Clarification response for technology appraisal:

Rituximab for the treatment of relapsed / refractory chronic lymphocytic leukaemia

Roche Products Limited

12 August 2009

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Section A: Clarification on effectiveness data

General

A1. As there is no published data available for the REACH trial, if available, please provide the full trial report.

The REACH clinical study report (CSR) was included along with the other references listed in the submission document on the CD-ROM originally sent to NICE. Roche have subsequently had confirmation from NICE that this has now been received. In addition to the CSR, an abstract of the REACH data that was submitted for presentation at the 50th meeting of the American Society of Haematology (ASH)[1] has been included on a second CD-ROM for your information (forwarded on separately). Please note, this publication was not identified in the original Biosis data-base search as it was submitted as a "late-breaking abstract" to the ASH meeting. As requested during the teleconference with NICE on 7th August 2009, a copy of the draft EPAR is also included for your information[2] as well as a draft version of the SmPC[3], which incorporates the revised wording following a positive opinion from the CHMP on 23rd July 2009 for rituximab in relapsed/refractory chronic lymphocytic leukaemia (CLL) in the EU.

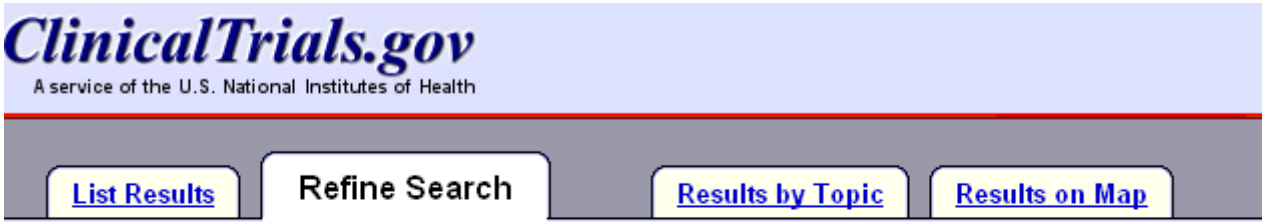
A2. At the cut-off date for REACH data analysis (2.1 years median follow-up), around 76% of patients were still alive or censored for overall survival and there is thus little informative data contributing to the survival curves for the Committee to consider. If available, please provide any additional data from the REACH trial for relevant outcomes after the cut-off for data analysis (23rd July 2008).

Roche can confirm that collection of overall survival data will continue, however, no additional data is yet available further to that submitted to NICE. Roche intends to submit one updated analysis on overall survival with a clinical data cut-off approximately 24 months after the cut-off for the final analysis (data cut-off for final analysis was July 23, 2008). The up-dated OS data will be submitted to the EMEA about 5 months later, ie around Dec 2010. It is expected that with this additional follow-up, about 40-50% of deaths will have been observed in the REACH study. Further follow-up for survival is not planned after the 2010 cut-off, since results of the primary analysis of the study were released to the public in November 2008 (ASH abstract included on CD-ROM) and substantial cross over to rituximab is expected to occur which will confound any future analyses. Accordingly, Roche considers it unlikely that an OS benefit will be observed at the next OS update or subsequently.

Identification of studies

A3. The submission states under 6.2.5 (p41) that there are no relevant ongoing trials from which additional evidence will be available in this time period. Please provide the search strategy for identification of ongoing and completed but unpublished trials.

In order to identify relevant ongoing and completed trials, the results from which have not yet been published and are unlikely to be available in the next 12 months, we conducted a search on ClinicalTrials.gov using the following advanced search criteria:



Refine your search here or Start Over.

Change your search with any or all of the fields below.
Search within your current results by adding more search terms.

Search Terms:		Search	Help
Recruitment:	All Studies		
Study Results:	All Studies		
Study Type:	Interventional Studies		

Targeted Search:

Conditions:	relapsed refractory chronic lymphocytic leukaemi	
Interventions:	rituximab	
Outcome Measures:		
Lead Sponsors:		Exact Match
Sponsors:		Exact Match
Study IDs:		

Locations:

State 1:	--- Optional ---
Country 1:	--- Optional ---
State 2:	--- Optional ---
Country 2:	--- Optional ---
State 3:	--- Optional ---
Country 3:	--- Optional ---
Location Terms:	

Additional Criteria:

Gender: All Studies

Age Group: ☐ Child (birth-17) ☑ Adult (18-65) ☑ Senior (66+)

Phase: ☐ Phase I ☑ Phase II ☑ Phase III ☑ Phase IV

Funded By: ☐ NIH ☐ Other U.S. Federal Agency ☐ Industry ☐ University/Organization

Safety Issue: ☐ Has an outcome measure designated as a safety issue.

