 23 patients. There was no difference in the number of SAEs between the two arms (FCM 11, FCM-R 12). Six out of seven (86%) patients who had 4 or more prior therapies reported an SAE compared to 17/45 (38%) patients who had less than 4. Sixteen SAEs were suspected to be related to FCM-R and 10 related to FCM. A further full publication is expected later in 2009, with a phase III randomized trial comparing FCR +/- M about to open in the UK.

Treatment: R-PC; (Lamanna et al[33])

In this open label, phase II study 46 patients with either previously treated CLL (n-32) or other low-grade B-cell neoplasms (n=14) were treated with rituximab combined with pentostatin and cyclophosphamide (R-PC). All enrolled patients had Rai classification intermediate- or high-risk disease as defined by the NCI working group. The median age was 62 (range 30-80) with 65% of patients male. The median number of prior regimens was 2 (range 1-7). The regimen was generally well tolerated, with the addition of rituximab seeming not to add significantly to the toxicity of PC (compared to a historic cohort). Myelosuppression was the most frequent toxicity, with grade 3/4 neutropenia, anaemia, and thrombocytopenia occurring in 53%, 9%, and 16% of patients respectively. Grade 3/4 infections occurred in 9 patients (28%); eight of these patients had pneumonia. There was one death from progressive pneumonia. The cytotoxic effects of this combination were rapid, as evidenced by the fact the asymptomatic tumour lysis was detected in 56% of patients treated. Twenty-three (72%) of 32 patients with CLL received the planned number of chemotherapy cycles. Five of the remaining 9 patients were removed from study secondary to infections. The other 4 patients were removed for a variety of comorbid conditions.

Treatment: R-PCM; (Lamanna et al[34])

The combination of rituximab with pentostatin, cyclophosphamide, and mitoxantrone (PCM) as treatment for CLL patients previously treated with R-PC or R-FC was presented by Lamanna et al at the American Society for Hematology (ASH) 2007 meeting. Twenty-one patients entered into the trial with either CLL (17 patients) or other low-grade B-cell neoplams (4 patients). The median age was 62 years (range 44-74) with 16 men and 5 women. The median

number of prior therapies was 2 (range 1-6). Preliminary results indicate that R-PCM is well tolerated in this setting.

Treatment: R-Cl +/- C; (Robak et al[35])

In this phase II trial, 46 patients with recurrent or refractory CLL were treated with rituximab combined with cladribine (RC) and RC plus cyclophosphamide (RCC). Eighteen patients were treated with RC and 28 with the RCC regimen. Median age was 59 (range 40-80) with 59% of patients male. The median number of prior therapies was 2 (range 1-5). Hypersensitivity to rituximab was the most frequent side-effect of RC/RCC therapy and occurred in 16 (33%) patients, mostly during the first infusion of the drug. Grade 3/4 neutropenia was observed in 6 patients (13%), with grade 3/4 thrombocytopenia and infection in 3 (9%) and 10 (20%) patients respectively. There were eight episodes of severe pneumonia. Eleven patients died between 4 and 19 months (median 6) from the start of treatment: 10 out of these 11 patients were non-responders.

Conclusions: These results indicate good tolerability of RC/RCC regimens even in heavily pre-treated CLL patients.

Treatment: R-B; (Fischer et al[36])

The combination of rituximab with bendamustine (R-B) as treatment for patients with relpased or refractory CLL was presented by Lamanna et al at the American Society for Hematology (ASH) 2008 meeting. The phase II study enrolled 81 patients with a median number of 2 (range 1-3) pretreatments. Median age was 66.7 years. In total, 123 CTC grades 3/4/5 AEs were reported, most frequently on myelosuppression and infections: grage 3/4 anaemia occurred in 6.1% of courses, with grade 3/4 neutropenia and thrombocytopenia in 11.9% and 9.1% of courses respectively. Sixteen episodes (4.9%) of CTC grade >3 infections were documented; most of them could be successfully managed. However, treatment-related mortailty occurred in 3.7% of patients: 3 died due to severe infections associted with treatment related neutropenia including 1 fatal pneumonia, 1 sepsis after diagnosis of Richter's syndrome, and 1 urosepsis. Ongoing follow-up analysis will define long term safety of this drug combination. In addition, a forthcoming German CLL study group trial will investigate the efficacy of R-B in comparison to fludarabine-based immunochemotherapy (R-FC) for first-line treatment of CLL.

Treatment: R-CHOP; (Eichhorst et al[37])

The combination of rituximab with CHOP (R-CHOP) as treatment for patients with fludarabine-refractory CLL or CLL with autoimmune haemolytic anaemia (AIHA) or Richter's transformation (RT) was presented by Eichhorst et al at the American Society of Hematology (ASH) 2005 meeting. In this multicentre phase II study, 34 patients were enrolled with either advanced stage Binet C or Binet B disease. Mean age was 66 (range 40-78). Nineteen patients with refractory CLL, 7 CLL patients with AIHA and 4 patients with RT were included. The mean number of previous treatments was 2.1, 48% of patients having recieved 3 pretreatments. R-CHOP was well tolerated. Main toxicities were myelosuppression (59% of all documented courses) with anaemias in 32%, thrombocytopenias in 29%, and leukopenias in 26%. Nausea and vomitting were in assessed in 26% and infections in 22% of all courses. Four episodes of severe, CTC grade 3 and 4

infections were observed. Twenty-six percent of patients developed alopecia. Side-effects, mostly mild fever and chills, occurred in 19% of 78 administered rituximb infusions. Ten percent of side-effects occurred during the first rituximab administration. No tumour lysis syndrome was reported so far. Six patients died so far, 2 due to infectious complications and 4 due to progressive disease.

Summary and Conclusions – 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.

Overall, there were no unexpected safety findings when previously treated CLL patients were treated with R-FC in REACH. Rituximab in combination with FC was well tolerated and the proportion of patients who discontinued therapy due to an AE was similar in each treatment arm (25% FC versus 26% R-FC).

The incidence of all Grade AEs, Grade 3/4 AEs and SAEs was slightly higher in the R-FC arm. When the frequency of AEs in both treatment arms was analyzed according to baseline lymphocyte count, Binet stage, age or creatinine clearance, there were no consistent trends to suggest that the frequency of AEs in the R-FC and FC arms differed when lymphocyte count, age, Binet stage or creatinine clearance were taken into consideration. The frequency and severity of AEs tended to be higher in older patients and patients with poor renal function but this applied to both arms of the study.

At the time of clinical data cut-off, more patients (25%) in the FC arm had died versus 23% in the R-FC arm. The incidence of treatment-related deaths was slightly higher in the R-FC arm (19/274 [7%]) R-FC versus 14/272 [5%] FC). The number of patients experiencing an AE with an outcome of death was higher in the R-FC than in the FC arm (13 % in R-FC versus 10% in FC). Most fatal AEs were due to infections and infestations.

Grade 3 and 4 neutropenia, febrile neutropenia and granulocytopenia occurred in at least 2% more patients in the R-FC arm, suggesting a potential relationship to rituximab treatment. The incidence of AIHA was similar in the two treatment arms. More patients in the FC arm experienced Grade 3/4 and serious AIHA events. One distinctive case of acute reversible infusion-related thrombocytopenia occurred in a patient on the R-FC arm but resulted in no adverse sequelae.

Although the incidence of Grade 3/4 infections or infestations (including opportunist infections) was comparable between the treatment arms, Grade 3/4 hepatitis B infection occurred uniquely in the R-FC arm (5 patients). The 7 cases of hepatitis B infection reported in R-FC arm (all grades) comprised 3 primary infections, 2 reactivations, 1 primary infection followed by reactivation, and 1 chronic infection. Due to small numbers, firm conclusions cannot be drawn.

As expected, infusion-related AEs occurred more frequently in the R-FC arm. Grade 3/4 infusion-related AEs occurred more frequently during the first treatment cycle and gradually decreased over subsequent cycles (however, the same trend was seen for AEs in the FC arm). Despite concerns that patients with

CLL might be at higher risk of serious rituximab infusion-related reactions than patients with NHL, almost all patients managed to complete their first cycle of rituximab therapy (97% received at least 90% of the planned dose in Cycle 1). No relationship was seen between baseline lymphocyte count and incidence of infusion-related AEs.

Tumour lysis syndrome prophylaxis was recommended in the study protocol, initially at the investigator's discretion and later for all patients, Fewer patients in the R-FC arm experienced TLS (6 patients in the R-FC arm [2%] versus 9 patients in the FC arm [3%]) and there were slightly more serious TLS events in the FC arm (5 FC, 2 R-FC). In 4 patients (2 FC, 2 R-FC), TLS resulted in or substantially contributed to the patient's death. These findings indicate the need for continued vigilance in treating patients with CLL with effective therapies but do not suggest an increase in risk with the addition of rituximab to FC.

The study was not designed to capture all second malignancies. Slightly more patients in the R-FC arm (8%) experienced malignant neoplasms than in the FC arm (6%) and there were more deaths in the R-FC arm (10 patients) than in the FC arm (2 patients) attributable to malignant neoplasms. If Richter's syndrome and non-malignant conditions are excluded, 18 patients in R-FC (20 events) versus 14 patients in FC (15 events) developed second malignancies. This resulted in 9 deaths in the R-FC arm compared to 2 deaths in the FC arm. Overall these findings are within the expected range for second malignancies in patients with CLL.

The safety profile of other R-chemotherapy regimes as reported in the published Phase II studies is in keeping with what was observed 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 and previously untreated CLL.

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.

6.8.2 Summary of methodology of relevant non-RCTs

6.8.2.1 Supporting studies that highlight the efficacy and tolerability of rituximab in combination with different chemotherapy regimes

Table 47. Supporting Studies – R-chemotherapy

Study: Wierda et al, 2005[3]
Chemotherapy with R-FC for relapsed and refractory CLL

Rationale and Purpose	To test the efficacy and tolerability of adding rituximab to the combination of fludarabine and cyclophosphamide for previously treated CLL, with the hope of increasing CR rates to greater than 25%.
Design	Single-arm, open label Phase II study of 177 patients.
Participants	177 patients aged 18 years or older with previously treated CLL requiring therapy as indicated by NCI 1996 guidelines. Median age was 59. 3% of patients had low-risk disease, 47% had intermediate risk disease, and 50% had high risk disease using the modified Rai staging criteria. Cytogenetics via conventional karyotyping was available for 129 patients; of these 2% had 13q deletion as the sole abnormality, 65% had diploid karyotype, and 33% had complex abnormalities, 11q deletion, 17p deletion, or trisomy 12 as sole abnormailites or as part of a complex abnormal karyotype. FISH, IgvH and ZAP-70 were not clinically available at the time of study recruitment. The median number of prior treatments was 2. 18% of patients had received only alkylating agent therapies; 82% had previously received fludarabine alone or in combination, 61% had fludarabine-sensitive disease, and 21% were refractory to fludarabine. 22 patients (12%) had previously received rituximab, either alone or in combination, and 7 had received rituximab as their only prior treatment. 34 patients (19%) were previously treated with FC; 30 of these had fludarabine sensitive disease and 4 were refractory to fludarabine.
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 25mg/m2 for 3 days each course and cyclophosphamide 250mg/m2 for 3 days each course.
Outcomes	Responses as according to NCIWG criteria, overall survival, failure-free survival, time to progression.
Added comments	

Study: Weirda et al, 2006[32]
Retrospective comparison of 3 sequential groups of patients with recurrent/refractory CLL treated with fludarabine-based regimens (R-FC vs FC vs F +/- P)

Rationale and Purpose	Compare 3 groups of relapsed/refractory CLL patients identified in phase II clinical trials carried out at the MD Anderson Cancer Centre, Texas to determine whether improvements in fludarabine-based treatment regimens have had an impact on survival.
Design	Retrospective analysis.
Participants	In total, 505 non-selected, non-overlapping patients were identified and evaluated in 3 groups. Eligibility criteria for the clinical trials were similar. In the first group, 251 patients were analysed who had been previously treated with fludarabine +/- prednisolone (F +/- P). In the second group and third groups, 111 and 143 patients were analysed who had previously been treated with FC and R-FC, respectively.
Interventions	F +/- P: Fludarabine was given at a dose of 25-30mg/m2 daily for 5 days of each 4 week course. Patients received 2 courses beyond best response and could have received up to 10 courses of treatment. FC: Fludarabine was given at 30mg/m2 and cyclophosphamide at 300mg/m2 for 3 days of each 4 week course for a total of six planned courses. R-FC: 6 cycles of R-FC given every 28 days. Rituximab: 375mg/m2 cycle 1, 500mg/m2 cycles 2-6; Fludarabine 25mg/m2 for 3 days each course and cyclophosphamide 250mg/m2 for 3 days each course.
Outcomes	Responses as according to NCIWG criteria, overall survival, time to disease progression.
Added comments	

Study: Hillmen et al, 2007[31]
Randomized phase II trial of FCM +/- R in previously treated CLL

Rationale and Purpose	To evaluate the efficacy and tolerability of fludarabine, cyclophosphamide, mitoxantrone +/- rituximab for treatment of relapsed/refractory CLL
Design	Phase II randomised study.
Participants	52 patients (26 in each arm) with progressive CLL requiring treatment, as defined by NCI criteria. The median age was 65 years (range 32-79) with 79% men. The median number of prior therapies was 2 (range 1-6); 31 had prior fludarabine and 6 (12%) were refractory to or relapsed <6 months after fludarabine. 26/44 (59%) had unmutated VH genes (15/22 FCM; 11/22 FCM-R). 11 patients had deletion of 11q (6 FCM; 5 FCM-R); and 1 patient had >20% 17p deleted cells (FCM-R).
Interventions	FCM: oral fludarabine (24mg/m2 for 5 days) and cyclophosphamide (150mg/m2 for 5 days) plus i.v. mitoxantrone (6mg/m2) on day 1 of each cycle for 6 cycles. FCM-R: identical to FCM regimen with rituximab on day 1 of each cycle (375mg/m2 cycle 1; 500mg/m2 cycles 2-6).

Outcomes	Primary endpoint was response by NCI criteria 2 months after therapy. In addition, minimal residual disease in the marrow was studied 2 months after therapy by 4-colur flow cytometry, with MRD negativity defined as <0.01% CLL cells.
Added comments	(1) Full publication on this study expected later this year. (2) The study design does not allow a statistical comparison between FCM and FCM-R (ie it is not sufficiently powered). For this reason, the study has not been included in section 6.2.3.

Study: Lamanna et al, 2006[33]

Combined use of pentostatin, cyclophosphamide, and rituximab for the treatment of relapsed/refractory CLL.

Rationale and Purpose	To investigate the efficacy and tolerability of rituximab in combination with pentostatin and cyclophosphamide in previously treated CLL patients.
Design	Single arm, Phase II study.
Participants	46 patients with either previously treated CLL (n=32) or other low-grade B-cell neoplasms (n=14). All CLL patients had Rai classification intermediate- (n=7) or high-risk disease (n=25) as defined by the NCI working group and required treatment for active disease as defined by NCI criteria. Median age was 62 (range 30-80) with 65% of patients male. 87% of patients were CD38 positive. The median number of prior regimens was 2 (range 1-7). Most patients had previously received fludarabine (78%) and alkylating agents (78%). Of those who had prior fludarabine therapy, 32% were refractory to fludarabine or fludarabine based combinations.
Interventions	Patients received pentostatin (4mg/m2), cyclophosphamide (600mg/m2), and rituximab (375mg/m2). All drugs were administered on the same day (rituximab omitted from cycle 1) with patients receiving 6 cycles at 3-weekly intervals.
Outcomes	Response rates, response duration, time to treatment failure, and overall survival.
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. Of the purine analogs active in CLL, pentostatin is the least myelosuppressive.

Study: Lamanna et al, 2007[34]

Combined use of pentostatin, cyclophosphamide, mitoxantrone, and rituximab for the treatment of CLL patients previously treated with PCR or FCR.

Rationale and Purpose	To investigate the efficacy and tolerability of rituximab in combination with pentostatin, cyclophosphamide, and mitoxantrone in CLL patients previously treated with PCR or FCR.
Design	Single arm, phase II study.
Participants	Twenty-one patients with either CLL (17 patients) or other low-grade B-cell neoplams (4 patients). CLL patients had either high risk (71%) or “active” intermediate risk disease (29%). Median β-2 microglobulin was 3.3mg/ml. Median age was 62 years (range 44-74) with 16 men and 5 women. The median number of prior therapies was 2 (range 1-

	6). 65% of CLL patients had previously been treated with chemoimmunotherapy using PCR or FCR.
Interventions	Pentostatin (4mg/m2), cyclophosphamide (600mg/m2), rituximab (375mg/m2), and mitoxantrone (dose escalated in phase I portion of study from 6-10mg/m2). All drugs were administered on the same day (rituximab omitted from cycle 1) with patients receiving 6 cycles at 28 day intervals.
Outcomes	Response rates using NCI criteria.
Added comments	This study follows on from the aforementioned 2006 study, which demonstrated that PCR was active and acceptably safe to administer to patients with relapsed/refractory CLL.

Study: Robak et al, 2007[35]

Combined use of rituximab plus cladribine with or without cyclophosphamide in patients with relapsed/refractory CLL.

Rationale and Purpose	Determine feasibility, effectiveness, and toxicity of combined regimens consisting of rituximab and cladribine (RC) and RC plus cyclophosphamide (RCC) in patients with relapsed/refractory CLL.
Design	Non-randomized, phase II study.
Participants	46 patients with relapsed or refractory CLL were treated with rituximab combined with cladribine (RC) and RC plus cyclophosphamide (RCC). 33 patients (72%) had relapsed disease and 13 (28%) were refractory to prior therapy. 12% of patients had Rai stage II disease at presentation, with 13% and 21% of patients with stage III and IV disease respectively. Eighteen patients were treated with RC and 28 with the RCC regimen. Median age was 59 (range 40-80) with 59% of patients male. The median number of prior therapies was 2 (range 1-5).
Interventions	RC: rituximab (375mg/m2) on day 1 and cladribine (0.12mg/kg) on days 2-6 f at 28 day intervals until maximal response or prohibitive toxicity. RCC: rituximab (375mg/m2) on day 1, cladribine (0.12mg/kg) on days 2-4, and cyclophosphamide (250mg/m2) on days 2-4 at 28 day intervals until maximal response or prohibitive toxicity..
Outcomes	Response rates using NCI criteria, progression-free survival, and overall survival.
Added comments	Cladribine, like fludarabine and pentostatin is a purine nucleoside analog. Previous to this study, several trials had indicated that adding rituximab to cladribine (and other purine analogs) may increase response rates and prolong PFS in indolent lymphoid malignancies.

Study: Fischer et al, 2008[36]

Combined use of rituximab with bendamustine in patients with relapsed/refractory CLL.

Rationale and Purpose	Evaluate efficacy and toxicity of rituximab plus bendamustine in patients with relapsed/refractory CLL.
Design	Single arm, phase II study.
Participants	81 relapsed/refractory CLL patients with a median number of 2 (range 1-3) pre-treatments. Median age was 66.7 years.
Interventions	70mg/m2 bendamustine on day 1 and 2 combined with 375mg/m2 rituximab for cycle 1 and 500mg/m2 for the second and subsequent cycles. Administered every 28 days for up to 6 courses.
Outcomes	Response rate using NCI criteria, duration of response, event-free survival, MRD response rate, and overall response rate in biological defined risk groups.

Added comments	Bendamustine is an alkylating agent with additional properties of a purine analog. This agent has shown considerable activity as monotherapy for solid and lymphoid malignancies, including CLL. Encouraging results have also been obtained using the BR combination in relapsed/refractory and previously untreated non-Hodgkin Lymphoma patients. This phase II trial is the first study to evaluate this combination in CLL.

Study: Eichhorst et al, 2005[37]

Rituximab plus CHOP in fludarabine refractory CLL or CLL with AIHA or Richter's transformation

Rationale and Purpose	Evaluate tolerability and efficacy of the R-CHOP regimen in CLL patients refractory to fludarabine or with autoimmune haemolytic anaemia (AIHA) as well as in patients with Richter's transformation (RT).
Design	Multicentre, single arm, phase II study.
Participants	34 patients with either advanced stage Binet C (72%) or Binet B disease (28%). Mean age was 66 (range 40-78). Nineteen patients with refractory CLL, 7 CLL patients with AIHA and 4 patients with RT. Mean number of previous treatments was 2.1, 48% of patients having received 3 pre-treatments.
Interventions	CHOP therapy consisting of cyclophosphamide (750mg/m2 IV, adriamycin (50mg/m2 IV), and vincristine (1.4mg/m2 IV) on day 1 plus prednisolone (100mg/m2 oral) for 5 days. From the second treatment course, rituximab (375mg/m2 IV) was given on day 0, if the leukocyte count was less than 50,000μl. Regimen was repeated every 21 days for up to 6 courses in CLL patients (up to 8 courses in RT patients).
Outcomes	Response rates using NCI criteria.
Added comments	R-CHOP has been shown to induce major responses in B-cell lymphoma. CHOP is also often an attractive treatment option for previously treated CLL patients not suitable for fludarabine-combination therapy. This is the first study to examine whether the addition of rituximab to CHOP can further improve outcomes in this patient group.

Study: Tam et al, 2008[38]

Salvage treatment with various R-containing regimens after failure of 1st-line R-FC for CLL.

Rationale and Purpose	Evaluate various salvage regimens after failure of 1st-line R-FC in a group of 300 patients treated at the MD Anderson Cancer Center in order identify optimal 2nd-line treatment options.
Design	Retrospective analysis
Participants	97/300 patients who had failed frontline R-FC and completed second-line therapy. Patients who failed R-FC therapy had high risk disease features including elevated β2m, unmutated IgVH and ZAP-70 positivity. Among 38 assessable patients, 7 (18%) had 17p- and 18 (47%) had 11q- by conventional karyotyping and/or FISH.
Interventions	Patients received treatment chosen at the discretion of individual treating physicians, including: R-FC (n=30), 17%; rituximab (n=25), 4%; alemtuzumab ± rituximab (n=16), 31%; R-FC + alemtuzumab (CFAR, n=9), 56%; lymphoma-type chemotherapy (n=5), 0%; other treatment (n=12), 0%.
Outcomes	Response rate, remission duration, and overall survival.

Added comments

6.8.2.2 Supporting studies that highlight the efficacy of rituximab-containing regimens in patients with fludarabine-refractory CLL.

The studies by Wierda et al (2005) and by Lamanna et al (2006) as previously outlined in Table 47 along with the following other non-randomised studies are submitted to support the argument that R-FC (and other rituximab-based regimens) are efficacious in fludarabine-refractory CLL patients.

Table 48. Supporting Studies – R-containing regimes in F-refractory CLL

Study: Woyach et al, 2009[39]
Rituximab and etanercept in patients with relapsed/refractory CLL and small lymphocytic lymphoma

Rationale and Purpose	Can disruption of TNF-α by etanercept improve response to rituximab in CLL?
Design	Phase I/II study
Participants	36 patients with CLL/SLL. All had received prior therapy, with a median of two prior treatment regimens (range 1-8). Twenty-six patients (72%) had received rituximab previously. 47% of patients had intermediate-risk Rai stage I–II disease and 53% had high-risk Rai stage III–IV disease. 50% were refractory to fludarabine therapy. All patients had baseline cytogenetics performed, and 50% had high risk cytogenetic abnormalities, including del(17p13.1) (22%), del(11q22.3) (14%) or complex karyotype (14%).
Interventions	Etanercept at a dose of 25 mg subcutaneously twice weekly (weeks 1–5). Third dose administered 1 hr before first dose of rituximab. Rituximab administered at 375 mg/m2 intravenously (i.v.) three times weekly during weeks 2–5. First rituximab dose given as a 100 mg i.v. bolus over 4 h.
Outcomes	Response rate using NCI criteria, progression-free survival, time to next treatment, overall survival, and toxicity
Added comments	Rituximab treatment is associated with tumor necrosis factor-α (TNF-α) release that can cause CLL proliferation and inhibit apoptosis. Etanercept is a TNF-α inhibitor. This study was designed to test the hypothesis that blocking TNF-α with etanercept would diminish initial infusion toxicity and to improve response rate and response duration.

Study: Castro et al, 2008[40]
Rituximab in combination with high-dose methylprednisolone (HDMP) for the treatment of fludarabine refractory high-risk CLL.

Rationale and Purpose	Evaluate efficacy of rituximab in combination with HDMP in patients with high-risk, fludarabine refractory CLL.
Design	Single arm, phase II study.
Participants	14 fludarabine refractory CLL patients (3 females and 11 males). 85% of patients were high risk. Mean age was 59 years. 21% had previously received rituximab therapy, either alone or in combination with other antineoplasics. Median number of previous treatments was

	2 (range 1-4). Eight patients (57%) had CLL cells that expressed unmutated IgVH, 11 patients (78%) had CLL cells that expressed ZAP-70 by flow cytometry, and nine patients (64%) had leukemia cells with high-level of CD38 expression (430%). Metaphase karyotype and FISH analysis were performed on the marrow aspirate of most patients and found chromosomal aberrations associated with high-risk disease in three patients, including 11q deletion in two patients and one with 17p deletion.
Interventions	HDMP administered at 1 gm/m2 I.V. over 90 min daily for five consecutive days. Rituximab administered at a dose of 375mg/m2 on days 1, 3, 5, 8, 17 and 22 during first course of treatment and on days 1, 7, 14 and 21 during courses 2 and 3. Patients received a new course of treatment every 28 days for a total of three courses.
Outcomes	Response rate using NCI criteria, duration of response, time to progression, time to next treatment, overall survival, and toxicity
Added comments	This study is based on pre-clinical observations that rituximab may have synergistic activity with glucocorticoids inducing apoptosis of leukemia cells.

Study: Faderl et al, 2003[41]

Rituximab plus alemtuzumab in relapsed and refractory lymphoid malignancies.

Rationale and Purpose	Evaluate the safety and efficacy of rituximab plus alemtuzumab in relapsed and refractory lymphoid malignancies.
Design	Single arm, phase II study.
Participants	48 patients with relapsed or refractory chronic lymphoid malignancies (32 with CLL, 9 with CLL/prolymphocytic leukemia [PLL], 1 with PLL, 4 with mantle cell leukemia/lymphoma, 2 with Richter's transformation). 39 patients (79%) had Rai stage III disease or higher. Median age 62 (range 44-79). 33 (69%) patients were male. Number of prior therapies was 4 (range 1-9). 32 (67%) patients had prior exposure to rituximab; 1 patient (2%) had prior exposure to alemtuzumab; and 4 (8%) patients had been exposed to both. 25 (52%) patients were alkylator refractory, 26 (54%) were fludarabine refractory, and 22 (49%) were refractory to both.
Interventions	Rituximab at a dose of 375 mg/m2 weekly for 4 weeks. Alemtuzumab given at the loading-dose schedule of 3 mg, 10 mg, and 30 mg on 3 consecutive days during week 1 followed by a dose of 30 mg on days 3 and 5 of weeks 2 to 4. Patients could receive a second 28-day cycle depending on response and toxicities.
Outcomes	Response rate using NCI criteria, time to progression, overall survival, and toxicity.
Added comments	Rationale for combining the 2 monoclonal antibodies in this trial was their reported single-agent activity at the time and possibility of synergistic effects.

Study: Nabhan et al, 2004[42]

Rituximab plus alemtuzumab in relapsed and/or refractory CLL.

Rationale and Purpose	Pilot study to evaluate the safety of rituximab plus alemtuzumab in heavily pre-treated CLL patients.
Design	Phase I pilot study.
Participants	Twelve patients (10 men, 2 women) with a median age 69.5 years (range 53 – 73). 9 patients had Rai stage IV disease and 3 patients had stage II disease. All patients were previously treated with alkylating agents and had failed purine analogue-based therapy (11

	fludarabine; 1 cladribine).
Interventions	Rituximab at 375 mg/m2/week for 4 doses (weeks 1, 3, 4, and 5), and alemtuzumab (CAM) on weeks 2 through 5. To establish safety, the first and second cohort of patients (3 in each cohort) received CAM at 3 and 10 mg thrice weekly (TIW). All subsequent patients (6 patients) received CAM at 30 mg intravenously TIW.
Outcomes	Response rate using NCI criteria and toxicity.
Added comments	

Study: Wierda et al, 2006[43]

Cyclophosphamide, Fludarabine, Alemtuzumab, and Rituximab (CFAR) in heavily pre-treated CLL patients.

Rationale and Purpose	Evaluate efficacy and safety of the CFAR regimen in relapsed/refractory CLL patients.
Design	Single arm, phase II study.
Participants	79 relapsed/refractory CLL patients. 59 were male. Median number of prior treatments was 3 (range 1–14). 43 pts previously treated with FCR. 10 pts previously treated with FC. Median age was 58 (range 39–79) yrs. 40 patients with Rai high risk disease. 32 fludarabine refractory patients. Cytogenetic abnormalities included: 17p del (16 patients), 11q del (15 patients), complex (5 patients), and 6q del (1 patient).
Interventions	Cyclophosphamide-250mg/m^2 d3–5; Fludarabine-25mg/m^2 d3–5; Alemtuzumab-30mg IV d1,3,5, and Rituximab-375–500mg/m^2 d2, each 28 days for 6 intended courses.
Outcomes	Response rate using NCI criteria, time to progression, overall survival, and toxicity.
Added comments	Previous data from the MDACC had demonstrated that R-FC is an active regimen for initial and salvage treatment of CLL. Alemtuzumab is highly effective at clearing disease from bone marrow, the usual site of residual disease following purine analogue-based treatment. This formed the rationale for the CFAR regimen for previously treated patients with CLL. This regimen is also being evaluated as frontline treatment for pts with high-risk CLL.

Study: Tsimberidou et al, 2008[44]

Rituximab, plus oxaliplatin, fludarabine, and cytarabine as combination therapy for patients with Richter's syndrome (RS) or fludarabine-refractory CLL.

Rationale and Purpose	(1) Determine whether oxaliplatin up to 25 mg/m2 daily for 4 days could be administered in the OFAR regimen without unacceptable toxicity (2) Identify dose-limiting toxicities of oxaliplatin (3) Determine pharmacodynamic end points (phase I) (4) Assess the efficacy and toxicity of the OFAR regimen (phase II)
Design	Phase I/II study.
Participants	21 patients with RS and 30 patients with fludarabine-refractory CLL. For patients with fludarabine-refractory CLL: median age was 59 years (range 34 - 77 years); 18 (60%) of patients had Rai stage III-IV disease; and median number of prior therapy courses was four (range, one to 11). Cytogenetic abnormalities at baseline included: 17p- (14 patients), 11q- (7 patients), trisomy 12 (5 patients). 1 patient had unmutated VH genes.

Interventions	Phase I: oxaliplatin (17.5, 20, or 25 mg/m2/d I.V.) days 1-4; fludarabine 30 mg/m2 IV days 2-3; cytarabine 1 g/m2 IV days 2-3; rituximab 375mg/m2 IV on day 3 of cycle 1 and day 1 of subsequent cycles. OFAR was repeated every 4 weeks for a maximum of 6 cycles. Phase II: As above but oxaliplatin 25 mg/m2/d IV for 4 days.
Outcomes	Response rate using NCI criteria, failure free survival, overall survival, and toxicity.
Added comments	Rationale for developing this regimen was based on preclinical data demonstrating synergistic cytotoxicity between cisplatin and the nucleoside analogs cytarabine and fludarabine.

Study: Klepfish et al, 2008[45]

Adding fresh frozen plasma to rituximab for the treatment of patients with refractory advanced CLL.

Rationale and Purpose	Evaluate whether concurrent administration of fresh frozen plasma (FFP) enhances the effect of rituximab in CLL.
Design	Prospective observational analysis
Participants	5 patients with advanced refractory CLL (3 male; 2 female). All 5 patients had Rai stage IV disease. All refractory to fludarabine plus three had failed treatment with rituximab.
Interventions	Two units of FFP followed by standard-dose rituximab as a single agent: 375 mg/m2 in most cycles, repeated every 1–2 weeks up to a total of 2–5 cycles.
Outcomes	Clinical and laboratory responses, overall survival, and toxicity.
Added comments	Hypothesis behind this study was that that the therapeutic effect of rituximab in CLL may be enhanced by the provision of complement through the concurrent administration of fresh frozen plasma (FFP).

Study: Winkler et al, 1999[46]

Rituximab monotherapy in fludarabine-refractory CLL.

Rationale and Purpose	Evaluate efficacy and safety of single agent rituximab in heavily pre-treated, fludarabine-refractory patients with CLL or leukemic variants.
Design	Single arm, phase II study.
Participants	10 patients (4 women, 6 men) with CLL and 1 male patient with a leukemic variant of mantle-cell NHL. Median age was 58 years (range 26-79 years). Four patients had CLL Rai stage IV, 3 patients Rai stage III, 2 patients Rai stage II, and 1 patient Rai stage I. Median number of prior treatment was 3 (range 2-5).
Interventions	Rituximab 375mg/m2 once weekly for 4 weeks.
Outcomes	Response rate and toxicity.
Added comments	

Study: Tam et al, 2007[47]

Salvage therapy for patients with fludarabine refractory CLL.

Rationale and Purpose	Evaluate the outcomes of patients with “double-refractory” CLL (ie refractory to both fludarabine and alemtuzumab) and “bulky fludarabine-refractory” CLL (ie ineligible for alemtuzumab) following treatment with a variety of salvage regimens.
Design	Retrospective analysis.
Participants	99 patients from the MDACC, Texas (58 double-refractory and 41 bulky fludarabine refractory) treated between 07/87 and 09/06. Median age 58 (range 25-79). Median number of prior regimens 4 (range 1-15). 77% of patients male. 31% Rai stage I-II and 69% Rai stage III-IV. Cytogenetics available for 41 patients prior to salvage

	therapy: 15 (37%) 17p-, 11(27%) 11q-, 15 (37%) other abnormalities. IgVH status known in 19 patients: 18 (95%) unmutated and 1 (5%) mutated.
Interventions	9 patients treated with intensive rituximab-based combinations and 19 with non-intensive combinations (including R-GMCSF, R-alemtuzumab, R-methylprednisolone, R-FC, and CFAR).
Outcomes	Response rate using NCI criteria, time to treatment failure, overall survival, and toxicity.
Added comments	Retrospective analysis, therefore some potential for overlap with other previously mentioned studies from the MDACC.

6.8.2.3 Supporting studies that highlight the efficacy of re-treatment with rituximab-containing regimens in patients with relapsed/refractory CLL

The studies by Wierda et al (2005), Lamanna et al (2006 and 2007), Winkler et al (1999), Woyach et al (2009), Castro et al (2008), and Klepfish et al (2008) as previously outlined in Table 47 and Table 48 along with the following other non-randomised studies are submitted to support the argument that R-FC (and other rituximab-based regimens) are efficacious in rituximab pre-treated CLL patients.

Table 49. Supporting Studies – R-containing regimes in R-pretreated CLL

Study: Herold et al, 2000[48]
Re-treatment of chemo-resistant CLL patients with rituximab.

Rationale and Purpose	Evaluate activity and tolerability of rituximab monotherapy in patients with chemo-resistant CLL.
Design	Case reports
Participants	2 case reports. Case 1: 57 year old female patient with Binet C CLL diagnosed in 1987. Chemotherapy with bendamustine, vincristine, and prednisolone induced a partial remission, and treatment was stopped in 1991. As a result of disease progression, chemotherapy with intermittent chlorambucil and prednisolone was started in 1996, inducing a partial remission. In December 1997, patient was re-admitted to hospital with progressive disease. Further chemotherapy protocols (bendamustine, vincristine, prednisolone; mitoxanthrone, chlorambucil, prednisolone) failed, as did high-dose immunoglobulins. Case 2: 63 year old male patient with Binet C CLL diagnosed in 1995. Chemotherapy included chlorambucil/prednisolone; cyclophosphamide, vincristine, prednisolone; mitoxanthrone, chlorambucil, prednisolone; bendamustin and fludarabine, but none of the treatment programs were effective.
Interventions	Rituximab (375 mg/m2 x 4) given in weekly intervals.
Outcomes	Clinical and laboratory responses, and toxicity.
Added comments	

Study: Zent et al, 2008[49]
Early treatment of high-risk CLL with rituximab and alemtuzumab.

Rationale and Purpose	Evaluate the efficacy and safety of rituximab plus alemtuzumab as early treatment for patients with high-risk CLL.
Design	Single arm, phase II study.
Participants	30 patients enrolled. Eligible for entry if 1) previously untreated, 2)

	had no NCI-WG 1996 criteria for treatment, and 3) had at least 1 marker of high-risk disease 17p132, 11q222, or a combination of unmutated IgVH and CD38+/ZAP70+. Median age 61 (range 29-77). 20 patients (67%) were male. 7 (23%) patients Rai stage 0; 21 (70%) patients Rai stage I; 2 (7%) patients Rai stage II. Risk group: 9 (30%) patients 17p-, 8 (27%) patients 11q-, 13 (43%) patients UM IgVH+ ZAP-70+ ± CD38+.
Interventions	Duration of treatment 31 days. Subcutaneous alemtuzumab with dose escalation (3 mg, 10 mg, 30 mg) over first 3 days (Wed to Fri) followed by 30mg per day on Mon, Wed, and Fri for next 4 weeks. Rituximab started on Day 8 (375 mg/m2 I.V.) repeated weekly for total of 4 doses.
Outcomes	Response rate using NCI criteria, MRD analysis, duration of response, time to progression, time to subsequent therapy, and toxicity.
Added comments	Patients with CLL usually are treated only for progressive disease. However, the discovery of biologic predictors of a high risk of disease progression, together with the development of newer, more targeted therapies, could change this paradigm. This study was an initial step to determine whether a short course alemtuzumab and rituximab could achieve a clinically relevant delay in the need for conventional therapy in patients with earlier stage high-risk disease.

Study: Gupta et al, 2002[50]

Rituximab-based chemotherapy for steroid-refractory autoimmune hemolytic anemia (AIHA) of CLL.

Rationale and Purpose	Evaluate efficacy and safety of a combination of rituximab, cyclophosphamide and dexamethasone in eight CLL patients with steroid refractory AIHA.
Design	Retrospective analysis.
Participants	Eight patients (7 males and 1 female) with steroid refractory AIHA of CLL. Median age 60 (46-70). 4 patients with Rai stage III disease and 4 patients with stage IV disease. All patients previously treated. Median number prior chemotherapies 2 (range 1-4). 6 patients previously treated with fludarabine and 5 with alkylating agents.
Interventions	Rituximab at 375 mg/m2 i.v. on day 1. Cyclophosphamide at 750 mg/m2 on day 2. 12mg dexamethasone I.V. on day 1, day 2 and orally from day 3-7. Cycles repeated every 4 weeks until best response.
Outcomes	Response in AIHA using blood counts and toxicity.
Added comments	AIHA is a well known complication of CLL. Steroids are standard first line treatment and there are limited effective treatment options for steroid refractory AIHA of CLL. Rituximab has been noted to be active in certain autoimmune hematologic disorders. This study evaluated the effectiveness of a rituximab-based combination in steroid-refractory AIHA of CLL.

6.8.3 Critical appraisal of relevant non-RCTs

The limitations of Phase II and other non-randomized clinical trials are understood; centre bias, selection bias and the lack of an adequately controlled comparator arm all mean that one should not over-interpret these 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 regimes **as a first step in the development of new treatment options** and before moving into the 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 (section 6.8.4.1) and does not cause alarming or unexpected toxicity (see section 6.7). Furthermore, these data support the use of R-FC and other rituximab-based combinations in fludarabine-refractory CLL patients (section 6.8.4.2) (who were excluded from entry in REACH), demonstrating that even in this poor prognosis group of patients R-chemotherapy may be a useful therapeutic option. Finally, data from more than 300 patients (section 6.8.4.3) demonstrate that rituximab-containing regimens, specifically repeat administrations of R-FC (and variants thereof), are a viable and useful therapeutic option for patients whose initial treatment consisted of rituximab.

6.8.4 Results of the relevant non- RCTs

6.8.4.1 Supporting studies that highlight the efficacy and tolerability of rituximab in combination with different chemotherapy regimes

Study Designs of the Supportive Studies

An overview of key design features of the supportive studies is shown in Table 5. Out of the 8 studies with information supporting rituximab in combination with chemotherapy for relapsed/refractory patients with CLL, two were randomized phase II studies (Hillmen et al, 2007[31]; Robak et al, 2007[35]), 5 were non-randomized phase II studies (Wierda et al, 2005[3]; Lamanna et al, 2006[33]; Lamanna et al, 2007[34]; Fischer et al, 2008[36]; Eichhorst et al, 2005[37]) and one was a retrospective review of salvage therapies (Tam et al, 2008[38]) .

All 8 supportive studies investigated the combination of rituximab with chemotherapy. In most of these supportive studies, chemotherapy consisted of a purine analog (fludarabine, pentostatin or cladribine) in combination with an alkylating agent (cyclophosphamide), with or without an anthracycline or anthracenedione (doxorubicin or mitoxantrone). One of the studies evaluated rituximab in combination with bendamustine, a novel alkylating agent with additional properties. Three of the 8 supportive studies used a rituximab regimen identical to that of the REACH study (Wierda et al, 2005[3]; Hillmen et al, 2007[31]; Fischer et al, 2008[36]). In the other 5 supportive studies, rituximab was used at a dose of 375 mg/m^2 for 5 or 6 cycles (Lamanna et al, 2006[33]; Lamanna et al, 2007[34]; Robak et al, 2007[35]; Eichhorst et al, 2005[37]) or the dose and regimen was not specified (Tam et al, 2008[38]) .

Efficacy Results

The primary endpoint of the pivotal REACH study was PFS, but most of the supportive studies were phase II studies and therefore the primary efficacy endpoint was response rate (according to NCI IWG criteria, where specified).

Progression-free survival data were available from one retrospective cohort analysis of rituximab in combination with fludarabine and cyclophosphamide (Wierda et al, 2006[32]), and one study of rituximab plus cladribine ± cyclophosphamide (Robak et al, 2007[35]).

Data on overall survival were available from one retrospective cohort analysis of rituximab in combination with fludarabine and cyclophosphamide (Wierda et al, 2006[32]), one study of rituximab in combination with pentostatin and cyclophopsphamide (Lamanna et al, 2006[33]), and (limited data) one retrospective review of salvage therapies after failure of first-line R-FC therapy (Tam et al, 2008[38]).

Patient populations in the supportive studies

In the supportive studies of rituximab in combination with chemotherapy in patients with previously treated CLL, the median age was in the range of 59 to 66 years. Patients enrolled in the supportive studies were slightly younger than the median age of diagnosis for CLL (65-72 years) but similar to patients in the pivotal study REACH. Apart from the study by Wierda et al. (in which half of the patients had Rai stage 0-2 disease), the majority of patients enrolled in the supportive studies had high risk disease (between 59% and 86% of patients had Rai stage ≥ 3 disease or approximately two-thirds of patients with Binet stage C disease), and treatment had failed after a median of two prior therapies for CLL.

Progression free survival (PFS)

Results of PFS were available from two studies in previously treated patients with CLL (Table 50):

- One retrospective cohort analysis comparing fludarabine alone with fludarabine/cyclophosphamide, and rituximab in combination with fludarabine and cyclophosphamide (Wierda et al, 2006).
- One study investigating the combination of rituximab and cladribine with or without cyclophosphamide (Robak et al, 2007).