First Received: From [ ] To [ ] (MM/DD/YYYY)

Last Updated: From [ ] To [ ] (MM/DD/YYYY)

Search Help

Below are the search results:

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home | Search | Study Topics | Glos

List Results | Refine Search | Results by Topic | Results on Map | Search Details

Found 29 studies with search of: Interventional Studies | relapsed refractory chronic lymphocytic leukaemia | rituximab | Adult Senior | Phase II III IV

Hide studies that are not seeking new volunteers. | Display Opt

Rank	Status	Study
1	Recruiting	Pentostatin, Alemtuzumab, and Rituximab in Treating Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Conditions: Leukemia; Lymphoma Interventions: Biological: alemtuzumab; Biological: rituximab; Biological: sargramostim; Drug: pentostatin; Genetic: polymerase chain reaction; Other: flow cytometry; Other: immunoenzyme technique; Other: immunohistochemistry staining method; Other: laboratory biomarker analysis
2	Active, not recruiting	Lenalidomide With or Without Rituximab in Treating Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia Condition: Leukemia Interventions: Biological: rituximab; Drug: lenalidomide
3	Recruiting	Lower But More Frequent Dose Rituximab to Treat Chronic Lymphocytic Leukemia Condition: Refractory Chronic Lymphocytic Leukemia Intervention: Drug: Rituximab
4	Recruiting	Pentostatin, Cyclophosphamide, and Rituximab Followed By Alemtuzumab in Treating Patients With Relapsed or Refractory B-Cell Chronic Lymphocytic Leukemia Condition: Leukemia Interventions: Biological: alemtuzumab; Biological: filgrastim; Biological: pegfilgrastim; Biological: rituximab; Drug: cyclophosphamide; Drug: pentostatin
5	Active, not recruiting	Epirubicin and Rituximab in Treating Patients With Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia Conditions: Leukemia; Lymphoma Interventions: Biological: rituximab; Drug: epirubicin hydrochloride
6	Not yet recruiting	Fludarabine, Rituximab, and Bevacizumab in Treating Patients With B-Cell Chronic Lymphocytic Leukemia That Has Relapsed or Not Responded to Treatment Condition: Leukemia Interventions: Biological: bevacizumab; Biological: rituximab; Drug: fludarabine phosphate
7	Recruiting	Bendamustine and Rituximab in Treating Patients With Relapsed Chronic Lymphocytic Leukemia Condition: Leukemia Interventions: Biological: rituximab; Drug: bendamustine hydrochloride
8	Recruiting	Vorinostat, Cladribine, and Rituximab in Treating Patients With Mantle Cell Lymphoma, Chronic Lymphocytic Leukemia, or Relapsed B-Cell Non-Hodgkin Lymphoma Conditions: Leukemia; Lymphoma Interventions: Biological: rituximab; Drug: cladribine; Drug: vorinostat; Other: laboratory biomarker analysis
9	Recruiting	Donor Natural Killer Cell Infusion, Rituximab, Aldesleukin, and Chemotherapy in Treating Patients With Relapsed Non-Hodgkin Lymphoma or Chronic Lymphocytic Leukemia Conditions: Leukemia; Lymphoma Interventions: Biological: aldesleukin; Biological: lymphokine-activated killer cells; Biological: rituximab; Drug: cyclophosphamide; Drug: fludarabine phosphate; Other: biomarker analysis; Other: pharmacogenomic studies; Other: pharmacological study
10	Active, not recruiting	Fludarabine and Rituximab With or Without Pixantrone in Treating Patients With Relapsed or Refractory Indolent Non-Hodgkin Lymphoma Conditions: Leukemia; Lymphoma Interventions: Biological: rituximab; Drug: fludarabine phosphate; Drug: pixantrone dimaleate
11	Recruiting	Bortezomib, Rituximab, Cyclophosphamide, and Prednisone in Treating Patients With Relapsed or Refractory Indolent Non-Hodgkin's Lymphoma Conditions: Leukemia; Lymphoma Interventions: Biological: rituximab; Drug: bortezomib; Drug: cyclophosphamide; Drug: prednisone
12	Recruiting	Rituximab in Treating Patients Undergoing Stem Cell Transplant for B-Cell Cancer That Has Relapsed or Not Responded to Treatment Conditions: Graft Versus Host Disease; Leukemia; Lymphoma; Lymphoproliferative Disorder; Multiple Myeloma and Plasma Cell Neoplasm; Precancerous/Nonmalignant Condition; Small Intestine Cancer Interventions: Biological: rituximab; Genetic: polymorphism analysis; Other: laboratory biomarker analysis; Other: pharmacological study
13	Active, not recruiting	Fludarabine Combined With Either Alemtuzumab or Rituximab in Treating Patients With Refractory or Relapsed B-Cell Chronic Lymphocytic Leukemia Condition: Leukemia Interventions: Biological: alemtuzumab; Biological: rituximab; Drug: fludarabine phosphate
14	Completed	Campath-1H Plus Rituximab for CD52- and CD20- Positive Refractory or Relapsed Chronic Lymphoid Disorders Condition: Chronic Lymphocytic Leukemia Interventions: Drug: Campath-1H; Drug: Rituximab
15	Active, not recruiting	Oxaliplatin, Fludarabine, Cytarabine and Rituximab in Richter's Syndrome, Refractory CLL and PLL Condition: Leukemia Interventions: Drug: Cytarabine; Drug: Fludarabine; Drug: Oxaliplatin; Drug: Rituximab
16	Active, not recruiting	Chemotherapy, Stem Cell Transplantation, and Graft-Versus-Host-Disease Prevention in Treating Patients With Refractory or Relapsed Hematologic Cancer, Myelodysplastic Syndrome, or Myeloproliferative Disorder Conditions: Chronic Myeloproliferative Disorders; Graft Versus Host Disease; Leukemia; Lymphoma; Multiple Myeloma and Plasma Cell Neoplasm; Myelodysplastic Syndromes; Myelodysplastic/Myeloproliferative Diseases Interventions: Biological: filgrastim; Biological: rituximab; Biological: therapeutic allogeneic lymphocytes; Drug: cyclophosphamide; Drug: cyclosporine; Drug: doxorubicin hydrochloride; Drug: etoposide; Drug: fludarabine phosphate; Drug: methotrexate; Drug: prednisone; Drug: vincristine sulfate; Procedure: peripheral blood stem cell transplantation
17	Not yet recruiting	R-CHOP and Alemtuzumab in Patients With Chronic Lymphocytic Leukemia Conditions: Chronic Lymphocytic Leukaemia; Patients Resistant to a Purine Analogous; Patients Relapsed With Purines Therapy Intervention: Drug: Rituximab-CHOP-Alemtuzumab
18	Recruiting	Oxaliplatin, Fludarabine, Cytarabine, and Rituximab in Patients With Richter's Transformation and Leukemias Conditions: Richter's Transformation; Leukemia Interventions: Drug: Oxaliplatin; Drug: Fludarabine; Drug: Cytarabine; Drug: Rituximab
19	Active, not recruiting	Motexafin Gadolinium, Rituximab, and Yttrium Y 90 Ibritumomab Tiuxetan in Treating Patients With Stage II, Stage III, or Stage IV Relapsed or Refractory Non-Hodgkin's Lymphoma Condition: Lymphoma Interventions: Biological: rituximab; Drug: motexafin gadolinium; Radiation: yttrium Y 90 ibritumomab tiuxetan