In the retrospective cohort analysis in previously treated patients who had received rituximab in combination with chemotherapy (Wierda et al, 2006) the median PFS was estimated to be 32 months for the R-FC regimen compared to 36 months for FC only. Here the addition of rituximab did not improve the median PFS in responders compared to the FC regimen. In contrast however, overall survival showed a clear benefit for R-FC. It is important to note here that PFS and OS results in non-randomized comparisons should be interpreted with caution.

In the phase II study by Robak et al., median PFS was 12 months in responders receiving rituximab plus cladribine, with or without cyclophosphamide (R-Cl± C).

Table 50. Overview of progression-free survival across studies in patients with relapsed/refractory CLL

Study	REACH		Wierda et al.#			Robak et al.
	FC N=276	R-FC N=276	F N=251	FC N=111	R-FC N=143	R-Cl± C N=46
Median FU, months	25.3		19	29	34	16
Median PFS, months (95% CI)	20.6 (18.1, 24.0)	30.6 (26.1, 38.2)	26	36	32	12 (range 4-46)
p-value	0.0002		< 0.01		ns	na

Results reported for patients with PR and CR only (59% of patients treated with F, 67% of patients treated with FC, 72% of patients treated with R-FC)
* measured from the time of first response to the time of documented disease relapse, progression or death
** including patients with PLL, MCL and Richter transformation
Abbreviations: ns = not significant; na = not available; FU = follow up.

Overall Survival

In the retrospective comparison of three sequential groups of patients with relapsed/refractory CLL (Wierda et al, 2006), estimated median survival times were significantly longer for patients in the R-FC cohort compared to patients in the FC or F cohort ($p = 0.05$ for R-FC vs FC and $p<0.01$ for R-FC vs F). Median OS was 49 months (R-FC), 31 months (FC) and 19 months (F), respectively. Note that OS results in non-randomized comparisons should be interpreted with caution.

In a small study including 34 poor prognostic patients with relapsed/refractory CLL (Lamanna et al, 2006) the median survival was 44 months for patients treated with rituximab in combination with PC.

In a retrospective review of patients receiving a range of salvage therapies after failure of first-line R-FC therapy, the median survival after first salvage therapy was 30 months and was significantly longer for patients who achieved a CR or nPR with first salvage therapy (median 46 months) than for those who only achieved a PR or no response (median 10 months). Duration of response to first-line R-FC, β2-microglobulin level and Rai stage predicted survival after salvage therapy but the actual salvage regimen did not (Tam et al, 2008).

Overall response rates

Although the supportive studies were heterogeneous in terms of chemotherapy regimen and design (retrospective analysis), the results on OR were in line with the observations from REACH and favourable for the rituximab plus chemotherapy groups with the exception of the OR data from the retrospective analysis regarding FC versus R-FC.

In relapsed/refractory patients treated with rituximab in combination with chemotherapy, ORRs were similarly high and ranged from 67% (rituximab in combination with cladribine) to 94% (rituximab in combination with PCM) (Table 51). In the retrospective analysis by Wierda et al., the ORR was significantly higher for patients who had received R-FC compared with patients who had received F ($p=0.008$), but not compared to patients who received FC alone.

However, the proportion of CRs was significantly higher in patients in the R-FC cohort compared to patients in the F and FC cohorts ($p<0.05$). In a retrospective analysis by Tam et al., the ORR to first salvage therapy was approximately 50% including the combination therapies R-FC +/- lumiliximab (ORR of 61% including 1 CR [6%]) and R-FC + alemtuzumab (ORR of 88% including 4 CRs [50%]).

Table 51. Overview of Response Rates in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Study	Wierda et al, 2006			Hillmen et al, 2007		Lamanna et al, 2006	Lamanna et al, 2007	Robak et al, 2007		Fischer et al, 2008	Eichhorst et al, 2005	Tam et al, 2008
	F N=251	FC N=111	R-FC N=143	FCM N=23[1]	R-FCM N=23[1]	R-PC N=32[2]	R-PCM N=16[1]	R-Cl N=18	R-ClC N=28	R-B N=23[1]	R-CHOP N=17[1]	Various N=79[5]
ORR (95% CI)	59%	67%	72%	57%	70%	75%	94%	67% (45-89)	78% (62-93)	77%	70%	49%
CR	13%	12%	28%	13%[3]	43%[3]	25%	25%	6%	7%	15%	0%	15%
PR[4]	46%	55%	44%	43%	26%	50%	69%	61%	71%	63%	70%	34%

(1) Patients evaluable for response
(2) Patients with CLL only
(3) Includes patients with CR(i)
(4) Nodular PR and PR
(5) Salvage regimens used: R-GMCSF (n=10), R-methylprednisolone (n=5), R-monotherapy (n=3), alemtuzumab monotherapy (n=4), R-alemtuzumab (n=11), R-FC± lumiliximab (n=18), R-FC + alemtuzumab (n=8), CHOP-like regimen (n=5), miscellaneous (n=15).

CHOP versus R-CHOP

As previously highlighted, the REACH study represents the only randomised phase III study to date to evaluate the activity and tolerability of rituximab in combination with chemotherapy in relapsed/refractory CLL patients.

At the ASH annual meeting 2006, Catovsky et al[57] reported long-term follow-up data for 180 patients in the UK-CLL4 trial who received second-line treatments: 125 originally in the chlorambucil arm, 44 in the fludarabine arm and 11 in the FC arm. The authors reported that 31% of fludarabine-treated patients went on to receive CHOP as second line therapy. Of these patients, 6 were Binet stage B/C and refractory to front-line fludarabine (Daniel Catovsky personal communication to Roche[58]). To examine the potential clinical benefit of adding rituximab to CHOP, we have conducted a simple cross trial comparison comparing these data with those from the study by Eichhorst and colleagues reported in 2005 (Table 52 below).

Table 52. CHOP vs R-CHOP – phase II cross-trial comparison

	UK-CLL4 (CHOP)	Eichhorst et al, 2005 (R-CHOP)
Mean age	65	66*
F-refractory patients	6	13
Binet C patients (%)	33	72*
No. prior treatments (median)	1	2.1 (48% had received 3 pretreatments)*
ORR (%)	67	69

***** Figures are for full patient population in the study. Assumption is made that this is representative of the subgroup of F-refractory patients**.**

Whilst ackowledging the low patient numbers and dangers of overinterpretting non-randomised inter-trial comparisons, these data would appear to concur with those from REACH, with overall response rates similar for R-CHOP and CHOP. This is despite a considerably greater number of poor risk patients in the R-CHOP study in the form of more patients with advanced stage disease and greater numbers of previous treatments administered. Limitations of this analysis withstanding, these data would imply that R-CHOP is superior to CHOP in this patient population and further support the anticipated broad R-chemotherapy licence. Furthermore, these data demonstrate that R-CHOP is a useful therapeutic option for poor-risk patients whose disease is refractory to prior fludarabine-containing therapy. These data are supported by data on other rituximab-containing regimens in fludarabine-refractory CLL, as discussed in detail in section 6.8.4.2.

Summary

The results of the pivotal REACH study demonstrate statistically significant and clinically meaningful benefit when rituximab is used in combination with FC chemotherapy in patients with relapsed/refractory CLL. These results are confirmed by published literature from a total of 8 supportive studies involving more than 480 previously treated patients treated with rituximab in combination with a range of chemotherapy regimens. In all these supportive studies, high response rates of $\geq$ 65% were achieved. Importantly, one retrospective cohort analysis comparing R-FC with FC or F alone demonstrated an OS benefit for the cohort treated with rituximab containing therapy compared to the cohorts treated with chemotherapy alone and this difference was considered by the authors to be medically (and statistically) significant.

Of note, the efficacy of rituximab in combination with chemotherapy was also recently reported in a meta-analysis by Schulz and colleagues in patients with indolent or mantle-cell lymphoma (Schulz et al, 2007[59]) [NB - SLL/CLL is categorized as an indolent non-Hodgkin lymphoma]. Among the patients in the 7 randomized trials included in this analysis (2 in previously treated and 5 in *de novo* patients), 1480 had histologically proven follicular lymphoma and 260 had mantle cell lymphoma. The remaining 203 patients were described as having indolent lymphoma (n = 121) or lymphoplasmocytic/cytoid lymphoma or CLL (n = 82). Results showed that patients treated with R-chemo had better overall survival (hazard ratio [HR] for mortality = 0.65; 95% confidence interval [CI] = 0.54 to 0.78), overall response (relative risk of tumor response = 1.21; 95% CI = 1.16 to 1.27), and disease control (HR of disease event = 0.62; 95% CI = 0.55 to 0.71) than patients treated with chemotherapy alone. Safety data also showed that patients treated with R-chemo had statistically significantly more leukocytopenia and fever than patients treated with chemotherapy alone, but there were no differences in the frequencies of infections or thrombocytopenia between the groups.

The authors of this manuscript suggest that the antilymphoma activity of rituximab in combination with any chemotherapy reflects their different modes of action and the ability of the antibody to modify molecular signaling pathways. This latter effect is associated with decreased expression of the antiapoptotic gene products, Bcl-2 and Bcl-xL, and the sensitization of drug-resistant B-cell non-Hodgkin lymphoma cells to chemotherapy (Jazirehi et al, 2005[60]; Jazirehi et al, 2005[61]; Bonavida et al, 2005[62]).

On the basis of the results from this analysis, it was conlcluded that concomitant treatment with rituximab and standard chemotherapy regimens should be considered the standard of care for patients with indolent (and mantle cell) lymphomas who require therapy.

6.8.4.2 Supporting studies that highlight the efficacy of rituximab-containing regimens in patients with fludarabine-refractory CLL.

Rationale for Excluding Patients who were Refractory to Fludarabine from the BO17072 (REACH) Study Population

Before analysing the supporting phase II data in closer detail, it is first necessary to adress why patients who were refractory to fludarabine were excluded from the REACH trial.

To enter REACH, patients had to have achieved a response (PR or CR) to single agent fludarabine (or other nucleoside analog) that lasted at least 6 months. Thus, there were no patients in the study who were refractory to fludarabine (defined as failure to achieve a PR or CR that lasted at least 6 months).

Exclusion of patients who were refractory to fludarabine was based on the view that such patients were relatively uncommon (about 29%-37% of patients treated with first-line fludarabine monotherapy (Johnson et al, 1996[52]; Leporrier et al, 2001[53], Rai et al, 2000[54])), have a poor prognosis, and were unlikely to benefit from further fludarabine-based therapy. This view was based mainly on a retrospective analysis of 147 patients with fludarabine-refractory CLL from the M.D. Anderson Cancer Center (MDACC), available at the time (Keating et al, 2002[55]). The response rate to first salvage therapy in this group of patients was 22% and the median survival was 10 months. The best response rates were noted in patients who underwent allogeneic stem cell transplant or received alemtuzumab. Accordingly, there was particular concern about patients with fludarabine-refractory CLL being randomised to the FC alone arm of the REACH trial since although the FC combination had been shown to be superior to fludarabine alone in patients with CLL (Flinn et al, 2000[63]), the efficacy of salvage FC in patients who failed to achieve a durable response to fludarabine alone, was expected to be low and alternative agents (including rituximab) might be available, at least within the context of a clinical trial.

Since then, additional efficacy data on patients with fludarabine-refractory CLL has become available from the MDACC. In a retrospective review of patients who were fludarabine-refractory and either refractory to alemtuzumab or ineligible for alemtuzumab because of bulky lymphadenopathy, overall response to first salvage therapies (other than stem cell transplantation) was 23% with no complete responses and a median survival of 9 months (Tam et al, 2007[47]). These data confirm the generally low response rates and short survival of patients with fludarabine-refractory disease. In addition, these data show particularly poor outcome for patients who are not eligible for alemtuzumab, intensive regimens or stem cell transplant. For example, the response rate to single agent cytotoxics (including purine nucleoside analogs) was 14% with a median overall survival of 5 months.

Data on R-FC Treatment in Fludarabine-Refractory CLL

Although the REACH study did not include patients who were refractory to fludarabine, data from the MDACC CLL group support the view that R-FC has worthwhile efficacy in these patients.

Wierda et al have reported outcomes of R-FC in 177 previously-treated patients with CLL (Wierda et al, 2005[3]; Wierda et al, 2006[32]). Overall, patients had received a median of 2 prior regimens (range 1-10). Thirty-two patients (18%) had received only alkylating agents and 145 patients (82%) had previously received fludarabine alone or in combination. One hundred and eight patients (61%) had fludarabine-sensitive disease, and 37 patients (21%) were refractory to fludarabine (defined as failure to achieve at least a PR with the last fludarabine-based treatment or progression within 6 months of treatment). Thirty-four patients (19%) were previously treated with FC; 30 of these patients had fludarabine-sensitive disease, and four patients were refractory to fludarabine. Response rates according to prior treatment are summarized in Table 53.

Table 53. Response to R-FC According to Prior Treatment in Patients with Relapsed/Refractory CLL Treated at the MDACC

Treatment		NCIWG Criteria Response Rate (%)				
	No. pts	CR	nPR	PR	OR	ED
Overall	177	25	16	32	73	3
Prior treatment						
Alkylating agent	25	28	12	36	76	12
Rituximab (only)	7	29	29	29	76	0
FC	34	24	15	35	74	0
F-sensitive	78	33	19	24	77	3
F-refractory	33	6	9	42	58	3

Abbreviations: NCIWG, National Cancer Institute Working Group; F, fludarabine; C, cyclophosphamide, CR, complete response/remission; nPR, nodular partial response/remission; PR, partial response/remission; OR, overall response; ED, early death; NS, not specified

Overall, CR and overall response rates were comparable for patients previously treated with alkylating agents and patients previously treated with fludarabine, with or without cyclophosphamide (suggesting that prior treatment with FC does not have a detrimental impact on response to R-FC). Patients who were refractory to fludarabine had an overall response rate of 58% with 6% CRs (2 patients) which is lower than in the other groups of patients (Weiss et al, 2003[64]; Bosch et al, 2002[18]). Univariate analysis revealed that achieving a CR was significantly associated with a range of pre-treatment variables including fewer prior treatments ($P<0.001$) and remission with last fludarabine-based regimen ($P=0.002$). Overall response was also associated with remission with last fludarabine-based treatment ($P=0.039$), but not with number of prior treatments. Although treatment failure (non-response to R-FC) was associated with fludarabine refractoriness in multivariate analysis, it was not found to be significantly associated with time to progression or survival.

Data on Other Rituximab-based Regimens in Fludarabine-Refractory CLL

Data on other rituximab-based regimens are summarized in Table 54 below. Overall, these data support the MDACC data on the efficacy of rituximab-containing regimens in patients with fludarabine-refractory CLL with overall response rates generally above 50% (lower response rates in patients treated with rituximab alone or in patients who were also refractory or unsuitable for alemtuzumab).

Table 54. Efficacy of Other Rituximab-containing Regimens in Patients with Fludarabine-refractory* CLL

Study (ref)	n	Salvage Treatment	Overall Response rate (CR rate)	Survival
Woyach et al, 2009	18 (of 36 total)**	R+ etanercept	28%	Median 53 months for responders versus 42 months for non-responders
Castro et al, 2008	14**	R+HDMP	93% (36% CR)	Median not reached after median follow up of 40 months
Faderl et al, 2003 †	32	R + A	63% (6% CR)	Median 11+ months for responders, 6 months for non-responders (overall, including pts with PLL, Richters etc)
Nabhan et al, 2004	11	R + A	9% (0% CR)	NS
Wierda et al, 2006†	32 (of 79 total)	CFAR	51% (13% CR)	Median 19 months for all pts (including non-refractory), 35+ months for CR, 18 months for PR and 7 months for non-responders (total pt population)
Tsimberidou et al, 2008†	30	OFAR	33% (6% CR)	89% 6 month survival
Lamanna et al, 2006	8	R-PC	75% (12% CR)	NS
Klepfish et al, 2008	5**	R + FFP	100%	NS
Winkler et al, 1999	8 (of 11 total)	R alone	12.5% (1 PR, 6 SD, 1 PD; lymphocyte counts improved in all pts)	NS
Tam et al, 2007†	9	Intensive R-combinations	22% (both responses in pts treated with OFAR)	NS
	19	Non-intensive R-combinations (including R + GMCSF, R+A, R+MP, R-FC, CFAR)	26% (all 5 responses in pts receiving R-FC)	NS

*Various definitions– includes patients who were not primary refractory (failed to achieve a CR or PR lasting at least 6 months) in some cases, and patients who were also refractory or unsuitable for alemtuzumab (Tam et al, 2007)

**Including some patients pre-treated with rituximab

From 4 trials included in review article

†Data from phase II and/or retrospective studies from the MDACC (potential for overlap with other studies)

NS: not specified; R: rituximab; HDMP: high dose methylprednisolone; A: alemtuzumab; CFAR: cyclophosphamide, fludarabine, alemtuzumab, and rituximab: OFAR: oxaliplatin, fludarabine, cytarabine, and rituximab; R-PC: rituximab, pentostatin, cyclophosphamide; FFP: fresh frozen plasma;

Woyach et al, 2009

In this phase I/II study, an overall response rate of 28% was reported in18 fludarabine refractory CLL/SLL patients (out of a total of 36) treated with rituximab plus etanercept. This compares favourably with an ORR of 29% for all patients in the study. Median time to next treatment and OS were also shown to be longer in responding patients vs non-responders (14.5 months vs 3 months and 53 months vs 42 months, respectively), although no distinction was made between fludarabine sensitive and refractory patients.

Conclusions: This trial demonstrates that the combination of etanercept and thrice weekly rituximab is clinically effective and produces a durable response in relapsed CLL patients, including those refractory to fludarabine. Thus, etanercept and rituximab may be a potential treatment for fludarabine-refractory patients who may not be candidates for more aggressive therapies.

Castro et al, 2008

In this phase II study, Castro and colleagues report an ORR of 96% (36% CR) in 14 high-risk fludarabine-refractory CLL patients following treatment with rituximab in combination with HDMP. After a median follow-up of 40 months, median OS for all patients had not been reached. Median time-to-progression was 15 months (range, 3.2–23 months). Moreover, the median time-to-progression for patients achieving CR, PR, or PD was 23.4, 12.5, and 3.23 months, respectively. The median duration of response to treatment measured by the time that took to next treatment was 22 months (49, 12.5, and 3.5 months for CR, PR and PD patients, respectively).

Conclusions: These data suggest that the HDMP-rituximab combination is an effective non-myelotoxic regimen for the treatment of patients with fludarabine-refractory disease. These results are highly encouraging with the median survival not yet reached and 64% of the patients still alive after a median follow up of 40 months. Of particular note, the CR (36%) and OR (93%) rates reported in this study are higher than those reported for HDMP alone in refractory CLL patients (0% and 55% respectively) (Thornton et al, 1999[65]). Furthermore, median time to progression was longer for patients responding to R-HDMP (15 months) compared to HDMP alone (8 months). Again, the limitations of cross study comparisons withstanding, these data further support the concept that altering the base regime does not preclude the clinical benefit associated with the addition of rituximab (as discussed at length in section 6.8.4.1).

Faderl et al, 2003

Faderl and colleagues report an ORR of 63% (6% CR) in 32 CLL patients treated with rituximab plus alemtuzumab. Importantly, no significant difference in response was noted in patients with fludarabine sensitive and refractory disease (54% of all patients). After a median follow-up of 6.5 months, median OS for responders was 11+ months vs 6 months for non-responders.

Conclusions: The combination of rituximab and alemtuzumab is feasible, has an acceptable safety profile, and has clinical activity with a short course in a group of CLL patients with poor prognoses, including those with fludarabine-refractory disease.

Nabhan et al, 2004

In this phase I pilot study, an ORR of 9% (0% CR) was reported in 11 fludarabine refractory CLL patients. All other patients (90%) had stable disease that lasted for a median duration of 101.5 days (3.4 months) [range 39 – 183 days].

Conclusions: Although this study did not show high response rates, the fact that all patients had stable disease (without increased toxicity) is clinically relevant in this population of patients with advanced disease refractory to alkylating agents and purine analogues.

Wierda et al, 2006

Wierda and colleagues report an ORR of 51% (13% CR) in 32 heavily pre-treated fludarabine-refractory patients following treatment with combined clyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR). After a median follow-up time of 12 months, median OS for all patients (including non-refractory) was 19 months (35+ mo for CR, 18 mo for PR and 7 mo for non-responders). Median time to progression for all responders was 26 mo (32 mo for CR and 18 mo for PR pts).

Tsimberidou et al, 2008

In this phase I/II study, 30 heavily pre-treated fludarabine refractory CLL patients (90% had received 2 or more prior regimens) achieved an ORR of 33% (6% CR). The 6 month failure-free and overall survival rates for fludarabine refractory patients were 48% and 89% respectively. Patients who achieved a CR or a PR also had longer survival than patients whose disease failed to respond to therapy.

Conclusions: This study demonstrates the efficacy (and tolerability) of the OFAR regimen in heavily pretreated patients with fludarabine-refractory CLL. A larger study of OFAR is currently being pursued by this group.

Lamanna et al, 2006

In this phase II study, Lamanna and colleagues report an ORR of 75% in 8 fludarabine refractory CLL patients treated with rituximab plus pentostatin and cyclophosphamide (R-PC). One (12%) of these patients achieved a complete response to treatment. Median survival for all 32 CLL patients in the study (8 fludarabine refractory and 24 fludarabine sensitive) was 44 months. As expected, patients with good responses (CRs and NRs) had superior OS compared to remaining patients (PRs and failures), with 100% vs 28% of patients alive at 36 months respectively.

Klepfish et al, 2008

In this prospective observational analysis, 5 patients with fludarabine refractory CLL were treated with rituximab in combination with fresh frozen plasma (FFP). A rapid and dramatic clinical and laboratory response was achieved in all patients (100% response rate). Lymphocyte counts dropped markedly followed by shrinkage of lymph nodes and spleen and improvement of the anaemia and thrombocytopenia. This could be maintained over 8 months (median) with

additional cycles of treatment if necessary. Treatment was well tolerated in all cases.