20 Terminated **Bortezomib and Rituximab in Treating Patients With Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma**
Condition: Lymphoma
Interventions: Drug: bortezomib; Drug: rituximab; Procedure: antibody therapy; Procedure: biological therapy; Procedure: enzyme inhibitor therapy; Procedure: monoclonal antibody therapy

21 Completed **FR901228 Alone or Combined With Rituximab and Fludarabine in Treating Patients With Relapsed or Refractory Low-Grade B-Cell Non-Hodgkin's Lymphoma**
Condition: Lymphoma
Interventions: Biological: rituximab; Drug: fludarabine phosphate; Drug: romidepsin

22 Recruiting **Vorinostat, Rituximab, Ifosfamide, Carboplatin, and Etoposide in Treating Patients With Relapsed or Primary Refractory Lymphoma or Previously Untreated T-Cell Non-Hodgkin Lymphoma or Mantle Cell Lymphoma**
Condition: Lymphoma
Interventions: Biological: filgrastim; Biological: pegfilgrastim; Biological: rituximab; Drug: carboplatin; Drug: etoposide; Drug: ifosfamide; Drug: vorinostat

23 Active, not recruiting **Radioimmunotherapy in Patients With Relapsed or Refractory Non-Hodgkin's Lymphoma**
Condition: Lymphoma
Interventions: Biological: ibritumomab tiuxetan; Biological: rituximab; Radiation: indium In 111 ibritumomab tiuxetan

24 Active, not recruiting **Rituximab and Liposomal Doxorubicin in Treating Patients With Relapsed or Refractory Non-Hodgkin's Lymphoma**
Condition: Lymphoma
Interventions: Biological: rituximab; Drug: pegylated liposomal doxorubicin hydrochloride

25 Active, not recruiting **Rituximab and Dexamethasone in Treating Patients With Recurrent or Refractory Indolent Non-Hodgkin's Lymphoma**
Condition: Lymphoma
Interventions: Biological: rituximab; Drug: dexamethasone

26 Recruiting **Radiolabeled Monoclonal Antibody Plus Rituximab With and Without Filgrastim and Interleukin-11 in Treating Patients With Relapsed or Refractory Non-Hodgkin's Lymphoma**
Condition: Lymphoma
Interventions: Biological: filgrastim; Biological: recombinant interleukin-11; Biological: rituximab; Radiation: yttrium Y 90 ibritumomab tiuxetan

27 Recruiting **Lenalidomide and Rituximab in Treating Patients With Follicular or Small Lymphocytic Non-Hodgkin Lymphoma That Has Relapsed or Not Responded to Treatment**
Condition: Lymphoma
Interventions: Biological: rituximab; Drug: lenalidomide; Genetic: protein analysis; Other: laboratory biomarker analysis

28 Active, not recruiting **Gemcitabine, Carboplatin, and Dexamethasone With or Without Rituximab in Treating Patients With Relapsed or Primary Refractory Lymphoma**
Condition: Lymphoma
Interventions: Biological: rituximab; Drug: carboplatin; Drug: dexamethasone; Drug: gemcitabine hydrochloride

29 Active, not recruiting **Rituximab and Combination Chemotherapy Followed by Bone Marrow or Peripheral Stem Cell Transplantation in Treating Patients With Relapsed or Refractory Non-Hodgkin's Lymphoma**
Condition: Lymphoma
Interventions: Biological: rituximab; Drug: carmustine; Drug: cytarabine; Drug: etoposide; Drug: melphalan; Procedure: autologous bone marrow transplantation; Procedure: peripheral blood stem cell transplantation

Below is a table clarifying reason(s) for exclusion of each study:

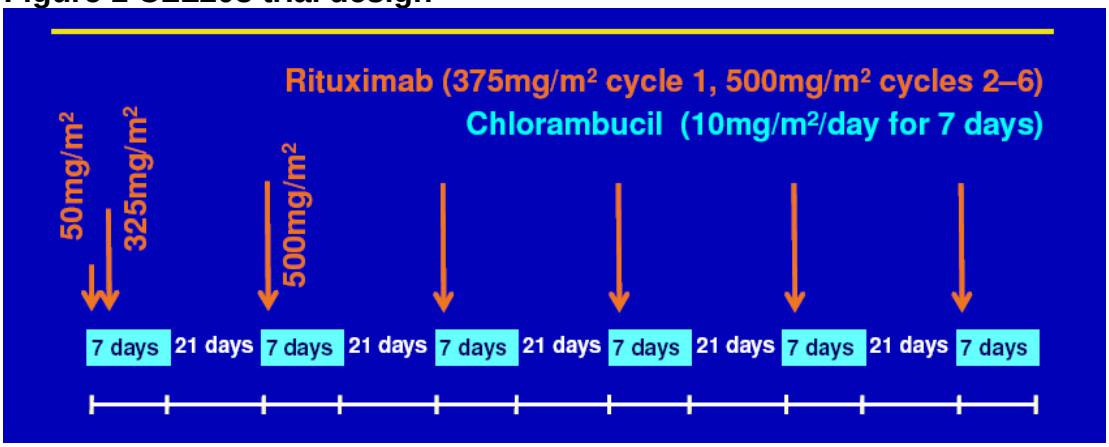
Study number	Reason for exclusion
1	Not consistent with expected licence (combination with other antibody)
2	Not consistent with expected licence (combination with other targeted investigational agent)
3	Not consistent with expected licence (rituximab monotherapy)
4	Not consistent with expected licence (combination with other antibody)
5	Mixed disease with other indolent B-cell malignancy included
6	Not consistent with expected licence (combination with other targeted investigational agent)
7	The data from the phase II portion of this study have been reported (Fischer et al., 2008) and are included in the submission (section 6.8.4.1). The study has since re-opened as a randomized phase III study and continues to recruit.
8	Mixed disease with other indolent B-cell malignancy included
9	Mixed disease with other indolent B-cell malignancy included
10	Not CLL
11	Not consistent with expected licence (combination with other targeted investigational agent); not CLL
12	Mixed disease with other indolent B-cell malignancies included; not consistent