Conclusions: Adding FFP to rituximab may provide a useful therapeutic option in patients with advanced CLL resistant to treatment.

Winkler et al, 1999

Winkler and colleagues report an ORR to rituximab monotherapy of 11% in 9 heavily pre-treated (median number of prior treatments = 3) fludarabine refractory CLL patients. Stable disease was reported in 6 patients with one case of progressive disease. In all cases, lymphocyte counts were shown to improve after infusion of rituximab.

Conclusions: Although response rates are poor in this early study, results demonstrate that even as single agent therapy some patients with high risk CLL may derive clinical benefit from rituximab.

Tam et al, 2007

Investigators from the MDACC, report data from a retrospective analysis of 99 fludarabine refractory CLL patients (58 double-refractory (to both fludarabine and alemtuzumab) and 41 bulky fludarabine refractory (ineligible for alemtuzumab)) treated with a variety of salvage regimens. 9 patients in the study received intensive rituximab-based combination therapy (ie rituximab + Hyper-CVAD, OFAR, and R-FC + oxaliplatin) as their first salvage regimen and achieved an ORR of 22% (both OFAR patients). In addition, 19 patients received non-intensive rituximab combinations (ie rituximab + GMCSF, rituximab + alemtuzumab, rituximab + methylprednisolone, R-FC, and CFAR), achieving a response rate of 26% (all R-FC patients).

Conclusions: The results of different salvage modalities presented in this study are retrospective and inherently subject to patient selection bias. Because of the heterogeneity of salvage regimens used, and the small number of patients receiving each therapy, no definitive conclusions could be drawn regarding whether any particular strategy is superior to the rest. Results do show, however, that rituximab-based salvage therapy is active in this very poor prognosis group of patients.

Summary

Data from the MDACC demonstrate that R-FC is a useful therapeutic option for patients whose disease is refractory to prior fludarabine-containing therapy. These data are supported by data on other rituximab-containing regimens in fludarabine-refractory CLL.

In addition, with the exception of data on allogeneic stem cell transplant (which is not a feasible option for most patients with CLL) and experimental regimens including alemtuzumab, there is no convincing data published indicating that regimens that do not contain rituximab produce better outcomes than regimens that do incorporate rituximab in fludarabine-refractory patients.

It is our opinion that excluding CLL patients who are refractory to fludarabine-based therapy from treatment with rituximab-based regimens such as R-FC would limit the available options for these poor prognosis patients and prevent them from receiving one of the most effective treatment regimens currently available.

These conclusions are further supported by the recently published "ESMO Clinical Recommendations for Diagnosis, Treatment and Follow-up" which recommend the use of fludarabine combinations (FC or FCM) ± monoclonal antibodies (R-F, R-FC or F-alemtuzumab) in fludarabine-refractory patients or patients who have relapsed after fludarabine-based therapy (Eichhorst et al, 2008[21]).

6.8.4.3 Supporting studies that highlight the efficacy of re-treatment with rituximab-containing regimens in patients with relapsed/refractory CLL.

Historical Rationale for Excluding Patients Treated with Monoclonal Antibodies from the BO17072 (REACH) Study Population

The REACH excluded patients who were previously treated with rituximab or other monoclonal antibodies. At the time of study planning in 2001 and 2002, patients who had received monoclonal antibody treatment in the first-line setting were considered rare. At the time (and for most of the recruitment period), no monoclonal antibodies were approved for the first-line treatment of patients with CLL. Standard first-line treatments were mainly fludarabine monotherapy and chlorambucil (with or without corticosteroids), the two first-line regimens that contributed most to the patient pool in REACH.

Current First-line Treatment in Chronic Lymphocytic Leukemia

During the last 5-7 years, use of first-line fludarabine and cyclophosphamide (FC) combinations has increased as a result of a number of randomised phase III trials showing superiority of fludarabine over chlorambucil (Johnson et al, 1996[52]; Leporrier et al, 2001[53]; Rai et al, 2000[54]), and of FC over fludarabine monotherapy (Eichhorst et al, 2006[66]; Flinn et al, 2000[63]; Catovsky et al, 2007[28]). Meanwhile, the the German CLL-8 trial has demonstrated that the addition of rituximab to FC (R-FC) is superior to FC alone, with higher response rates and complete response (CR) rates, and longer progression-free survival (PFS) reported (Hallek et al, 2008[67]). Accordingly, it is expected that R-FC will rapidly become the combination of choice for patients with previously untreated CLL who are suitable for fludarabine-based therapy. However, the CLL-8 study data also indicate that although patients treated with R-FC benefit from the longest PFS yet reported in a randomised CLL trial, ultimately most patients will still relapse and require further therapy.

Evidence to Support Rituximab Re-Treatment

1. Data on Subsequent Rituximab Treatment after First-line R-FC

The use of rituximab-containing regimens after failure of first-line rituximab-containing therapy has been explored in CLL by the pioneers of the R-FC

regimen, the MDACC CLL group headed by Dr Michael Keating (Tam et al, 2008[2]). In one study, the group looked at subsequent treatment of 300 patients initially treated with first-line R-FC. Results were first reported in an oral presentation at the American Society of Clinical Oncology's Annual Meeting ASCO in 2007 (Keating et al, 2007[68]) and subsequently updated at the American Society of Haematology's Annual Meeting ASH 2008 (Tam et al, 2008[38]). Results show that rituximab-containing salvage therapy following R-FC treatment in first-line is feasible and a viable option for patients relapsing after initial response to a rituximab containing regimen.

Of the initial 300 patients treated with R-FC in first-line CLL, 116 patients (39%) had an event after a median follow-up of 6 years. These included 103 patients whose disease relapsed, and 13 patients who were primary refractory to first-line R-FC. Of these 116 patients, data were available on 97 patients who completed subsequent therapy. Patients received treatment chosen at the discretion of the individual treating physicians. Median follow-up after salvage therapy was 32 months.

Compared with patients in ongoing remission, the relapsed/refractory patients constituted an adverse prognostic group. They had more adverse baseline characteristics including a greater proportion with performance status 1 (71% vs 53% p=0.002), elevated β2m (54% vs 36% p=0.002), white cell count ≥150 x 10^9/L (25% vs 12% p=0.003), unmutated IgVH (81% vs 44% p<0.001) and ZAP-70 positivity (78% vs 49% p<0.001).

The CR rate following second-line therapy was as follows:

- R-FC (n=30): 17%
- Rituximab alone (n=25): 4%
- Alemtuzumab ± rituximab (n=16): 31%
- R-FC plus alemtuzumab (CFAR, n=9): 56%
- Lymphoma-type chemotherapy (n=5): 0%
- Other treatment (n=12): 0%

The median overall survival for all patients relapsing after R-FC and receiving rituximab-based salvage treatment was 32 months.

Although CR rates were relatively low (compared with first-line R-FC in the same population and in the CLL-8 trial, and compared with second-line R-FC in the REACH trial, CR rates were still higher than with chemotherapy alone or with other non-rituximab-containing regimens. Moreover, overall response rates ranged from 40% to 88% with rituximab-containing regimens (61% for R-FC +/- lumiliximab and 88% for R-FC + alemtuzumab) indicating that a substantial proportion of patients benefitted from rituximab-containing therapy. These results need to be considered in light of the fact that the patients were all either refractory to initial R-FC or had relapsed relatively early after R-FC: a group of patients with resistant disease and a poor prognosis. It is likely that outcomes would be better

in the overall group of patients receiving second-line rituximab-containing therapies, i.e. including patients with extended remissions (who were not part of this analysis because they had not yet relapsed).

2. Data on R-FC Treatment after Previous Rituximab

In the first report of R-FC in the relapsed CLL setting, Wierda and coworkers (also from the MDACC) reported outcomes in 177 previously-treated patients (Wierda et al, 2005[3]; Wierda et al, 2006[32]). This group of patients included 22 who were previously treated with a rituximab-containing regimen (Keating, 2008[69]). It is not clear whether any of these patients were also included in the data described above from Keating et al. Overall, patients had received a median of 2 prior regimens (range 1-10). Thirty-two patients (18%) had received only alkylating agents and 145 patients (82%) had previously received fludarabine alone or in combination. One hundred and eight patients (61%) had fludarabine-sensitive disease, and 37 patients (21%) were refractory to fludarabine (defined as failure to achieve at least a PR with the last fludarabine-based treatment or progression within 6 months of treatment). Twenty-two patients (12%) had previously received rituximab, either alone or in combination, and 7 patients had received rituximab as their only prior treatment. Thirty-four patients (19%) were previously treated with FC; 30 of these patients had fludarabine-sensitive disease, and four patients were refractory to fludarabine. Response rates according to prior treatment are summarized in Table 55.

Table 55. Response to R-FC According to Prior Treatment in Patients with Relapsed/Refractory CLL Treated at the MDACC

Treatment		NCIWG Criteria Response Rate (%)				
	No. pts	CR	nPR	PR	OR	ED
Overall	177	25	16	32	73	3
Prior treatment						
Alkylating agent	25	28	12	36	76	12
Rituximab alone or in combination	22	18	9	36	64	NS
Rituximab (only)	7	29	29	29	76	0
FC	34	24	15	35	74	0
F-sensitive	78	33	19	24	77	3
F-refractory	33	6	9	42	58	3

Shaded row: unpublished information (verbal communication from MDACC)
Abbreviations: NCIWG: National Cancer Institute Working Group; F: fludarabine; C: cyclophosphamide, CR: complete response/remission; nPR: nodular partial response/remission; PR: partial response/remission; OR: overall response; ED: early death; NS: not specified

Overall, CR and overall response rates were comparable for patients previously treated with alkylating agents and patients previously treated with fludarabine, with or without cyclophosphamide. Although numbers are small, these data also show that patients previously exposed to rituximab had response rates that were comparable to the rest of the patient population, and even patients who were refractory to fludarabine had an overall response rate of 58%. The median overall survival for the group of rituximab-pretreated patients was 48 months, compared with 42 months for the overall group of 177 patients.

3. Data from Other Studies Using Repeated Administrations of Rituximab in CLL

Rituximab re-treatment has also been evaluated in a variety of other settings in patients with relapsed CLL, and the data published in small series or case reports. Although endpoints and duration of follow-up vary in these studies, and details of rituximab pre-treatment is not always reported, re-treatment with rituximab monotherapy or rituximab-containing combination regimens was generally considered feasible and successful. At retreatment, rituximab was given alone or in combination with other immunomodulatory drugs (eg. eternacept, methylprednisolone) or chemotherapy (pentostatin, mitoxantrone, cyclophosphamide). A summary of available data is presented in Table 56 below.

Table 56. Overview of other Studies Including Rituximab Re-Treatment in CLL

	n	Initial Treatment	Re-Treatment	Overall Response rate (CR rate)	Survival
Lamanna et al., 2006	7 (of 32 CLL pts)	Rituximab + chemotherapy	R-PC	NS (75%, including 25% CR for all CLL pts)	NS (median 44 months for all CLL pts)
Herold et al., 2000	1 (of 2 CLL pts)	Rituximab monotherapy	Rituximab monotherapy	Both pts responded (PR)	NS
Zent et al., 2008	9 (of 30 CLL pts)	Rituximab + Alemtuzumab	Rituximab + Chemotherapy	78% (44% CR)	NS
Gupta et al., 2002†	5	R-CD	R-CD	100% AIHA responses	NS
Winkler et al., 1999	1	Rituximab monotherapy	Rituximab monotherapy	Not reported (the patient's autoimmune thrombocytopenia improved)	Not reported
Lamanna et al., 2008	11	R-PC or R-FC	R-PC + Mitoxantrone	91% (19% CR)	NS
Woyach et al., 2009	26	Rituximab +chemotherapy	Rituximab + Etanercept	33%	NS
Castro et al., 2008	3 (of 14 CLL pts)	Rituximab + chemotherapy	Rituximab + HDMP	Overall 93% (all but one pt responded)	NS
Klepfish et al., 2008	3	Rituximab + chemotherapy	Rituximab + FFP	100%	Survival 7, 8+ and 15+ months

Abbreviations: R-PC: rituximab, pentostatin, cyclophosphamide; R-CD: rituximab, cyclophosphamide, dexamethasone; R-FC: rituximab, fludarabine, cyclophosphamide; FFP: fresh frozen plasma; HDMP: high dose methyprednisolone

† CLL patients treated for autoimmune-hemolytic anemia (AIHA).

Lamanna et al, 2006

In this phase II study, 7 out of a total of 32 previously treated CLL patients had received prior rituximab therapy. Efficacy data in this sub-group of patients was not reported by the authors, although an ORR of 75% (25% CR) and median OS of 44 months was reported for all CLL patients.

Herold et al, 2000

Herold and colleagues report the successful re-adminstration of 4 sucessive courses of rituximab monotherapy (375 mg/m2 x 4 in weekly intervals for the first 3 courses and 375 mg/m2 x 2 once a week for course 4) in a heavily pre-treated male CLL patient.

Conclusions: In this particular patient, the authors have demonstrated that re-treatment with rituximab monotherapy is applicable and effective. This also confirms reports of a phase-II trial presented around the same time (Davis et al, 1998[70]).

Zent et al, 2008

In this phase II study, Zent and colleagues report an ORR of 78% (44% CR) in 9 high-risk CLL patients treated initially with rituximab plus alemtuzumab and then salvaged with another rituximab-based combination regimen (ie rituximab plus alemtuzumab (n=1), CFAR (n=2), PCR (n=4), FCR (n=1), and R-CVP (n=1). The responses to the first retreatment regimen were: alemtuzumab and rituximab, clinicalcomplete response (CCR) (n = 1 patient); CFAR, PR (n = 1 patient) and progressive disease (n = 1patient); PCR, CR (n = 1 patient), PR (n = 2 patients), and progressive disease (n = 1 patient); FCR, CCR (n = 1 patient); and R-CVP, CCR (n = 1 patient). It is noteworthy that 2 of these patients received further subsequent retreatment with alemtuzumab and rituximab and achieved responses (PR) that were at least as good as their initial responses to this regimen.

Gupta et al, 2002

Gupta and colleagues report results from 8 pateints with steroid refractory AIHA of CLL following treatment with rituximab, cyclophosphamide, and dexamethasone (RCD). Out of the initial eight patients, five patients had a relapse of AIHA after a median of 13 months (range 7–23+). All five patients were retreated with RCD and median number of RCD cycles given was 2 (range 1–3). All five patients achieved a second remission of their AIHA following RCD. Median duration of response was 7+ months (range 3–9+).

Conclusions: Although in the context of AIHA of CLL rather than CLL itself, these data futher support the feasibility and effectiveness of re-treatment with rituximab based chemotherapy.

Winkler et al, 1999

In this single arm, phase II study a single CLL patient (out of a total of 10) was re-treated with 4 x 375mg/m2 rituximab 3 months after completion of a first course of rituximab monotherapy. Although reponse data for this patient were not reported in the final publication, the patients autoimmune thrombocytopenia was documented to have improved.

Lamanna et al, 2007

Following on from their 2006 study, Lamanna et al report the impressive activity of the PCRM regimen (pentostatin, cyclophosphamide, rituximab, and mitoxantrone) in 11 CLL patients previously treated with PCR or FCR. The authors report that prior therapy with PCR or FCR did not adversely affect the frequency of response, with 91% of these patients responding (19% CR and 73% PR).

Conclusions: These preliminary results indicate that PCRM therapy is very active (and well tolerated) even in patients who have received previous FCR or PCR.

Woyach et al, 2009

In this phase I/II study of rituximab plus etanercept in 36 relpased.refractory CLL patients, 26 had received prior rituximab plus chemotherapy. In these patients, an ORR of 33% was reported (8 of 24 patients; 2 not evaluable for response).

Conclusions: This trial demonstrates that the combination of etanercept and thrice weekly rituximab is clinically effective and produces a durable response in relapsed/refractory CLL patients, including patients who have failed prior rituximab.

Castro et al, 2008

In a single arm, phase II study, Castro and colleagues report an ORR of 100% (1 CR and 2 PRs) in 3 fludarabine refractory high-risk CLL patients who had received prior rituximab therapy (fludarabine plus rituximab), following treatment with rituximab plus high-dose methylprednisolone (HDMP).

Klepfish et al, 2008

Klepfish et al report an ORR of 100% in 3 patients with advanced refractory CLL who had failed prior treatment with rituximab (rituximab monotherapy (n=1) and rituximab + CHOP-like chemotherapy (n=2)), following concurrent administration of rituximab and fresh frozen plasma. Overall survival for these patients ranged from 7 to 15+ months.

In addition to these reported outcomes of patients who had been retreated with rituximab, data from both the first-line R-FC vs FC trial in CLL (CLL-8) and from study REACH demonstrate that investigators opted to treat patients with rituximab again at relapse. In study CLL-8, of 44 patients who had been treated at relapse in the R-FC arm, 19 patients (44%) received rituximab either in combination with a chemotherapy regimen or as single agent compared. In study REACH, the corresponding numbers are 14 out of 47 patients.

Summary

Data from more than 200 patients in non-randomized studies demonstrate that rituximab-containing regimens, specifically repeat administration of R-FC (and variants thereof) are a viable and useful therapeutic option for patients whose initial treatment contained rituximab.

Importantly, there is no data published to suggest that regimens that do not contain rituximab produce better outcomes than regimens that do incorporate rituximab in this setting.

To support the data in CLL, there is also a significant level of evidence in another indolent lymphoproliferative disorder, follicular lymphoma, to suggest that patients previously treated with rituximab can be successfully re-treated on disease progression (Cohen Y et al, 2003[71]; Davis T et al, 1999[70]; Lemieux B, et al 2004[72]; Hainsworth et al, 2006[73]; Dreyling et al, 2006[74]). Furthemore, data from the pivotal EORTC_20981 study (van Oers et al, 2006[75]; van Oers et al, 2008[76]) in relapsed-refractory follicular lymphoma clearly demonstrates that patients treated with rituximab-containing induction therapy (ie R-CHOP) benefited significantly, in terms of extended PFS, from subsequent treatment from single agent rituximab (in the form of maintenance therapy; p=0.043). Although the study was not designed to compare the 2 groups, results also showed that patients treated with R-CHOP followed by R-maintenance actually had better outcomes than those treated with CHOP alone followed by maintenance. Indeed, on the basis of these data and a successful licence application by Roche to the EMEA, NICE published guidance in February 2008 (NICE TA137, Feb 2008[77]) stating that:

" Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed stage III or IV follicular non-Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab."

It is also of relevance to the current submission that in the same technology appraisal of guidance, NICE do not restrict the use of R-chemo induction therapy in relapsed follicular lymphoma patients to rituximab naïve patients, stating that:

"Rituximab, within its marketing authorisation, in combination with chemotherapy, is recommended as an option for the induction of remission in people with relapsed stage III or IV follicular non-Hodgkin's lymphoma."

This is despite the fact that (similar to REACH) none of the patients in the pivotal EORTC_20981 study had received prior rituximab. In section 4.5 of TA137, NICE suggest that this decision was based on consideration of the same dossier of evidence outlined above, indicating that "*follicular non-Hodgkin's lymphoma could be re-treated with rituximab with little or no loss of efficacy"*.

In conclusion, it is our opinion that excluding CLL patients who have previously received rituximab-containing therapy from treatment with rituximab-containing combinations at relapse would seriously limit the available options for these patients and prevent them from receiving the most effective treatment regimen currently available. It would be especially counterintuitive to prevent rituximab retreatment of patients who achieved a profound and prolonged response to initial rituximab-containing therapy. Indeed, this would directly contravene ESMO guidelines which state that "*the first-line treatment may be repeated if the relapse*

or progression occurs >12 months after the initial therapy" (Eichhorst et al, 2008[21]).

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 herein relates to appraising rituximab in relapsed/refractory 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 treatment for previously treated patients, but in those patients where non-rituximab therapy is used, single agent chlorambucil and fludarabine combination therapy (FC) are generally preferred as treatment options (as highlighted for the United Kingdom by market research data presented in section 4). Less often, clinicians may use combination regimens such as 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, chlorambucil, and CHOP (the three comparators noted in the decision problem). There is, however, only one Phase III trial available, REACH, with FC as the comparator - which is highly pertinent. Results from this study form the backbone of this submission and are discussed at length in section 6.4. With regards to the other main comparators, there is no phase II/III data for rituximab in combination with chlorambucil in previously treated patients and a single phase II study examining the combination of rituximab and CHOP. This trial plus 7 other supportive studies is presented involving more than 480 previously treated patients treated with rituximab in combination with a range of chemotherapy regimens. These studies add valuable information that is readily interpretable – highlighting that changing the base regime still allows efficacy with an acceptable toxicity profile. As previously discussed, experience in follicular lymphoma Phase III studies with rituximab (eg Marcus et al, 2005[78]; Hiddemann et al.[79]) have consistently highlighted that varying the base regime does not alter the additional benefit that rituximab gives to these patients.

Regarding the population described in the decision problem, patients who were refractory to fludarabine were excluded from entry into REACH, as were patients who had previously recieved rituximab. The rationale for exclusion of these subgroups is sound on the basis of when the trial was designed. Despite exclusion of these populations from the pivotal study, we propose that they are not excluded from final guidance (in line with the anticipated licence and current

ESMO guidelines) based on the wealth of evidence submitted in section 6.8.4 supporting the effectiveness of R-chemotherapy in these patients.

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[16]).

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 supports this submission, the endpoints assessed (both primary and secondary) are of direct relevance to benefits that would be experienced by patients in practice. Time spent progression-free is highly relevant as discussed above and all the secondary endpoints are standardly measured in oncology trials. The supportive phase II studies also analysed a number of these standard endpoints.

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[80]), 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[81]), 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 REACH and supporting data

has been shown to be rituximab-based chemotherapy) will lead to the best health-related quality-of-life.

The QoL assessment in REACH using FACT-G over the period of one year did not reveal any differences between the treatment groups. The initial QoL scores were similar and high in both treatment arms and continued as such over the 1 year assessment period. Since QoL was not captured in patients with disease progression and was captured in patients who started a new CLL treatment before progression, biases may not have been minimised when addressing comparative QoL. However, when this data is considered with the results of the Q-TWiST analysis of REACH, it is reasonable to assume that R-FC improves patient outcomes by enabling patients to experience less time with symptoms of relapse or treatment toxicity.

Quantifying HR-QoL

Despite the significant improvement in outcomes seen with R-FC in the Phase III study, it is important to determine whether the magnitude of the gain achievable in efficacy is justifiable in relation to the toxic effects of chemotherapy. Again, intuitively one would think that as the excess toxicity of rituximab in the Phase III study was minimal, the balance would favour R-FC.

A Q-TWiST analysis (Quality adjusted Time Without Symptoms of disease or Toxicity of treatment) was conducted on the REACH data to evaluate the effect of study treatment on the durations of the clinical health states that affect HR-QoL. It is reasonable to assume that a patient with no symptoms or toxicity from treatment has a better HR-QoL than one with symptoms/toxicity. In particular, the Q-TWiST analysis quantified the mean time spent in health states defined by treatment toxicity (TOX), time without symptoms of relapse or treatment toxicity (TWiST), and time after disease relapse (REL), and weighted the states TOX according to their relative QoL (i.e. utility). Each utility weight ranged from 0 to 1, where 0 represents a state as bad as death, 1 represents a state as good as TWiST and these scores can be collected prospectively or inferred.

The Q-TWiST was based on 30.75 months median follow-up data from REACH (clinical cut-off date of July 23, 2008), where 276 patients were treated with R-FC and 276 patients were treated with FC. Because of shorter follow up time in the FC arm, the data was truncated at 52.53 months; the longest follow up in the shortest PFS curve of the comparator, to exclude follow-up time bias in favor of R-FC.

R-FC patients gained a mean of 6.38 months TWiST (95% CI, 3.92-8.93, $p<0.0001$), spent a mean of 4.82 months less time in relapse (95% CI, 1.40-8.43 $p<0.0009$) compared with patients treated with FC, without a significant increase in the burden of toxicity (mean difference 0.06 months (95% CI, 0.39-0.50, $p=0.404$). With utility coefficients of 1.0 for all health states, the unadjusted mean difference in survival between R-FC and FC was 1.50 months (95% CI, 0.84-3.69, $p=0.0401$).

Using the utility of 0.6 for REL derived by Hancock et al[7] , an assumed utility of 0.6 for TOX, and a utility of 1.0 for TWiST, R-FC patients experienced a mean of 3.45 months longer Q-TWiST compared with FC (95% CI, 1.69-5.14, $p<0.0001$).

The key driver for these results is the substantial (40.9%) reduction in the time spent in the relapsed health state due to the addition of rituximab to FC.

All utility combinations for TOX and REL (0.1-0.9) with a TWiST utility of 1 resulted in a statistically significant ($p<0.002$) gain in Q-TWiST for R-FC patients. A second sensitivity analysis was conducted using 0.80 for TWiST and varying the REL and TOX utilities from 0.1 to 0.9. Each of these utility combinations resulted in a significant Q-TWiST outcome for R-FC relative to FC ($p \leq 0.039$). For utilities TOX and REL combinations greater than 0.6 there was a trend towards significance. However, such combinations are clinical extremes and unlikely to present in clinical practice.

Conclusion

Using 30.75 months of follow-up data, this analysis showed that, when compared with patients who received FC alone, previously treated CLL patients receiving R-FC:

- Gained an average of 6.38 months without disease symptoms or treatment toxicity
- Spent an average of 4.82 months less time in relapse
- Achieved an average of 3.45 months longer quality-adjusted survival time without any increase in the burden of toxicity.

These benefits were achieved after a median of only 30.75-months follow-up. It is likely that the quality-adjusted survival benefits in patients treated with R-FC will be further increased with extended follow-up.

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 9 centres in the United Kingdom, and has already received ethics approval through The Royal Bournemouth Hospital. The study is currently ongoing in 4 sites. It is anticipated that the first data from this study will be available in September 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 treatment of symptomatic relapsed/refractory 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 REACH) 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 REACH, rituximab added to FC led to a highly significant 35% 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 REACH 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 increase in grade 3/4 neutropenia/leukopenia (asymptomatic adverse events), not matched by an increase in the Grade 3/4 infection rate.

HR-QoL is of critical importance in this disease. The evidence presented herein highlights 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 (REACH), both fludarabine and cyclophosphamide were administered intravenously (i.v.). An oral formulation of fludarabine became available in 2001, and bioavailability studies identifed that a higher oral dose is required to obtain the equivalent iv dose (55% bioavailability, Foram et al, 1999[82]). 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[83]). 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[84]). An analysis comparing the two groups of patients separated by the protocol amendment in the UK study (ie 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, 2005[85]). 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 REACH 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 REACH, where the median age of patients was 63, and only 17% 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.

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 between 40-50% of patients at first relapse. It should be noted that in terms of the selection of patients to actually start treatment in the clinical trials (ie 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.

Relevance of Dosing Schedules Used in Clinical Trials

The main study used in support of this submission (REACH) 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 for both previously untreated and relapsed/refractory patients.

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 relapsed / refractory 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 57. The search strategy is provided in Appendix 3.

Table 57. 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 relapsed / refractory CLL in the UK. Please see Appendix 3 for a description of the excluding studies identified and the rationale behind their exclusion.

7.2 De novo economic evaluation(s)

Manufacturer economic model described in detail below.

7.2.1 Technology

7.2.1.1 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 2009[86]). Each cycle was 28 days in length. The assumed doses for each drug are described in the table below.

Table 58: Drug dose and frequency included within the economic model

Drug	Dose	Dose Frequency
Rituximab (infusion)	375mg/m^2	Day 0 of the first cycle
	500mg/m^2	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)

The doses listed in this table for intravenously administered rituximab were taken from the ML17072 (REACH[30]) phase III randomised control trial. The doses listed for oral fludarabine and cyclophosphamide were taken from the CLL-4 trial (Catovsky et al 2007[28]).

7.2.1.2 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 timepoint. 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 REACH accounts for any patients stopping treatment after 3 cycles (see Section 6.3.5).

7.2.2 Patients

7.2.2.1 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 REACH. 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.

7.2.2.2 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 REACH study was not powered to show significant differences between subgroups. Consequently, any subgroup analyses are exploratory in nature. However, exploratory subgroup analyses on the primary endpoint PFS in the pivotal study BO17072 demonstrated a consistent treatment effect across almost all the pre-specified subgroups analyzed with hazard ratios ranging from 0.2 (patients with ZAP70-positive/mutated IgVH CLL) to 1.04 (CD38-negative patients). Of note, the risk of disease progression or death was reduced by the addition of rituximab to FC for all Binet subgroups. Furthermore, the licensed indication for rituximab is not restrictive in terms of the population and hence the intention to treat (ITT) population within the REACH 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.

7.2.2.3 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, REACH 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.

7.2.2.4 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 REACH 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 comparator within the economic evaluation was FC. The final scope also suggested that bone marrow tranplants, chlorambucil, and CHOP should also be considered valid comparators.

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 REACH, 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 assumption has previously been accepted as stated in the NICE FAD (Section 4.5) for the 1st line CLL submission for rituximab published in June 2009[87], "The Committee accepted that the efficacy of both methods of administration was equivalent as long as doses were adjusted to ensure equivalent bioavailability." .

Bone marrow transplants are not commonly performed in the UK with only 47 transplants in total carried out for CLL in 2008[6]. These are performed in very specific patients who are often younger and have a suitable donor for an allograft. There is no generalisable clinical decision point currently where a physician must decide between a transplant and (rituximab based) chemotherapy. It was therefore determined that it would be inappropriate to consider these procedures as a comparator for this submission.

Due to the likely differences in patient characteristics of those who receive different chemotherapies in relapse/refractory CLL it would be inappropriate to compare R-FC versus chemotherapies other than FC (for example, R-FC compared to chlorambucil or R-FC compared to CHOP). This is because fludarabine-based combination therapy is usually administered to younger and/or fitter CLL patients, whereas chlorambucil is often reserved for the more frail and elderly. Similarly, CHOP is often reserved for patients in whom fludarabine is contraindicated. Instead, for each

chemotherapy comparator, the appropriate intervention arm should be rituximab in combination with the comparator chemotherapy (i.e. R-chlorambucil versus chlorambucil; R-CHOP versus CHOP). There is no data currently on the combination of rituximab with chlorambucil in relapse/refractory CLL. One phase II trial for R-CHOP in fludarabine refractory patients is used as the basis for a simple cross trial comparision provided in section 6.8.4.1. In addition, a wealth of phase II data is included in this submission demonstrating the efficacy and tolerability of rituximab in combination with any base chemotherapy regime. Where these evidence gaps exist, a simple threshold analysis is utilised to consider the potential cost-effectiveness associated with these "R-chemo" interventions.

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 25 years) in order to follow the vast majority of the original cohort of patients within the model to death (i.e. 99.4% of the cohort are estimated to have died by 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

7.2.6.1 a) Model-based evaluations

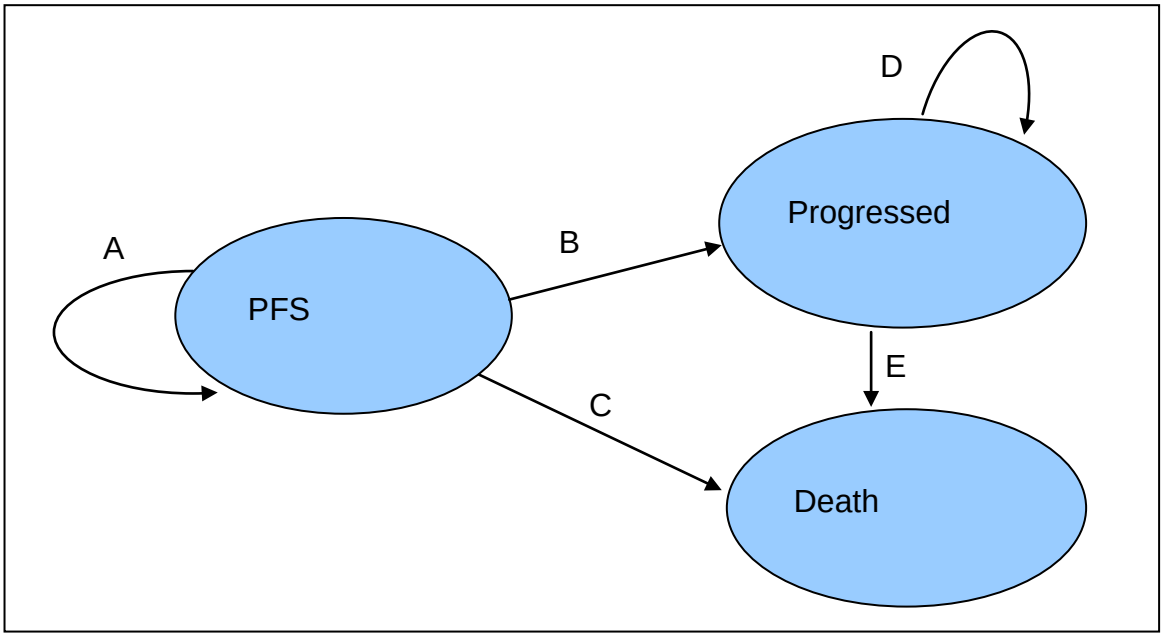
7.2.6.2 Please provide the following.

A description of the model type.

The model mirrors the key outcomes of the REACH 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 15: 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 REACH 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 59. Model Parameters and Values

Model Variable	Value	Source
Transition Probabilities (tp)		
PFS to PFS	Time dependent based upon Weibull extrapolation of PFS	REACH[30]

	trial curves	
PFS to Progression	1 – [tp(PFS to PFS) + tp(PFS to death)]	REACH[30]
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[88] or REACH[30]
Progression to Progression	1 - tp(Progression to death)	REACH[30]
Progression to death	Constant hazard of dying obtained from modelling the REACH post-progression population survival as a single population due to the non-significant difference in survival between the treatment arms	REACH[30]
Costs		
Supportive-care costs		
Monthly PFS health state supportive care • Consultation	£28.67	Eichhorst et al. 2008[21]; NHS reference costs, 2007/8[89]
• Blood Transfusion 1- Per one unit pack 2- Per infusion	£159.01 £285.94	Agrawal et al, 2006[90] inflated by PSSRU 2008[91]
• Bone Marrow Transplant	£50,653	NHS reference costs, 2007/8[89]
Monthly Progressed health state supportive care • Consultation • 2nd-line and later therapy	£86 £106.58	NHS reference costs, 2007/8[89] BNF 57[92], REACH[30]
Drug costs†		
Rituximab per month • For Month 1 • For Months 2-6	£1,328.81 £1,708.47	BNF 57[92]
FC per month	£428.06	BNF 57[92]
Drug administration costs†		
Rituximab administration per cycle	£123.92	NHS reference costs, 2007/8[89]; PSSRU 2008[91]
FC administration per cycle	£320.68	NHS reference costs, 2007/8[89]; PSSRU 2008[91]
Utilities		
Progression Free Survival Health State	0.8*	Hancock et al, 2002[93]
Progressed Health State	0.6*	Hancock et al, 2002[93]

Discount rates		
Costs	3.5%	Guide to Methods, NICE[94]
QALYs	3.5%	Guide to Methods, NICE[94]

*Utilities values are planned to be updated in Q4 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 REACH 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 treatment failure, 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 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 REACH 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 (REACH[30]). 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

possible QoL impacts was considered an un-necessary complication in model design given the scale of its impact upon the final ICER. However, approximate costs associated with each adverse events were included in the economic analysis for good measure.

7.2.6.3 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 2.1 years, maximum observed follow-up = 4.7 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.

7.2.6.4 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 REACH trial, as defined by the REACH protocol.

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

The main source that informed the model structure was the REACH clinical trial for R-FC and FC. 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[88] were used to supplement the trial data sources.

7.2.6.6 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.

7.2.6.7 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.

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

A half cycle correction was applied within the model.

7.2.6.9 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?

This economic model uses patient level data for the ITT population to calculate primary efficacy, and consisted of 552 patients (276 patients in FC, 276 patients in R-FC). At the time of the clinical cut-off (July 23, 2008), the Kaplan-Meier estimated median PFS was improved by 10 months, from 20.6 months with FC to 30.6 months with R-FC. The risk of progression or death was reduced by 35% for patients in the R-FC arm compared to patients in the FC arm, which was statistically significant (unadjusted HR 0.65; p= 0.0002, Wald test). Significantly more patients in the R-FC arm than in the FC arm responded to therapy, and this was mostly due to a significantly higher complete response rate. At clinical cut-off, overall survival data were too premature to demonstrate any statistically significant advantage when rituximab was added to FC. At the time of analysis (2.1 years median follow-up), 75.36% and 77.54% of patients in the FC and R-FC arm of the REACH 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.

It is important to note that improvements in PFS and other efficacy parameters do not always translate into improvements in survival in randomized studies in patients with malignant diseases. This is largely due to cross-over, which is particularly likely to occur in diseases with a long time course (like CLL) and when the 'experimental agent' is readily available (like rituximab). Cross-over is already known to have occurred in the BO17072 study. In the FC arm, 34/69 patients who relapsed have received subsequent therapy for CLL are known to have received rituximab, either in combination with a chemotherapy regimen or as single agent (and 2 more have received another anti-CD20 antibody). This compares with 14/47 of patients who

relapsed have received subsequent rituximab containing therapy for CLL in the R-FC arm. Consequently, in this economic analysis of BO17072, patients who remained in PFS but crossed over to alternative CLL therapy were censored at the time of cross-over. In this way the confounding affect of subsequent treatments was avoided.

Table 60. REACH results: clinical cut-off July 23, 2008; median observational time 2.1 years

REACH	R-FC (n= 276)	FC (n=276)
Mean progression free survival (months) Median progression free survival (months) p value Log-Rank test Hazard ratio (unadjusted / unstratified) p value Log-Rank test Hazard ratio (adjusted /stratified) Percentage of patients censored for overall survival	32.93 (se 1.3882) 29.8 (CI 25.5-39.0) P =0.0002 0.673 (CI 0.528-0.857) P<0.0002 0.678 (CI 0.525-0.875) 77.54% (n=214)	25.03 (se 1.2178) 20.6 (CI 18.0-24.5) 75.36% (n=208)
Mean overall survival (months) p value Log-Rank test	41.58 (se 1.0577) p=0.2874	40.45 (se 1.1644)

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 16. Progression Free Survival of R-FC versus FC: median follow-up 2.1 years

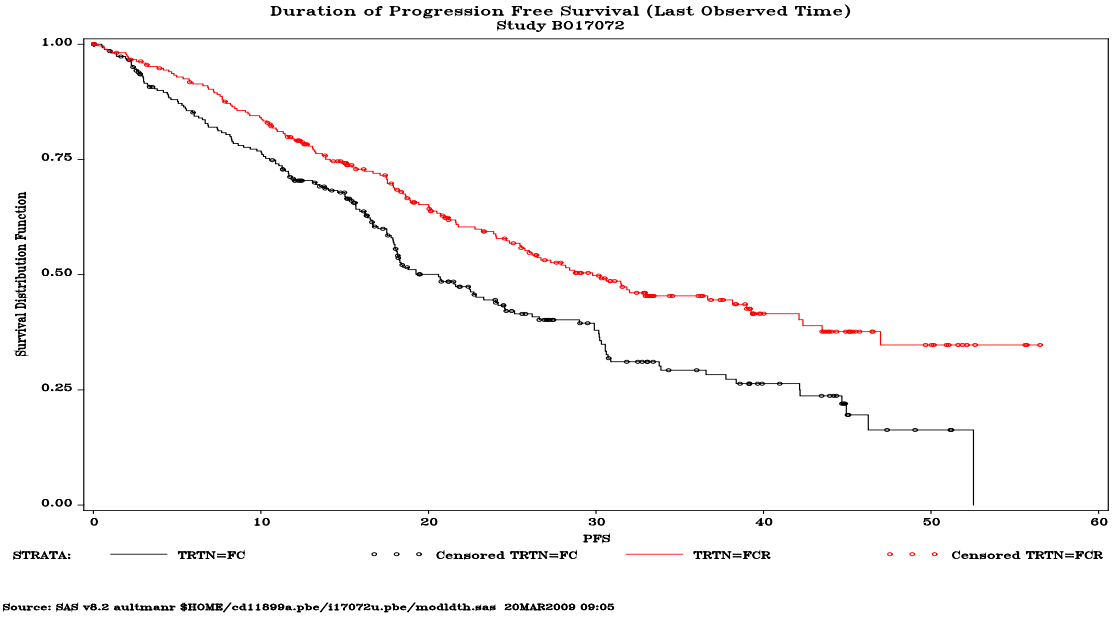
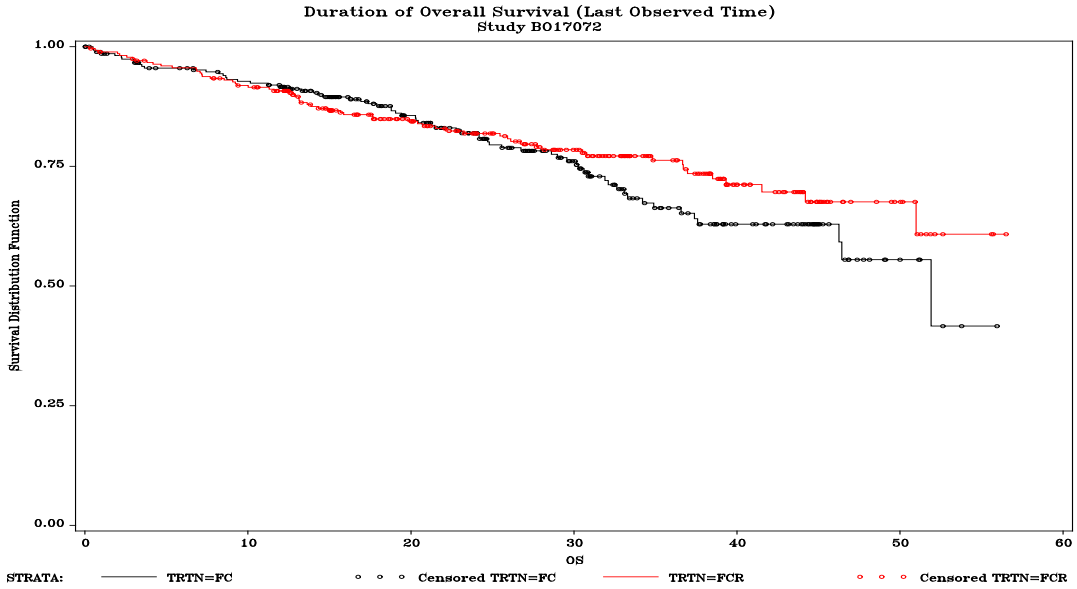


Figure 17. Overall Survival of R-FC versus FC: median follow-up 2.1 years



Source: SAS v8.2 aultmanr $HOME/cd11899a.pbc/i17072u.pbc/modldth.sas 20MAR2009 09:05

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, δ parameters of a Generalized Gamma survival function) are estimable. The parameters for the endpoint PFS under the assumption of a parametric survival function were estimated using the clinical data. Various parametric functions were available (e.g. Log Logistic, Log Normal, etc.) 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 Logistic, Log Normal, Gompertz, Gamma and Exponential.

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

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

To estimate future progression free survival (PFS) an extrapolation of the PFS curve from the REACH 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 19).