	with expected licence (rituximab monotherapy)
13	Not consistent with expected licence (combination with other antibody)
14	Not consistent with expected licence (combination with other antibody)
15	Mixed disease with other indolent B-cell malignancies included
16	Mixed disease with other indolent B-cell malignancies included
17	Not consistent with expected licence (combination with other antibody)
18	Mixed disease with other indolent B-cell malignancies included
19	Not CLL
20	Not CLL
21	Not CLL
22	Not CLL
23	Not CLL
24	Not CLL
25	Not CLL
26	Not CLL
27	Not CLL
28	Not CLL
29	Not CLL

A4. On p31 the submission states that the efficacy of chlorambucil with rituximab is being investigated in the UK CLL201 trial (phase II). Please confirm that this should be 'CLL208' and indicate whether this should be considered a relevant ongoing trial.

This is a typographic error. UK CLL201 is the ongoing trial of FCM +/- rituximab in previously-treated CLL patients who are fit for fludarabine-based therapy (discussed in section 6.8.4.1). In the context of the paragraph on p31 of the submission, the intention was to refer (as suggested) to the UK CLL208 trial, which is currently investigating the efficacy and safety of rituximab in combination with chlorambucil in untreated CLL patients unfit for fludarabine-based therapy (see trial design below).

Figure 1 CLL208 trial design



Clearly, this study is not a directly relevant ongoing trial for the purpose of this submission as it is in <u>previously untreated</u> CLL patients.

Study selection

A5. On p35 of the submission the identification of studies is described. Please provide the formal inclusion and exclusion criteria with reference to eligible/non-eligible study designs, population characteristics, intervention therapies, comparator therapies and outcomes for:

i) randomised controlled trials

ii) non-randomised studies

The formal inclusion and exclusion criteria for study selection are outlined in Section 6.2.5 within the CONSORT flow charts. This is re-iterated below:

i) <u>randomised controlled trials</u>

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

***Inclusion criteria*: all remaining trials**

ii) <u>non-randomised controlled trials</u>

<u>Supporting non-RCTs highlighting the efficacy and tolerability of rituximab in combination with different chemotherapy regimes</u>

***Exclusion criteria*: duplicates; first-line CLL or mixed disease with other indolent B-cell malignancies included; not CLL; not a clinical trial; no rituximab; comparative RCT; trial not consistent with expected licence (eg including maintenance, monotherapy or combination with other antibodies, investigational agents)**

***Inclusion criteria*: all remaining trials**

<u>Supporting non-RCTs highlighting the efficacy of rituximab-containing regimens in patients with fludarabine-refractory CLL</u>

***Exclusion criteria*: duplicates; first-line CLL or mixed disease with other indolent B-cell malignancies included; not CLL; not a clinical trial; no rituximab; comparative RCT; no outcomes reported for fludarabine-refractory patients**

***Inclusion criteria*: all remaining trials**

<u>Supporting non-RCTs highlighting the efficacy of re-treatment with rituximab-containing regimens in patients with relapsed/refractory CLL</u>

***Exclusion criteria*: duplicates; first-line CLL or mixed disease with other indolent B-cell malignancies included; not CLL; not a clinical trial; no rituximab; comparative RCT; no outcomes reported for rituximab pre-treated patients**

***Inclusion criteria*: all remaining trials**

A6. Please clarify the flow charts (Figures 2, 3, 4 and 5, p41-44) in accordance with the formal inclusion and exclusion criteria.

As outlined in section 9.2 of the submission, the same data-base searches were initially used to extract randomised and non-randomised studies of rituximab in CLL (351 studies in total). Studies then underwent two rounds of screening using the formal exclusion criteria outlined in A5. to filter out all studies deemed irrelevant to the decision problem. Any studies remaining thereafter were included as part of the randomised or non-randomised trial cohorts.