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 REACH study. 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 best fit to the PFS data was obtained with the generalized Gamma function. However, the Weibull function was chosen as the default function for the following reasons. The value of the AIC was 1,266.67 and 1,267.99 for the Gamma and Weibull, respectively - with the Weibull slightly more conservative with respect to the time horizon. This difference is negligible with respect to fit of the data. However the primary reason for choosing the Weibull function instead of the Gamma function is because the Weibull provides more sensible results when extrapolating than the Gamma..This phenomenon associated with the gamma function is rare but can occur when the uncertainty in the parameter estimates is excessive and is induced when running PSA. For example, the absolute probability of dying in PFS is a product of the observed probability of dying in PFS and the number at risk of dying from the previous cycle. This absolute value with the gamma function can exceed the number of patients transitioning out of PFS from the previous cycle. However, both parametric functions are assess deterministically in the sensitivity analyses section. Table 61 gives the goodness of fit results for PFS for all functions evaluated.

Table 61: 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	1273.17 / 1281.79 (0.00158 / 0.0122)
Gamma	1266.67 / 1283.92 (0.00125 / 0.0000114)
Log Logistic	1267.73 / 1280.67 (0.0000571 / 0.00235)
Log Normal	1280.16 / 1293.1 (0.00136 / 0.0000905)
Weibull	1267.99 / 1285.25 (0.00309 / 0.000647)
Gompertz	1341.49 / 1354.44 (0.00399 / 0.00234)

MSD = Mean Square Deviance.

The Weibull survival function is defined as

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

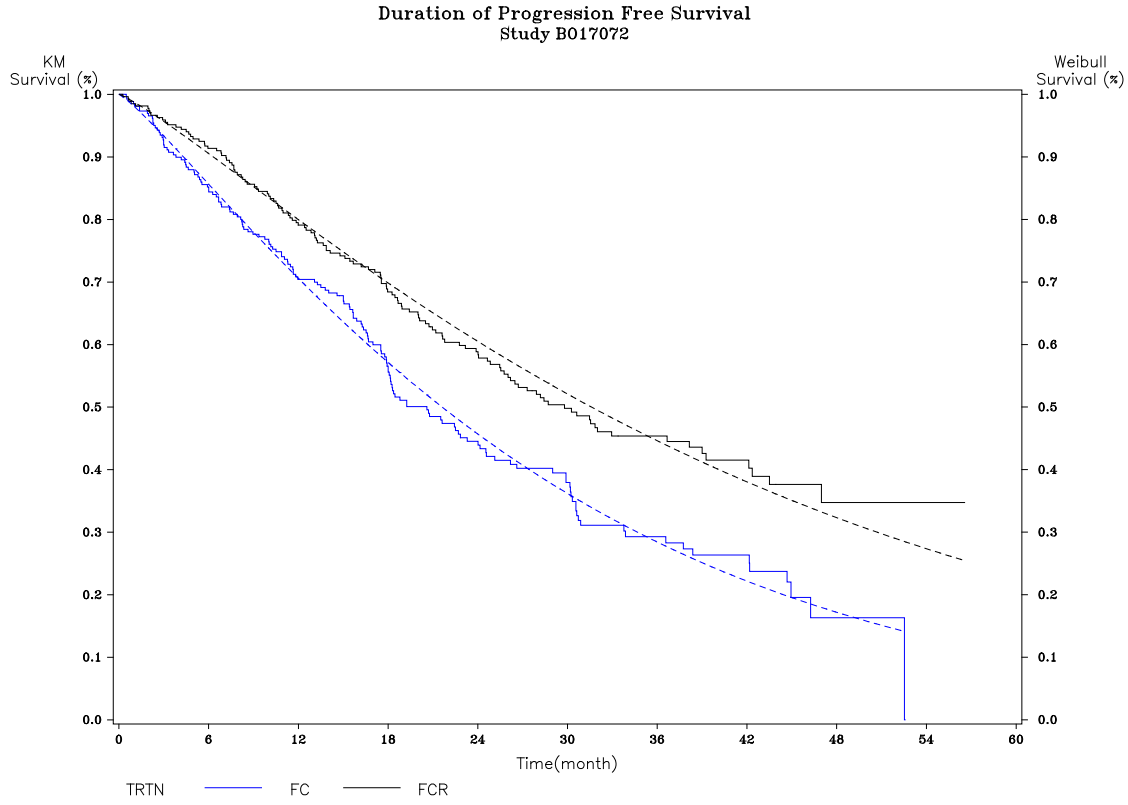
The probability of staying in this health state is determined by the cumulative ½-cycle corrected survival probabilities obtained from same shaped Weibull function for PFS. Table 62 summarizes the Weibull parameter estimates used to describe the distributions specifying the monthly probability of transitioning from PFS to progressed or death by treatment arm. Additionally the ratio of the lambda

parameters is consistent (HR=0.642) with the study reported hazard ratio. Figure 22 represents the KM PFS curves from REACH 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 62. Weibull parameters for PFS progression

Efficacy Endpoint	R + FC	FC Alone
Progression Free Survival (PFS)		
Lambda	0.012247453	0.019089139
Gamma	1.168851232	1.168851232

Figure 18. Extrapolated Progression Free Survival curves (Weibull)



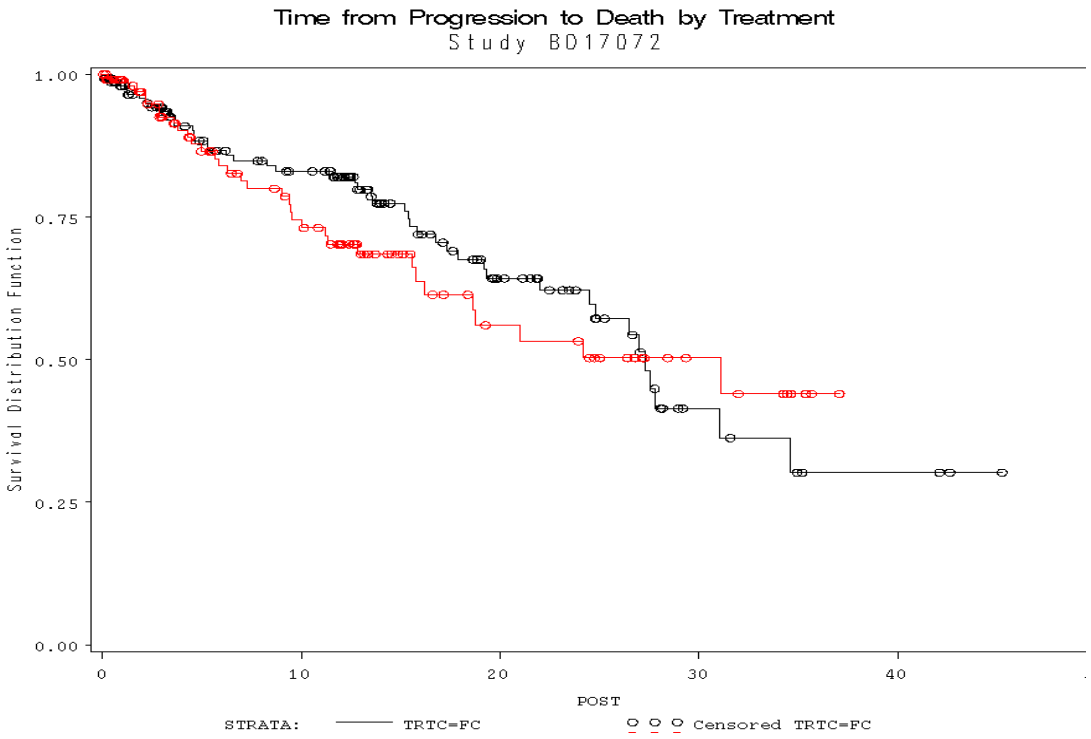
Source: SAS v8.2 aultmanr $HOME/cd11899a.pbe/i17072u.pbe/modldth.sas 20MAR2009 09:05

- **Estimating Survival for Progressed patients**

The progression health state is defined by surviving patients who have experienced disease progression. Patients will transition from this state to the absorbing state (Death) at a constant rate, determined by having modeled 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 assessed by stratifying by protocol treatment regimen (R-FC or FC) for treatment differences using the Kaplan-Meier method. The log-rank was found to be non-significant (p=0.5596) for treatment differences (Figure 23) 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 19. Post Progression Survival by Treatment (REACH)



Given that the overall survival follow-up is incomplete for both study treatment arms in REACH, 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 log of the progression survival was regressed (linear) on the time variable with the estimated time probability (slope) serving as the statistic for the single parameter exponential distribution. The rate was then converted to a monthly probability (p = 0.02566) of dying and applied to all progressed patients. (Table 63). It was considered reasonable to assume that this mean rate and its associated uncertainty encompass the age-specific increase in mortality.

- **Estimating Death**

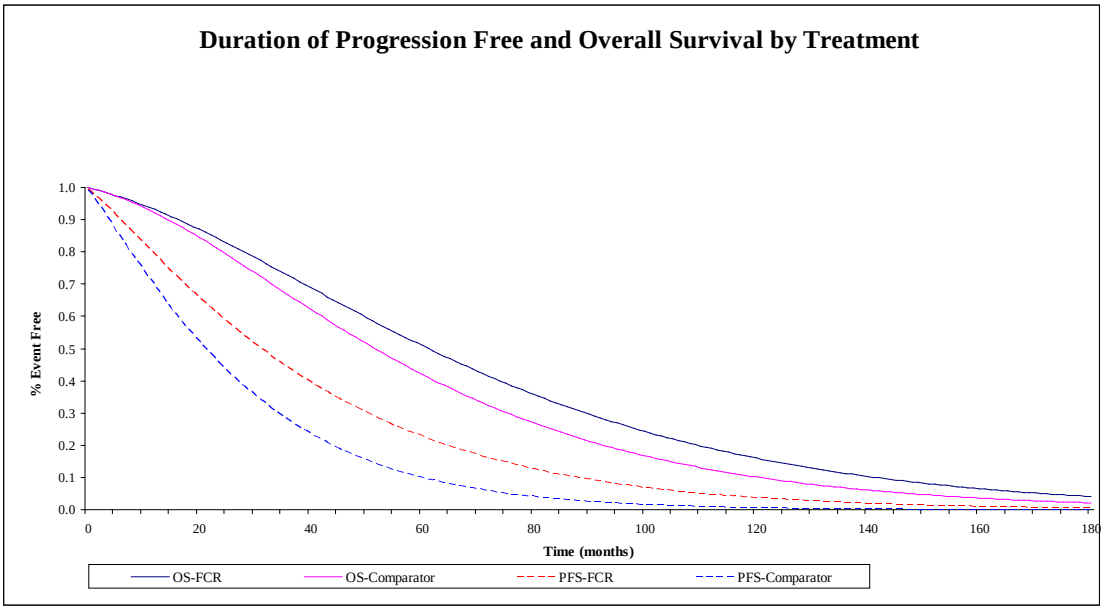
This state includes those patients who died from any cause (standard UK all-cause background mortality) or due to advanced disease. No costs are attached to this health state and the utility attached is zero. A number of patients die while in PFS and, along with those patients that die while in progression, 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 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 (BO17072). This is expressed as a monthly rate. For example, 29 of the 276 patients in the R-FC arm died whilst in PFS. These deaths occurred over a period of 6,128.46 person-months. The monthly rate of death in the R-FC arm is calculated as 29/(6,128.46) = 0.004732021. Then, 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) = 0.004720842. The number of patients that are at risk of progressing or dying in PFS is a function of the transition probabilities obtained from the Weilbul PFS function. Each month a number of patients leave the PFS health state and of these patients some will die and the others will move into the progression health state. This approach was preferred to utilising the trial data alone; due to the low number of events in REACH, 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[88] 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[95]).

Table 63: Mortality rates for health states

Markov Transition	Monthly probability	Data source
PFS to death	R-FC = 0.004720842 FC = 0.004741291	Maximum of age-specific background mortality or monthly rate at which patients died while in PFS from the REACH study
Progression to death	0.025661138	Progression to death population from REACH treated as a single population with mean time to death converted to a constant hazard of dying

Figure 20. Extrapolated PFS and OS curves of R-FC versus FC



b) Non-model-based economic evaluations

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

7.2.7 Clinical evidence

7.2.7.1 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 REACH trial results for FC.

7.2.7.2 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.

7.2.7.3 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 treatment for CLL (see Section 7.2.8.3).

7.2.7.4 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?

In the REACH study, slightly higher rates of grade 3 or 4 adverse events (AEs) were noted in the R-FC arm (65%) versus FC (60%). The frequency of grade 3 or 4 infections were similar, and there was no difference in bacterial, viral, or fungal infections between the two arms. Overall, these results are reassuring since they

indicate that despite a higher incidence in all Grade 3/4 AEs of the blood and lymphatic system (notably neutropenia) in patients treated with R-FC, this did not translate into a substantially higher incidence of infections or fatal infections.

Table 64. Adverse events from REACH

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

PNEUMONIA	4	3	3
PYREXIA	3	4	6
SEPSIS	3	0	3
SEPSIS	4	1	0
SEPTIC SHOCK	4	1	1
SINUSITIS	3	0	2
TACHYCARDIA	3	0	3
THROMBOCYTOPENIA	3	18	26
THROMBOCYTOPENIA	4	5	5
VOMITING	3	5	6

Costs were estimated for each adverse event, irrespective of the severity grade of that event. These costs were tested in the sensitivity analysis.

7.2.7.5 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, resource utilisation associated with adverse events, and validation of the international REACH trial reported subsequent treatment for a UK setting. These are described further in Section 7.2.9.2.

7.2.7.6 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

7.2.8.1 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.

7.2.8.2 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.

7.2.8.3 How were health effects measured and valued?

A utility score was applied to each health state in the model (Table 65). 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 65. Health state utilities

	Utility	*Reference*
PFS Health State	0.80	Hancock 2002[93]
Progressed Health State	0.60	Hancock 2002[93]
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[93]), 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 results expected in Q4 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.

An interim analysis of this study based on 11 patients (provided to NICE for the 1st line rituximab CLL appraisal) supported the use of 0.8 as the utility value for progression-free survival. There was insufficient data on progressed patients to draw any conclusions regarding the appropriate utility value for these patients.

Roche will make a second interim analysis available to both the ERG and appraisal committee upon request. However as the sensitivity analysis will demonstrate, we do not expect any uncertainty around the utility values to fundamentally affect the cost effectiveness conclusions.

7.2.8.4 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.

In REACH , quality of life was assessed using the FACT-G was collected over a one year period with assessments at screening, 3 months, 6 months, and 6 months after the end of treatment (i.e. 1 year after study entry). The Functional Assessment of Cancer Therapy – General (FACT-G), version 4.0, translated into over 40 languages, is a patient reported questionnaire that measures general aspects of Quality of Life (QoL) among cancer patients. Scoring guidelines for each subscale as well as handling of missing data was in accordance with described methodology put forth in the Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System version 4 (Nov 1997).

If a patient went into the survival follow-up phase prior to the 1 year assessment for any reason, no further QoL assessments were performed. This means that patients with PD and patients withdrawn from the study for AEs or other reasons were lost at or before the 1 year time point. However, patients with SD who started an alternative CLL treatment should have continued to provide QoL data until PD or 1 year.
The maximum score on FACT-G is 112. In the REACH study, the initial scores at screening (median 79.5 and 80.0 in the FC and R-FC arms respectively) were high and these did not change substantially over the study period. The QoL scores in the two study arms were similar at every time point tested (Table 65).

Table 66. Summary of FACT-G total score and sub-scores over time (ITT)

FACT-G Parameter/Timepoint	FC (n=276)	R-FC (n=276)
Screening		
Mean	78.50	79.61
SD	14.57	14.48
Median	79.50	80.00
Min	36.00	21.00
Max	108.00	108.00
N	263	265
After cycle 3		
Mean	79.33	79.92
SD	14.47	14.47
Median	80.87	81.82
Min	46.50	31.00
Max	108.00	108.00
N	206	218
After cycle 6		
Mean	81.99	81.92
SD	15.58	14.70
Median	84.00	84.00
Min	22.50	23.00
Max	108.00	108.00
N	166	187
Month 12		
Mean	82.16	82.86
SD	15.97	15.94
Median	83.10	85.00
Min	32.60	25.00
Max	107.00	108.00
N	162	182

Analysis of the FACT-G score change from baseline over time also showed no meaningful difference in QoL between the two treatment arms. The QoL assessment using FACT-G over the period of one year did not reveal any differences between the treatment groups. The initial QoL scores were similar and high in both treatment arms and continued as such over the 1 year assessment period. Since QoL was not captured in patients with disease progression and was captured in patients who started a new CLL treatment before progression, biases may not have been minimised when addressing comparative QoL.

The economic analysis presented in this submission utilises utility values associated with health states (PFS and progressed) rather than treatment-specific effects (R-FC, and FC) thereby reflecting these findings.

7.2.8.5 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

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

1) Drug costs for rituximab and FC
2) Drug administration costs for rituximab and FC
    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
7) Adverse event costs

The following section describes each resource in detail.

7.2.9.2 How were the resources measured?

1) Drug costs for rituximab and FC

Drugs costs were calculated according to the actual adult dose observed in REACH and wastage was assumed for all therapies. Recommended doses were included in the sensitivity analysis.

Table 67. Drug doses and costs for rituximab

Assumptions	Value	Description
Body surface area m^2	1.86	Average body surface area (from REACH)
Unit price per vial (£)		
• 100mg	174.63	BNF 57[92]
• 500mg	874.15	
Recommended dose (mg/m^2)		
• Cycle 1	375	Recommended adult dose as per SPC
• Cycle 2-6	500	
Average adult Dose (mg) including wastage		
• Cycle 1	700	Actual dose from REACH (rounding up to nearest vial)
• Cycle 2-6	900	
Cost per infusion/cycle (£)		
• Cycle 1	1,328.81	500ml @ £873.15 + 2* 100ml @ £174.63
• Cycle 2-6	1,708.47	500ml @ £873.15 + 4* 100ml @ £174.63
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 (£)	**9,871.15**	£1,328.81 + 5 * £1,708.47

Table 68. Drug doses and costs for FC

Assumptions	F (oral)	C (oral)	Description
Body surface area m^2	1.86	1.86	Average adult body surface area
Unit price per mg (£)	1.86	0.0024	BNF 57[92]
Recommended dose (mg/m^2)	24	150	Recommended adult dose
Average adult daily dose (mg)	42	265	Actual dose from REACH multiplied by adjustment factor of 24/25 for fludarabine and 150/250 for chlorambucil to account for oral treatment
Days of treatment per cycle	5	5	Recommended adult dose
Cost per infusion/cycle	390.60	3.20	F: ~ £1.86 * 42mg/day *5 days C: ~ £0.0024 * 265mg/day *5 days
Number of cycles of treatment	6	6	Administered on day 1 of each cycle of chemotherapy in 28 day cycles
Total drug cost per patient (£)	2,343	19.22	F: £390.60 * 6 cycles C: £3.20 * 6 cycles

2) Drug administration costs for rituximab and FC

a) Administration cost

To estimate the resource utilisation associated with the drug administration of R-FC and the comparator, the appropriate reference costs (National Schedule of Reference Costs 2007-08[89]) associated with daycase chemotherapy administration were utilised.

Table 69. 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)	£201
R (in combination with FC)	Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance (SB14Z)	£307

In each cycle, the patient in the R-FC arm entered the hospital on day 1 for rituximab infusion for £307 and on the same day collected their FC treatment to administered at home over the next 5 days (for no additional costs). In this case, rituximab can be considered to incur a marginal cost of £106 (the difference between the R-FC and

comparator arms. 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 £201.

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 £86 per cycle was taken from the National Schedule of Reference Costs 2007-08[89] - consultant led follow up attendance outpatient face to face with a clinical oncologist. 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 £32/hour. This was derived from the PSSRU, Section 12.6, Hospital pharmacist: Unit costs available 2007/2008[91]. It was assumed that oral preparations 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).

3) Blood transfusion events

Blood transfusions (BT) associated with CLL patients were recorded in the REACH study and included in the model in the supportive care costs for the progression-free health state. A total of 113 and 137 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(£)[90] was identified and the relevant costs were inflated to 2008 level (HCHS pay and price inflation index from PSSRU 2008[91]). An average cost of £159.01 was applied to each unit of blood dispensed as well as an average cost of £285.94 was applied to each blood transfusion event.

4) Bone marrow transplant events

Bone marrow transplant (BMT) associated with CLL patients were recorded in the REACH study and included in the model in the supportive care costs for the progression-free health state. Only 3 and 4 BMT events occurred in the R-FC and FC arms of the trial, respectively.

An average cost of £50,653 was applied to this event. This cost was taken from the National Schedule of Reference Costs 2007-08 - NHS Trusts Elective Inpatient HRG Data for a Bone Marrow Transplant - Allogeneic Graft (Volunteer Unrelated Donor) 19 years and over[89].

5) Outpatient consultations

The recent ESMO guidelines (Eichhorst et al., 2008[21]), 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 (£28.67 per month; £86/3). This cost was taken from the National Schedule of Reference Costs 2007-08 - consultant led follow up attendance outpatient face to face with a clinical oncologist[89].

It was assumed in the progressed health state that the frequency of visits would increase to one per month. Therefore a cost of £86 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 REACH 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 5% of the patient population were costed by utilising standard doses for each therapy of interest and applying unit costs from BNF 57. The average patient cost for 2nd-line treatment was £2,744. 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 (26.8 months). This resulted in a monthly cost applied to the progressed state of £102.60. The table below presents the subsequent therapies from the REACH trial which were used to determine the cost of subsequent CLL treatments.

Table 70. Subsequent CLL treatments from the REACH trial included in the costing

Progression Therapy	Number of Patients	
	FC	R-FC
Alemtuzumab	18	9
Allopurinol	8	3
Cyclophosphamide	27	16
Doxorubicin	8	3
Fludarabine	15	11
Prednisone	9	8
Rituximab	26	12
Vincristine	9	10

6) Adverse event costs

Each adverse event observed in REACH was considered in turn with regards to the standard resource utilisation potentially required in order to provide an associated cost. For simplicity, it was assumed that Grade 3 and 4 events would incur the same costs.