A7. The list of relevant non-randomised studies (Table 5 (p37)) lists appears to include a randomised phase II trial (Hillmen 2007).

i) Please confirm whether this trial is a randomised study, and if so, please explain its exclusion from the randomised trials.

As outlined in Section 6.2.3 of the submission, the study by Hillmen et al is a randomised phase II study involving fludarabine, cyclophosphamide, and mitoxantrone (FCM) with or without rituximab in previously treated CLL. Despite this study being randomised, it is <u>non-comparative</u> as the design of the study did not allow a statistical comparison between the rituximab-containing and –non-containing arms. As such, the study was omitted from the list of relevant randomised controlled trials that "compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem". As highlighted, however, this study does add important data about efficacy and safety in the relevant population at hand and is therefore included in the list of trials in Section 6.2.4 of the

submission and is discussed fully with the non-randomised studies in Section 6.8.

ii) If Hillmen 2007 is eligible for inclusion, please provide the trial report or any further details that are available.

Please see part i) above.

Summary of methodology of relevant RCTs

A8. The submission states on p67 that patients without a PFS event were censored at their last tumour assessment date. Please provide information regarding a) the number of scheduled assessments for each arm, and b) the number of completed scheduled assessments for each arm.

(a) The following tumour assessments were scheduled to be completed for each arm according to the schedule in Table 1 below:

Tumor assessment:

– Binet stage at diagnosis and study entry.

– Lymphocyte immunophenotype by flow cytometry: all patients had to be CD20 positive at study entry. Additional lymphocyte phenotyping was done to determine CD3, CD5, CD23, FMC7, CD79b, SmIg intensity and CD38 (optional). During the study, CD20 staining was replaced by CD19 staining.

– Bone marrow biopsy (single site with satisfactory trephine sample) and aspirate. Performed in all patients at baseline and to confirm a CR.

– CT scans of neck (if found to be involved on physical examination), chest, abdomen, and pelvis to document nodal disease. The 6 largest dominant nodes or nodal masses were chosen as indicator lesions and measured in 2 perpendicular dimensions.

– Liver and spleen size by physical examination or CT scan.

Table 1 Schedule of Assessments

	Screening	Treatment Period Visits												Follow-up Visits					
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Month 7	Month 8	Month 9	Month 12, 15, 18, 21, 24, 27, 30 & 33	Every 6 month until 5 years[p]	Every year until 8 years
Assessment	Day -28 to -1[k]	D1	D8 15 22	D1	D8 15 22	D1	D8 15 22	D1	D8 15 22	D1	D8 15 22	D1	D8 15 22						
ECOG – Performance status	×	×		×		×		×		×		×		×	×	×	×	×	
B symptoms	×	×		×		×		×		×		×		×	×	×	×	×	
CT scan assessment[q]	×							×						×[q,i]		×[q,j]	×[q,j]		
Tumor assessment[o]	×							×						×	×	×[o]	×[o]	×	
Bone Marrow Examination	×															×[c]	×[c]		
Serum Pregnancy test[m]	×[b]																		
Hematology[h]/blood chemistry	×[b]	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	
Cr CL according to Cockcroft and Gault formula (prior to each cycle)	×	×		×		×		×		×		×							
Coombs test	×																		

o: Tumour/disease assessment included peripheral blood count, assessment of B symptoms and evaluation of hepatosplenomegaly and peripheral lymphadenopathy by physical examination, and/or, where scheduled, CT scan of the neck (if clinically involved), chest, abdomen and pelvis

(b) A full listing of completed scheduled response assessments over time for each patient in both arms of the study is included in the list of references for your information[4].

Please note, the "difference" in actual versus protocol scheduled response assessments in each arm of the trial was not included in either the main body of the REACH CSR or the list of secondary data displays. This analysis can, however, be programmed by the study statistician and forwarded to NICE subsequent to this document if required.

A9. In table 26 (p80) at the entry against "allocation concealment" (process that prevents foreknowledge of treatment assignment) there is no information about how allocation concealment was conducted. Please elaborate on any procedures that were followed in order to achieve concealment.

Five hundred and fifty two (552) patients were enrolled in total into REACH (276 patients per arm).

Patients who had completed the screening visit and fulfilled all entry requirements 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.

Patients were assigned a randomization number from a list generated by Roche. Each randomization number had a treatment group associated with it. The patient randomization numbers were allocated sequentially by ClinPhone in the order in which the patients were enrolled. A series of unique CRF (Patient) numbers were provided to each site and the

investigator provided the CRF number and other stratification information during the randomization call to ClinPhone.