Table 71. Cost per episode of each adverse events

Adverse event	Costs (£;2008)	Comments	Source
AGRANULOCYTOSIS	£0	No intervention	
ALANINE AMINOTRANSFERASE INCREASED	£0	No intervention	
ANAEMIA	£0	Blood transfusion - resource use already captured separetly in REACH	
ANAEMIA HAEMOLYTIC AUTOIMMUNE	£21	Assume same cost as haemolytic anaemia	
ANGINA PECTORIS	£1,229	Average direct NHS costs for patients experiencing angina pectoris. Inflated from 2000 to 2009.	Stewart, S. et al.[96] Inflated.
APLASIA PURE RED CELL	£0	No intervention	
BICYTOPENIA	£0	No intervention	
BRONCHITIS	£6	Antibiotic Penecilin (co-amoxiclav 625mg three tmies a day for 7 days; 500/125 (amoxicillin 500 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £6.32)	BNF 57[92]
CHILLS	£0	No intervention	
CYTOMEGALOVIRUS INFECTION	£948	Ganciclovir (as sodium salt). Net price 500-mg vial = £31.60. Initial (induction) treatment:10mg/kg/day for 21 days assume 70 kg	BNF 57[92]
DIARRHOEA	£262	Assume same cost calculated at expert meeting for the erlotinib 2006 submission; inflated.	Erlotinib NICE submission[97]; Inflated
FEBRILE BONE MARROW APLASIA	£2,286	Assume same cost as febrile neutropenia	NICE DSU 2007[98]
FEBRILE NEUTROPENIA	£2,286	Cost per episode calculated by NICE DSU 2007.	NICE DSU 2007[98]
GRANULOCYTOPENIA	£0	No intervention	
HAEMATOTOXICITY	£0	No intervention	
HAEMOGLOBIN DECREASED	£0	Blood transfusion - resource use already captured separetly in REACH	
HAEMOLYSIS	£21	Blood transfusion (already captured in REACH) + Prednisolone 60mg (2*5mg+2*25mg) per day for 10 days; calculation of the costs: 98p for a 28-tab 5mg pack + £20 for a 56-tab 25mg pack = £20.98	BNF 57[92]
HAEMOLYTIC ANAEMIA	£21	Blood transfusion (already captured in REACH) + Prednisolone 60mg (2*5mg+2*25mg) per day for 10 days; calculation of the costs: 98p for a 28-tab 5mg pack + £20 for a 56-tab 25mg pack = £20.98	BNF 57[92]
HYPOTENSION	£0	No intervention	
LEUKOPENIA	£0	No intervention	
LYMPHOPENIA	£0	No intervention	
NEUTROPENIA	£0	No intervention	
NEUTROPENIC INFECTION	£2,286	Assume same cost as febrile neutropenia	NICE DSU 2007[98]
NEUTROPENIC SEPSIS	£2,286	Assume same cost as febrile neutropenia	NICE DSU 2007[98]

PANCYTOPENIA	£3,393	G-CSF (Granocyte (19.2 million units/m2 daily started the day after completion of chemotherapy, continued until neutrophil count stable in acceptable range (max. 28 days); 33.6 million-unit (263-microgram) vial = £67.09).> For an average adult is one vial per day needed (19.2*1.75=33.6 mio. units) -> £67.09*28=1879) + blood platelet transfusion (assume 2 bags/pools -> £757*2 = £1514; HRG used = SA13Z) + blood transfusion (already included in REACH)	BNF 57[92] / Tariff information: confirmation of Payment by Results (PbR) arrangements for 2009-10
PNEUMONIA	£2,494	5 day stay inpatient 2493 (see Reference Costs Bronchopneumonia without CC; 8.83 days cost £4403 -> 5 days cost 2493) + stronger antibiotica (ciprofloxacin 500mg twice a day for 5 days; 10-tab pack 500mg cost £1.19)	National Schedule of Reference Costs 2007-08 / BNF 57[92]
PYREXIA (FEVER)	£0	No intervention	
SEPSIS	£2,286	Assume same cost as febrile neutropenia	NICE DSU 2007[98]
SEPTIC SHOCK	£4,236	Assume similar cost to febrile neutropenia but longer inpatient stay (14 days instead of 8.5 days assumed for febrile neutrapenia)	NICE DSU 2007[98] and further calculation
SINUSITIS	£6	Antibiotic Penecilin (co-amoxiclav 625mg three tmies a day for 7 days; 500/125 (amoxicillin 500 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £6.32)	BNF 57[92]
TACHYCARDIA	£0	No intervention	
THROMBOCYTOPENIA	£0	No intervention	
VOMITING (Nausea)	£266	Assume same cost calculated at expert meeting for the erlotinib 2006 submission; inflated.	Erlotinib NICE submission[97]; Inflated

7.2.9.3 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 REACH 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.

7.2.9.4 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 treatment failure 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 REACH 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.

7.2.9.5 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 and resource utilisation associated with adverse events), internal expert clinical opinion from a former NHS haematologist was used to assign standard dosages in UK clinical practice to different therapies and events. Drug preparation costs, which were assumed to differ between the rituximab arm and the oral treatments, 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.

7.2.9.6 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).

7.2.9.7 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.

7.2.9.8 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 2007/2008, BNF 57, and PSSRU 2008. 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.

7.2.9.9 Were resource values indexed to the current price year?

For those costs obtained from sources prior to 2008 (i.e. blood transfusion costs), values were inflated to 2008 levels using the HCHS pay and price inflation index obtained from the PSSRU 2008.

7.2.9.10 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, bone marrow transplantation costs, and adverse events costs which were taken from the REACH 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 REACH 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.

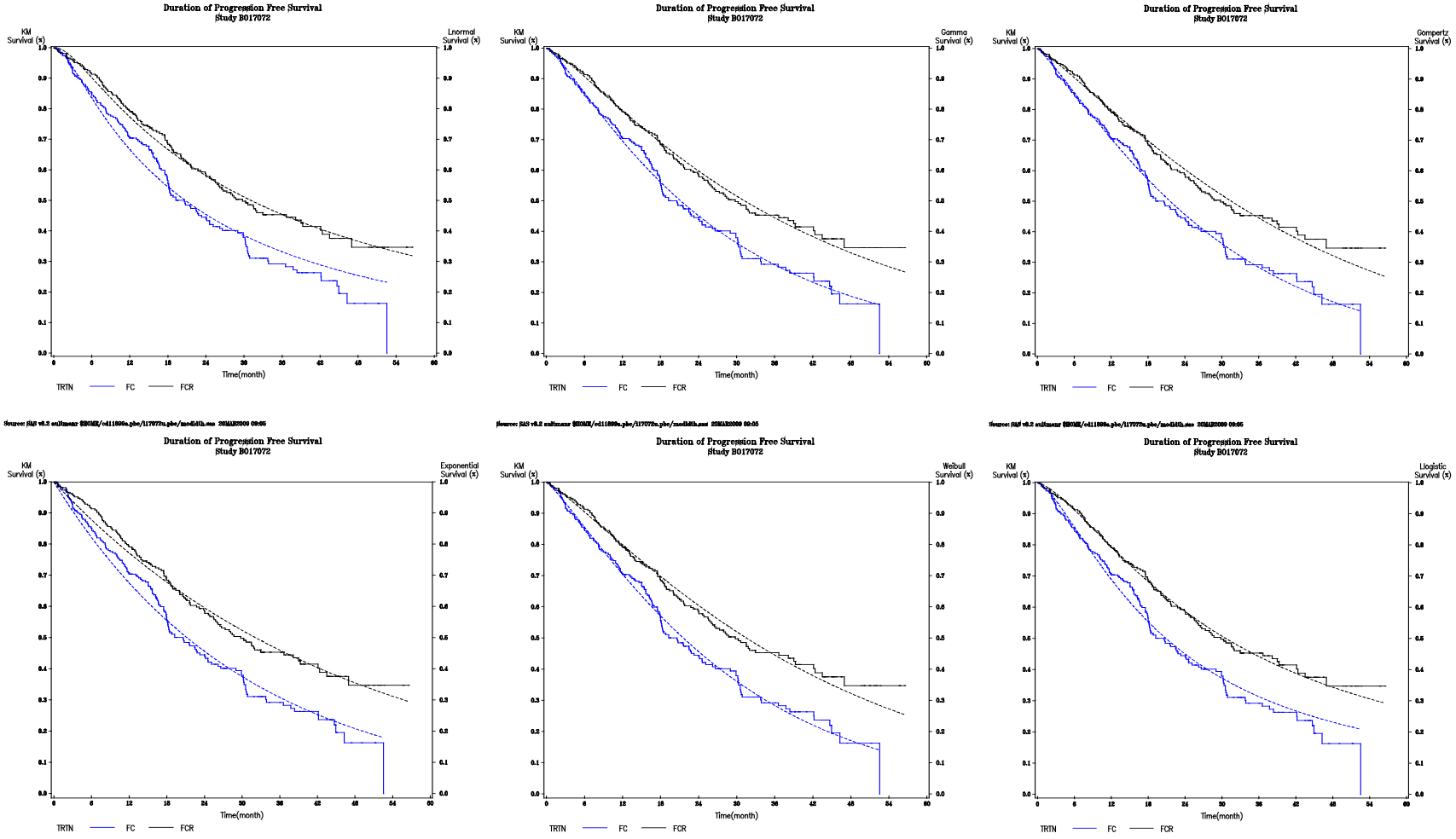
7.2.11 Sensitivity analysis

7.2.11.1 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 altenrative 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 generalized Gamma and Weibull functions were found to be comparably the best fits to the PFS data and therefore, the Weibull was 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 21: Graphical Fit of Parametric functions to KM data (top: lognormal, gamma, gompertz; bottom: exponential, weibull, log logistic)



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

1.) Recommended doses

The utilisation of actual dosages of R-FC and FC from the clinical trial (including any wastage) were considered in the base case analysis. This sensitivity analysis explores the planned licensed dose. 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.

2.) Adverse event costs

Adverse event costs were both increased and decreased by 50%.

3.) Monthly supportive care costs

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

4.) 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 72. 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

5.) Drug administration costs

The upper (£272 and £406) and lower (£139 and £211) quartiles for “Deliver exclusively Oral Chemotherapy” and “Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance” respectively (from reference costs 2007/08) were tested.

6.) Progression mortality rate

Due to the uncertainty associated with the mortality rate post-progression, this sensitivity analysis allowed for differential rates between the two treatment arms, using two methods:

a.) The estimated mortality rate was calculated in each arm individually from REACH (instead of combined as a single population in the base case). This

resulted in a monthly probability of death of 0.02758 in the R-FC arm and 0.02676 in the FC arm.

b.) COX proportional hazards model was performed to estimate the protocol defined treatment impact via the hazard ratio on survival for all patients that experienced at least one day of progression. The HR estimate of FC vs R-FC was 0.874 (95% CI: 0.557, 1.327) with the confidence intervals reflecting the degree of uncertainty of the HR due to extensive censoring (29% died, 71% censored). To estimate the monthly probability of dying whilst in progression in the FC arm using the hazard ratio, the log of the R-FC Kaplan-Meier survival probabilities were multiplied by the hazard ratio obtained from the Cox analysis. The resulting FC log survival estimates were then regressed against the time parameter to arrive at the log estimated rate of death (-0.0248 se: 0.0044008). This resulted in a monthly probability of death of 0.02758 in the R-FC arm (as described above) and 0.02420 in the FC arm.

7.) Scenario analysis: R-chemo / Re-treatment threshold analysis

A scenario analysis was performed to consider the impact of R-chemo on potential cost-effectiveness results. In addition, due to the recent NICE guidance (July 2009) for the 1st line treatment of CLL with rituximab, the impact of retreatment with rituximab in the relapse setting is also considered.

7.2.11.3 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 and in the progressed health state including further line treatments and supportive care costs. 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 using the lower and upper quartile for "Deliver exclusively Oral Chemotherapy" and "Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance" (from reference costs 2007/08).

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

Table 73. 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
Blood transfusion	£289.73	£173.84	£405.62
1 Unit of blood	£161.11	£96.67	£225.26
Cost	**Base case**	**Lower Quartile**	**Upper Quartile**
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

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

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

Table 74. PSA values for the Weibull parametric function for PFS and OS

	Deterministic analysis	
	Lamda	**Gamma**
R-FC PFS	0.012247453	1.168851232
FC PFS	0.019089139	1.168851232
R-FC OS	0.003724939	1.362977234
FC OS	0.006262217	1.362977234

- **Monthly probability of death** (applicable to the progressed health state): Under the assumption that the underlying distribution of the post-progression data by the protocol defined treatment arms follows an exponential distribution, the log of the survival probabilities were regressed against the time parameter. The estimated rate of death and its standard error was then taken from estimated slope obtained from the regression analysis. The probability of moving to the death state was thus is calculated as the inverse of the restricted means from the Kaplan-Meier based on last observed time . This was varied by the Normal function. Following from the deterministic sensitivity analysis, the monthly probability of death is calculated separately for the R-FC and FC arms.

Table 75. PSA values for monthly probability of death from the progressed state for R-FC and FC separately

	Log Survival over time		Mean monthly probability of death
	Mean	Standard error	
R-FC	-0.02837	0.00050332	0.027583774
FC	-0.0275	0.00124	0.02676073
All patients	-0.02634	0.00046883	0.025661138

7.2.12 Statistical analysis

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

Please see Section 7.2.6.8 above.

7.2.12.2 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 REACH was deemed to be 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. 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.

7.3 Results

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

Costs

Table 76 indicates that rituximab given in combination with fludarabine and cyclophosphamide is associated with an additional average per-patient costs of £8,332 over the analyzed patients' lifetime period (25 years) when compared to fludarabine and cyclophosphamide therapy alone.

Table 76: Total average per-patient cost for the two compared treatment groups over a lifetime period (deterministic analysis) using REACH trial data

Cost component (£)	R-FC	FC	Incremental
Mean cost of PFS	£15,285	£6,403	£8,882
Costs of Rituximab	£8,226	£0	£8,226
Administration costs of Rituximab	£620	£0	£620
Cost of Fludarabine	£2,233	£2,197	£37
Administration costs of Fludarabine	£843	£829	£14
Costs of Cyclophosphamide	£18	£17	£1
Administration costs of Cyclophosphamide	£843	£800	£43
Cost of supportive care in PFS	£1,066	£752	£315
Cost of Bone Marrow Transplantation	£565	£756	-£191
Cost of Blood Transfusions	£366	£498	-£132
Cost of Adverse Events	£504	£555	-£50
Mean cost of Progression	£4,743	£5,293	-£550
Mean Total Cost	£20,028	£11,696	£8,332

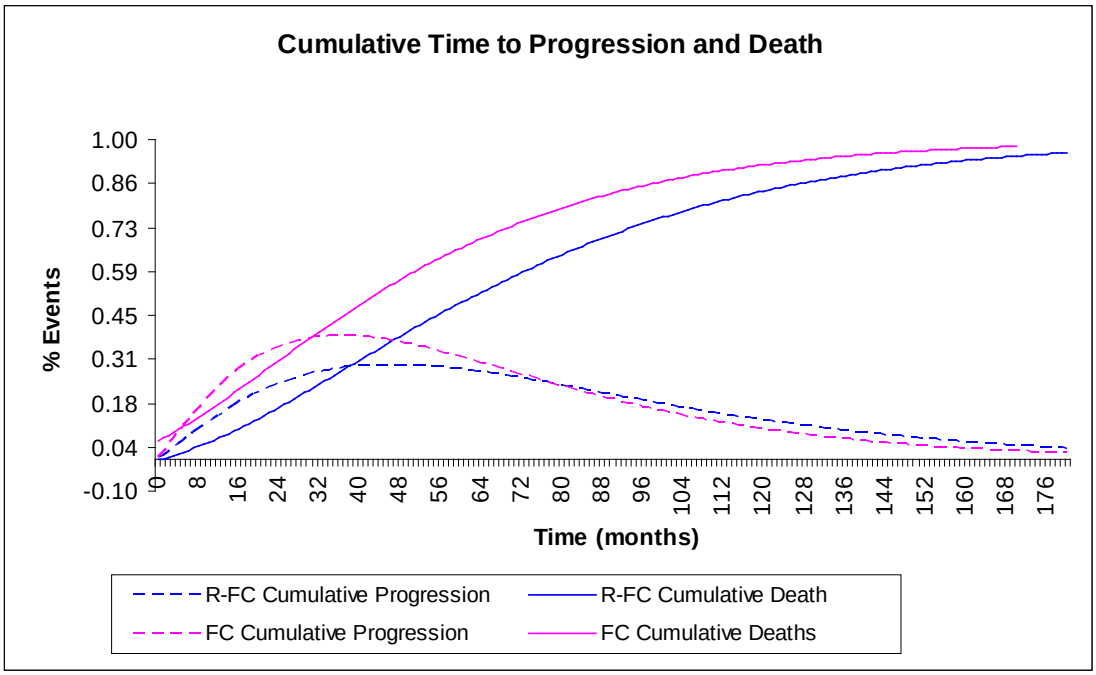
Life Years and Quality-Adjusted Life Years

Table 77 shows that the combination of rituximab plus fludarabine and cyclophosphamide results in a mean gain of 0.670 life years and 0.585 quality-adjusted life years (QALYs) when compared to Fludarabine and Cyclophosphamide alone over the analyzed lifetime period. This finding is related to a QALY gain due to a longer stay in the health state of progression-free survival (PFS) for the patients assigned R-FC than that observed for patients assigned FC alone. This is further illustrated in Figure 26 where patients in the FC arm progress quicker and have a shorter time to death than R-FC patients.

Table 77: Total mean QALYs per patient for the two compared treatment groups over a lifetime period (deterministic analysis) using REACH trial data

Outcome measure	R-FC	FC	Incremental
Mean Life Years (yrs)	5.206	4.536	0.670
Mean Life Years in PFS (yrs)	3.099	2.185	0.915
Mean life Years in Progression (yrs)	2.107	2.351	-0.244
Mean QALYs	3.744	3.158	0.585
Mean QALY in PFS	2.479	1.748	0.732
Mean QALY in Progression	1.264	1.411	-0.147

Figure 22: Cumulative time to progression and death for R-FC and FC using REACH trial data



Incremental Cost-Utility Ratio

Based on the assumptions used for the core model analysis, a cost per QALY of £14,240 for the RF-C combination therapy relative to FC therapy was calculated (Table 78)

Table 78: Cost per life year/cost per QALY gained ratios for R-FC versus FC over a lifetime period (deterministic analysis) using REACH trial data

Cost-utility results	R-FC	FC	Incremental
Mean Life Years (yrs)	5.206	4.536	0.670
Mean QALYs	3.744	3.158	0.585
Mean Total Cost	£20,028	£11,696	£8,332
Cost per Life Year Gained (£)			£12,429
Cost per QALY Gained (£)			£14,240

7.3.2 Subgroup analysis

7.3.2.1 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

7.3.3.1 What were the main findings of the sensitivity analyses?

The following tornado diagram ranks these scenarios in terms of impact on the ICER.