The randomization list is available from Roche on request.

A10. The submission discusses on p81 the randomisation technique. Please comment on any methodological strengths and limitations of using dynamic randomisation.

The dynamic allocation method described in the submission (minimization with biased coin assignment) is based on the minimization principles published in a paper by Pocock & Simon[5]. Minimization can be classified as a "dynamic allocation" or "covariate adaptive" method as the allocation depends on the characteristics of patients already recruited. This is distinct from "response adaptive" methods where the allocation can depend on the interim results of the study.

<u>Advantages and disadvantages</u>

The primary reason for using minimization is the desire to achieve balanced groups with respect to both the numbers in each treatment arm and the characteristics of each group. The use of minimization can, however, also lead to indirect benefits including increased persuasiveness and credibility by presenting data indicating that prognostic variables are closely balanced within each treatment group[6]. It has also been suggested that planning to use minimization is a good discipline for making trialists think about prognostic factors before a study starts and for helping ensure adherence to the protocol as the trial progresses[7].

Other benefits of the minimization method have been proposed, such as the ability to include more patient factors than for stratified randomization: this can be particularly valuable in smaller trials in which several factors are known to affect outcome[8]. In addition, minimization can control confounding without the drawback of splitting the patient sample into too many strata[9].

Disadvantages of minimization have also been cited. Peto et al. consider the gains in efficiency and balance relative to complete randomization negligible[10]. They also consider the use of any stratified method of randomization unnecessary as the added complexity can harm recruitment and adjustments for covariates can be made at the end of the trial. Their arguments have, however, been countered by a number of authors[11, 12, 13].

In a recently published review article by Scott et al, minimization was cited as a highly effective allocation method with a recommendation that its use is more widely adopted in the conduct of randomized controlled trials[14].

A11. In REACH the investigators were generally unable to blind for understandable reasons (p81). Please comment on the potential for bias in outcomes where blinded assessment was not possible.

As highlighted in Section 6.3.6 of the submission, the REACH trial was open-label in design, therefore no procedures were followed to conceal treatment knowledge after randomisation (all phase III rituximab studies to date have been open-label). Please note that placebo infusions of rituximab were not given for practical reasons and because of the difficulty of maintaining a blind in the face of probable infusion-related reactions with rituximab.

Whilst accepting that the lack of treatment group blinding may introduce some potential for bias, it is unlikely that the assessment of treatment outcomes were unfairly influenced given that the endpoints measured were objective. Furthermore, the validity of the investigator's assessment has now been formally confirmed by independent review (see A12. below).

Of note, although empirical evidence does endorse a reduction of bias when adequate blinding strategies have been implemented, blinding does not guarantee an absence of bias. Indeed, allocation concealment (before randomisation) is thought to have a stronger influence on the reduction of bias than blinding (after randomisation)[15,16].

A12. On p81, the submission indicates that assessors may have been aware of treatment allocation. The submission indicates that response and progression data that were assessed in a blinded manner (at interim and final analysis) are not yet available. Please confirm that this remains the case and indicate when they are likely to be available.

Whilst the primary statistical analysis of progression-free survival and the analysis of response rates in REACH were based on the investigator's assessment, an exploratory analysis based on the assessment of an independent review board was performed (at both the interim and final analysis) to confirm the results for these two parameters.

The independent interim review committee (IRC) assessed all patients in a blinded manner for response and progression based on peripheral blood counts, bone marrow biopsy results, CT scans and reports of physical examination.

Data from all patients participating in the study have been now been reviewed by the IRC and their findings reported as an addendum to the CSR[17] (included on the second CD-ROM sent to NICE containing additional references). There is strong evidence from the IRC assessment of efficacy that rituximab in combination with FC chemotherapy is effective in reducing the risk of disease progression or death and prolonging PFS in patients with relapsed/refractory CLL. This benefit was shown to be robust and consistent with response rates and

subgroup analyses of disease progression. Overall, these data are supportive of the Investigator assessments of efficacy (Section 3.2, REACH CSR), and safety data suggest that there is no clinically important increase in toxicity compared to FC alone (Section 3.4, REACH CSR).

A13. The submission indicates that many patients were censored for progression free and overall survival (Figures 8 and 9 (p89, 91)). We are interested in numbers of patients censored because a) they reached the end of the trial without an event and b) because they were lost to follow-up before reaching the end of the trial. We are also interested in the reasons for loss to follow-up. Please provide further information on censoring and loss to follow-up, some example tables are provided in a separate attachment as a guide.