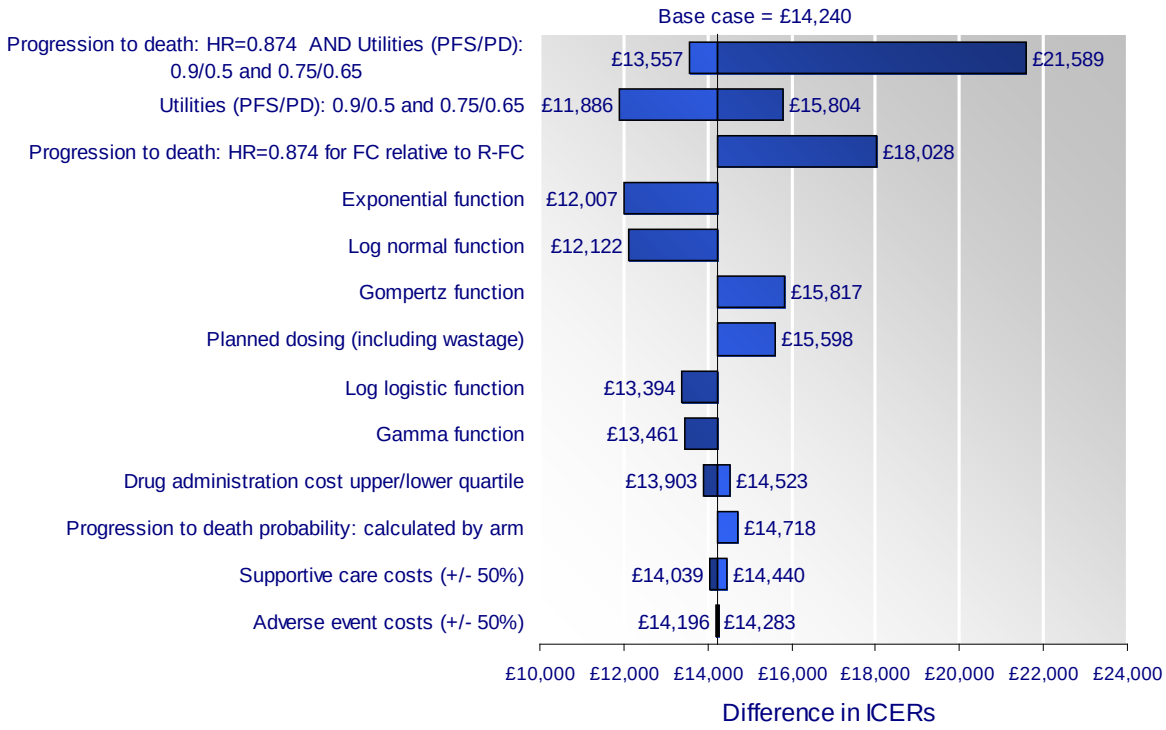
Table 79. One-way sensitivity analyses: R-FC versus FC

Sensitivity analyses	ICER
Base case (Weibull)	£14,240
Gamma function	£13,461
Exponential function	£12,007
Log logistic function	£13,394
Log normal function	£12,122
Gompertz function	£15,817
Planned dosing including wastage	£15,598
Utilities: PFS=0.9; Progressed = 0.5	£11,886
Utilities: PFS=0.75; Progressed = 0.65	£15,804
Adverse event costs increased by 50%	£14,196
Adverse event costs decreased by 50%	£14,283
Monthly supportive care cost increase by 50%	£14,039
Monthly supportive care cost decrease by 50%	£14,440
Drug administration cost upper quartile	£14,523
Drug administration cost lower quartile	£13,903
Progression to death probability: calculated by arm	£14,718
Progression to death probability: HR=0.874	£18,028
Progression to death probability: HR=0.874	£13,557

& Utilities: PFS=0.9; Progressed = 0.5	
Progression to death probability: HR=0.874 & Utilities: PFS=0.75; Progressed = 0.65	£21,589

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

Figure 23: Tornado diagram of one-way sensitivity analyses: R-FC v. FC



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

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

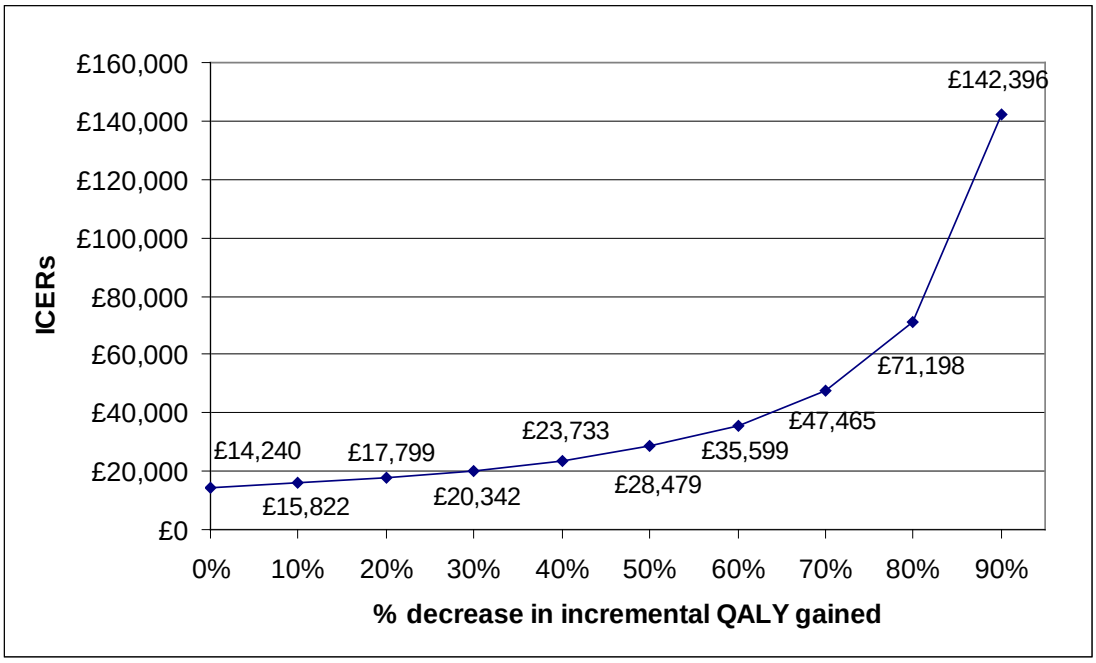
The results from the Phase II trials (section 6.8) describe the assessment of efficacy and tolerability of other rituximab combination chemotherapy. This included R-CHOP (34 patients), R-PC (rituximab, pentostatin and cyclophosphamide – 17 patients) and R-FCM (R-FC and mitoxantrone – 52 patients). The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

Without a comparator arm to represent baseline risk, it would not be possible to perform a reliable and comprehensive cost-effectiveness analysis of these alternative rituximab based combinations. However, in order to assess the potential differences in cost-effectiveness when utilising alternative background chemotherapies with rituximab compared to FC, scenario and threshold analysis may be informative for the purposes of decision making.

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

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

Figure 24: ICERs associated with decreased incremental QALYs gained from base case of R-FC versus FC



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

R-CHOP is a potential option for patients refractory to fludarabine. In Section 6.8.4.1, a simple comparison of the overall response rates among fludarabine-refractory

patients from the phase II R-CHOP study was compared to CHOP patients from unpublished follow-up data from the phase III CLL-4 study. The comparison confirmed that the overall response rates (and subsequently the potential duration of progression-free and overall survival) may be improved for R-CHOP treated fludarabine-refractory patients. The absolute magnitude of the improvement of efficacy cannot be measured in a manner suitable for the economic evaluation, however from the threshold analysis we can be certain that the incremental QALYs associated with this comparison could be half that observed for R-FC versus FC and still remain cost-effective.

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

Probabilistic sensitivity analyses

When using a sufficiently high number of Monte Carlo simulations - as example 1,000 iterations - the model produces probabilistic health and economic outcomes that are comparable to that obtained from the deterministic analysis. The PSA is based on the scenario which allows for two separately progression to death probabilities for R-FC versus FC (and therefore also allows for the different levels of uncertainty across these two variables) which resulted in a deterministic ICER of £14,718 per QALY gained. Below are the mean cost and outcome results from 1,000 runs resulting in an ICER of £14,826 per QALY gained.

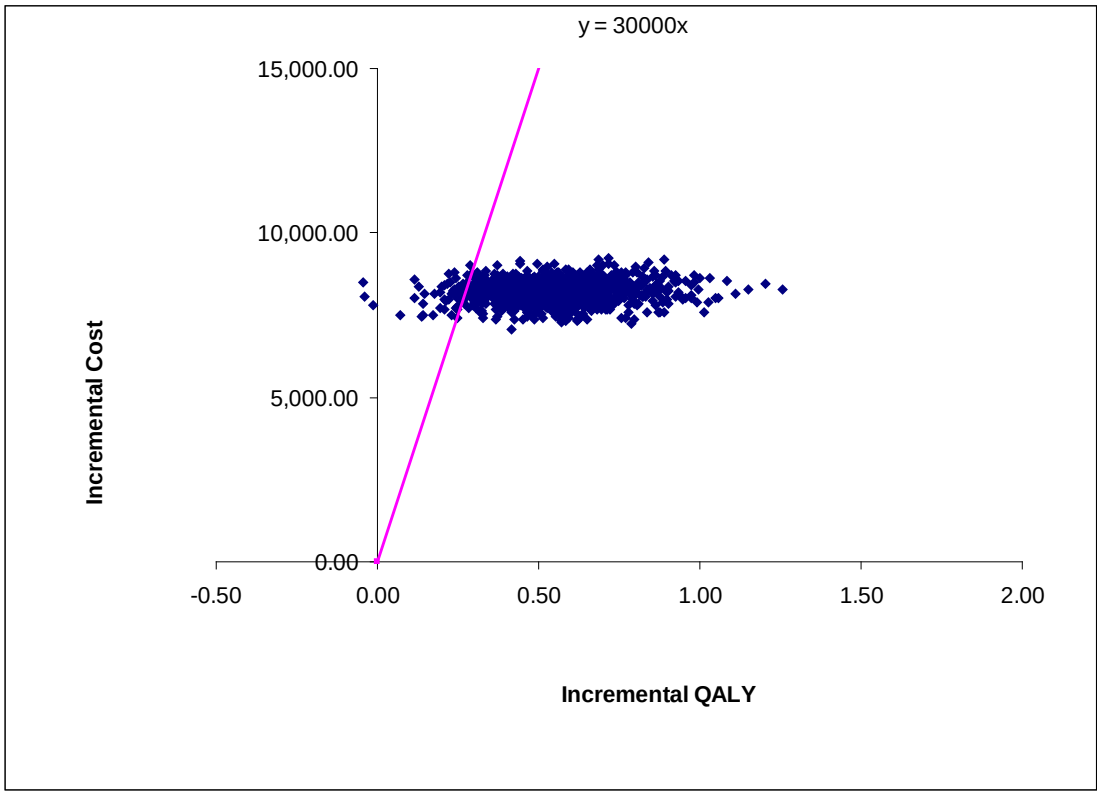
Table 80. Mean Cost Effectiveness results for R-FC versus FC (1000 runs)

Cost-utility results	R-FC	FC	Incremental
Mean Life Years (yrs)	5.080	4.461	0.619
Mean QALYs	3.668	3.115	0.553
Mean Total Cost	£19,898	£11,698	£8,200
Cost per Life Year Gained (£)			£13,246
Cost per QALY Gained (£)			£14,826

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.

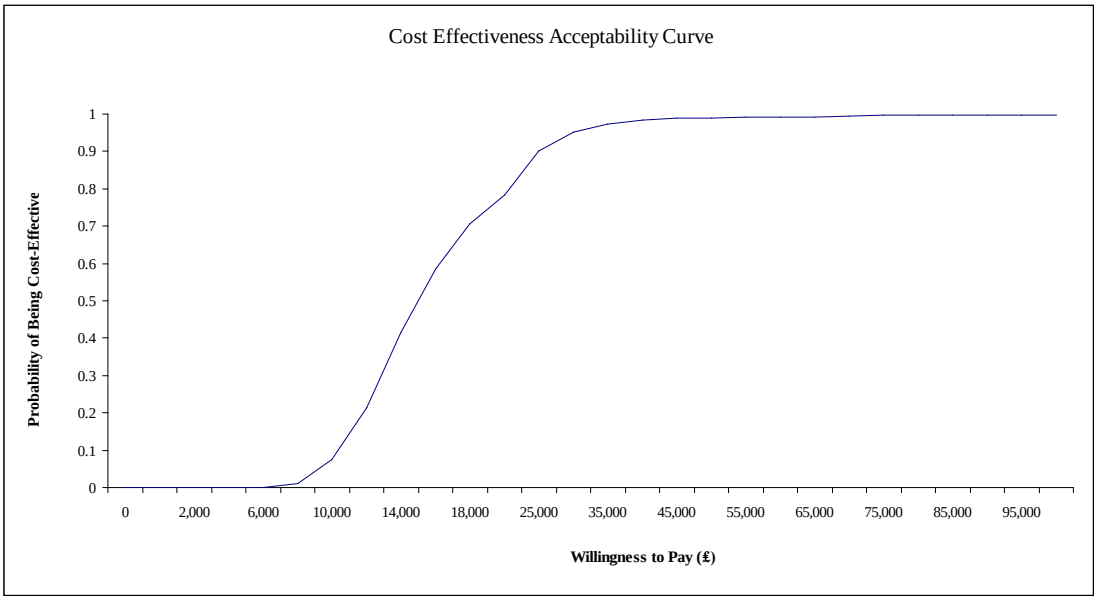
Figure 25: Scatter plot of cost per QALY for R-FC vs. FC (example:1,000 Monte Carlo simulations)



Cost-effectiveness acceptability curve (CEAC)

The CEAC graph shows the likelihood of the R-FC treatment being cost-effective at different WTP per QALY thresholds. The probability of R-FC not surpassing the commonly used threshold of £20,000 compared to FC is 79.3% and the probability of not surpassing the £30,000 threshold is 94.4%. Therefore, the PSA illustrates the robustness of the cost-effectiveness of R-FC compared to FC.

Figure 26: Cost-effectiveness acceptability curve of R-FC vs. FC (example: 1,000 Monte Carlo simulations)



7.3.3.2 What are the key drivers of the cost effectiveness results?

Large changes to the utility value and differing assumptions regarding the mortality rate across arms in the progressed state (indirectly impacting life years gained) had the largest impact on the ICERs. However, when using the range of plausible values, these results still remained well within commonly accepted cost-effectiveness thresholds. Utilising different parametric functions, 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

7.3.4.1 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 rituximab in relapsed/refractory CLL based on RCT data have been published. However, results are still quite comparable to other indications previously evaluated by NICE for the combination of rituximab with chemotherapies in B-cell lymphoma, follicular lymphoma, and 1st line CLL which all resulted in cost-effectiveness ratios less than £30,000 per QALY gained.

7.3.4.2 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 REACH 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.

7.3.4.3 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 the largest 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 relapsed/refractory CLL.

b) The extrapolation of the primary endpoint, PFS, from the REACH study is based on a relatively long and the very latest follow up period of over 2.1 years with follow-ups for some patients extending to nearly 5 years.

c) 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.

Weaknesses

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

c) The assumption of a constant risk of death from the progressed health state across both arms of the trial may not appear the most reasonable of assumptions. To overcome this limitation, uncertainty was built into this estimate in both the deterministic and probabilistic sensitivity analysis. The results of these additional analyses still remained cost-effective.

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.

e) A systematic literature review revealed that little Phase III evidence is available in standard chemotherapies used in relapsed/refractory CLL, thereby making indirect comparisons difficult. As a result, it is impossible to provide a robust economic evaluation of rituximab in combination with other chemotherapies. However, Phase II data for R-CHOP in fludarabine-refractory patients (Section 6.8.4.1) and retreated patients (Section 6.8.4.3) report consistent efficacy benefits for rituximab. In the context of the available data, the threshold analysis is therefore deemed the most reasonable approach to determine the extent to which incremental benefit would need to differ from that observed in REACH to no longer be considered cost-effective.

7.3.4.4 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 in Q4 2009.

In addition to utilities, the following analyses would further enhance the model results:

a) Extrapolation of PFS and OS outcomes for R-FC and FC based upon longer follow-up of the REACH 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 treatment failure.

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 patients in remission from CLL.

f) A direct RCT comparison for rituximab in combination 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 an uptake of 100% per annum over the next three years the estimated budget impact of the addition of rituximab to the current treatment regimens for the treatment of relapsed/refractory CLL patients is £10,954,972 in the 1st year, £11,039,092 in the 2nd year and £11,122,680 in the 3rd year. All the above figures include administration costs.

An additional £10,923 is needed for every eligible CLL patient treated with rituximab each year based on the recommended dose, assuming a body surface area of $1.8m^2$ and the full recommended dose of rituximab.

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 who have been previously treated and either relapsed or did not respond to the treatment. The CLL incidence rate in 2004 was 0.0041% (Cancer Research UK, February 2008[99]). 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 55,319,249 in 2010 (first year of rituximab marketing authorisation), 55,744,028 in 2011 and 56,166,122 in 2012 (GAD, 2006-based principal projections[100]). The CLL incidence rate of 0.0041% will result in 2,268 new CLL patients in 2010, 2,286 in 2011 and 2,303 in 2012.

Approximately a third (33%) of patients with previously untreated CLL will never need treatment (Dighiero G., 2000[101]) 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 approximately two thirds (70%) will relapse or do not respond at all (Genactis Q2 2009[86]). The total eligible population for 2010, 2011 and 2012 is 1,003, 1,011 and 1,018 respectively. The calculations are summarised in Table 81.

Table 81. Estimated number of patients eligible to receive treatment

Assumptions	Percentage	Value 2010	Value 2011	Value 2012
Local population		55,319,249	55,744,028	56,166,122
Incidence of CLL	0.0041%	2,268	2,286	2,303
Proportion of patients requiring treatment	67%	1,520	1,531	1,543
Proportion of previously treated patients who either relapsed or did not respond.	66%	1,003	1,011	1,018
Total number of relapsed/refractory CLL patients per annum		**1,003**	**1,011**	**1,018**

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)?

Given that rituximab is currently used in the treatment of diffused large B-cell lymphoma, follicular lymphoma, as well as 1st line CLL within the NHS, it is assumed that clinicians will be familiar with the medication's characteristics. Therefore an uptake of 100% per annum over the next three years has been assumed. As shown in Table 81 the total number of patients that are expected to be treated with rituximab combination therapy is 1,003, 1,011 and 1,018 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. 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 £1,573. Hence five cycles of this dosage will cost £7,858. The total cost of a full course of treatment is £9,081 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 2007/2008[89] were used to determine the cost of each visit. The published costs provide a tariff for a day-case hospital visit ('Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance'; HRG code: SB14Z); this is valued at £307 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 £307. Specifically, the additional cost incurred will be the difference between £307 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 £1,842 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 REACH study, there are potential savings from delayed expenditure on subsequent CLL treatments.

9 Appendices

9.1 Appendix 1

Summary of Product Characteristics (Draft)


Adobe Acrobat 7.0 Document

9.2 Appendix 2: search strategy for section 6

9.2.1 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 (REACH) and any other information not obtained elsewhere.

Please note the same searches were used to extract randomised and non-randomised studies.

9.2.2 The date on which the search was conducted.

MEYY: 18/06/2009 **Cochrane Library:** 01/07/2009

EMYY: 18/06/2009

MEIP: 12/06/2009

EMBA: 12/06/2009

BIYY: 12/06/2009

9.2.3 The date span of the search.

Medline, Embase and Biosys databases were searched from 01/01/1993 to the present. The Cochrane library was tested in its entirety.

9.2.4 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	56551
2	MEYY	B–Lymphocytes#.DE.	unrestricted	33334
3	MEYY	1 OR 2	unrestricted	88355
4	MEYY	rituximab.RN.	unrestricted	3816
5	MEYY	3 AND 4	unrestricted	844
6	MEYY	5 AND chronic	unrestricted	316
7	EMYY	Rituximab#.W..MJ.	unrestricted	3095
8	EMYY	Chronic–Lymphatic–Leukemia#.MJ.	unrestricted	5276
9	EMYY	7 AND 8	unrestricted	191
10	MEYY	6 AND PT=CLINICAL–TRIAL#	unrestricted	59
11	EMYY MEYY	combined sets 9, 10	unrestricted	250
12	EMYY MEYY	dropped duplicates from 11	unrestricted	36
13	EMYY MEYY	unique records from 11	unrestricted	214

Search Strategy for BIYY

No.	Database	Search term	Info added since	Results
1	BIYY	PT=MEETING-ABSTRACT OR PT=MEETING-POSTER	unrestricted	2345589
2	BIYY	rituximab.TI.	unrestricted	3328
3	BIYY	(chronic ADJ lymphocytic ADJ leukemia OR CLL).TI.	unrestricted	6983
4	BIYY	2 AND 3	unrestricted	267
5	BIYY	4 AND 1	unrestricted	185
6	BIYY	5 AND HUMANS# AND ABSTRACT=YES	unrestricted	151
7	BIYY	relapsed OR relaps$ OR refractory OR refrac$ OR previously ADJ treated	unrestricted	93501
8	BIYY	6 AND 7 AND HUMANS# AND ABSTRACT=YES	unrestricted	85

Search Strategy for EMBA

No.	Database	Search term	Info added since	Results
1	EMBA	rituximab OR rituxan	unrestricted	157
2	EMBA	chronic ADJ lymph$ ADJ leuk$ OR CLL	unrestricted	105
3	EMBA	1 AND 2	unrestricted	13

Search Strategy for MEIP

No.	Database	Search term	Info added since	Results
1	MEIP	rituximab OR rituxan	unrestricted	341
2	MEIP	chronic ADJ lymph$ ADJ leuk$ OR CLL	unrestricted	217
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 leukemia OR CLL)” in Cochrane Central Register of Controlled Trials.

9.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

None done and therefore not applicable.

9.2.6 The inclusion and exclusion criteria.

As discussed in section 6, no randomised controlled studies relevant to the decision problem were excluded.

9.2.7 The data abstraction strategy.

As detailed above.

9.3 Appendix 3: search strategy for Section 7

9.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

9.4 Medline

9.5 Embase

9.6 Medline (R) In-Process

9.7 Health Economic Evaluation Database

9.8 NHS Economic Evaluation Database (NHS EED).

9.9 ISPOR Research Digest

Dialog Datastar was used to search Medline (MEYY), Medline in process (MEIP), Embase (EMYY).

9.3.2 The date on which the search was conducted.

All searches were conducted on the 24th of June 2009

9.3.3 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.

9.3.4 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:

No.	Database	Search term	Info added since	Results
1	EMYY	rituximab	unrestricted	12406
2	EMYY	Rituximab#.W..MJ.	unrestricted	3092
3	EMYY	Economic-Evaluation#.DE.	unrestricted	96481
4	EMYY	Cost-Benefit-Analysis#.DE. OR Cost-Effectiveness-Analysis#.DE. OR Cost-Minimization-Analysis#.DE.	unrestricted	79841
5	EMYY	chronic ADJ lymphatic ADJ leukemia OR chronic ADJ lymphocytic ADJ leukemia	unrestricted	9552
6	EMYY	Chronic-Lymphatic-Leukemia#.MJ.	unrestricted	5276
7	EMYY	1 OR 2	unrestricted	12406
8	EMYY	3 OR 4	unrestricted	96481
9	EMYY	5 OR 6	unrestricted	9552
10	EMYY	7 AND 9	unrestricted	1306
11	EMYY	10 AND 8	unrestricted	24
12	MEYY	rituximab.RN.	unrestricted	3811
13	MEYY	chronic ADJ lymphatic ADJ leukemia OR chronic ADJ lymphocytic ADJ leukemia	unrestricted	7051
14	MEYY	Cost-Benefit-Analysis#.DE. OR Cost-Control#.DE.	unrestricted	50716
15	MEYY	Economics#.W..DE. OR Economics-Medical#.DE. OR Economics-Pharmaceutical#.DE.	unrestricted	250620
16	MEYY	14 OR 15	unrestricted	250620
17	MEYY	12 AND 13	unrestricted	254
18	MEYY	17 AND 16	unrestricted	1
19	EMYY MEYY	combined sets 11, 18	unrestricted	25
20	EMYY MEYY	dropped duplicates from 19	unrestricted	1
21	EMYY MEYY	unique records from 19	unrestricted	24

The twenty-four records found were all excluded. There reasons for the inclusions are provided below.

Exclusion	Number of articles
Not an economic evaluation	20
Literature review	2
Not representative of the UK	1
Rituximab not assessed	1

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.

9.3.5 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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