Progression-Free Survival (Investigator Assessment)

At the time of analysis (clinical cut-off date of July 23, 2008), 158 patients [57%] on FC versus 132 patients [48%] on R-FC had experienced an event (progression or death). As highlighted in Table 2 below, 118 patients in the FC arm versus 144 patients in the R-FC arm had not progressed (or died) or were censored for PFS at the cut-off date.

Table 2 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

Overall Survival

At the time of 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. As highlighted in Table 3 below, 208 patients in the FC arm versus 214 patients in the R-FC arm were still alive or were censored for OS at the cut-off date.

Table 3 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.

Patients withdrawn prematurely from the study (censored)

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 (Table 4). 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.

Table 4 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.
EX11_tt_i 24SEP2008:12:32:21

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 (patients 44218/6604 and 44219/7001) 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 (patients 36908/2702, 36916/2102, 44214/9501) who refused treatment on the FC arm did so immediately after randomization and patient 36930/2907 from the FC arm refused treatment after 2 cycles in order to have rituximab-containing therapy. Six patients (patients 44215/9605, 44215/9605, 36944/3705, 44212/6406, 44217/8403, 44226/9809) refused after 1 cycle for unspecified reasons. Patient 44219/7002 refused after 2 cycles (no details available) and patient 44216/6807 refused after 4 cycles having achieved a CR (after 3 cycles of treatment).

Of the 5 patients who withdrew from R-FC for "other reasons", patient 36930/2980 was withdrawn at the investigator's discretion due to myelosuppression, patient 36946/3507 had study treatment delayed for > 2 weeks despite having only Grade 2 neutropenia, patient 36959/5201 was withdrawn due to a misunderstanding of how many cycles of treatment he had had, patient 38722/7107 chose to withdraw and patient 44227/9903 withdrew at the investigator's discretion at Cycle 3 having achieved a CR.

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.

A full listing of treatment withdrawals is available on request.

Patients Withdrawn Prematurely from the Follow-up Phase

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 5). 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 5 Summary of 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).
EX11_fue_i 28OCT2008:16:43:08

Of the 8 patients in the FC arm who withdrew from follow-up for "other" reasons, patient 36909/2807 was withdrawn after progressing and receiving a new treatment for CLL, patient 36909/2809 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), patient 36918/1701 relocated to another country, patient 36931/3311 was diagnosed with PLL upon study entry and was excluded from the study, patient 36959/5202 received another treatment, patient 38704/6304 received a subsequent treatment for Richter's syndrome, patient 44214/9518 was too ill to follow the study procedures, and patient 61287/8901 was withdrawn at the investigator's discretion.

A full listing of patient withdrawals from follow-up is available on request.

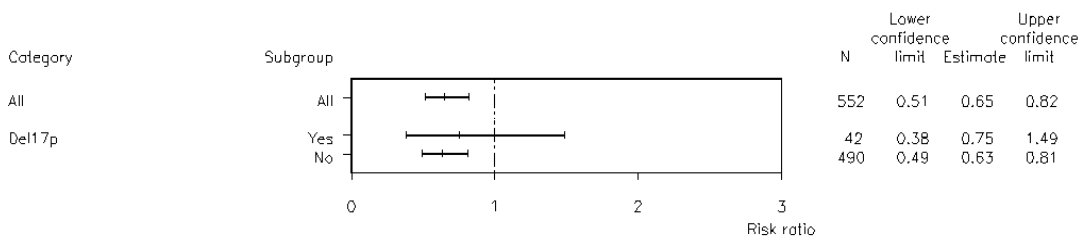
Regarding numbers of patients who reached the end of the trial without an event (and were not withdrawn for any reason), because no patient up to now has had a chance to complete the full 8 years of follow-up, no such patients were censored. In terms of patients who reached the clinical cut-off date without an event (and were not withdrawn for any reason), this analysis has not been performed. If required by NICE however, this analysis can be programmed by the study statistician and forwarded on subsequent to this document.

Results of the relevant comparative RCTs

A14. On p102 of the submission a sub-group analysis for del17 positive patients is presented for best overall response. Were sub-group analyses performed for progression free survival or other outcomes?

Yes. A Cox-regression analysis showed consistent PFS results across all 48 subgroups evaluated (Figures 11 and 12 in submission). All except two subgroups (patients $\geq$10 years from first diagnosis and patients with CD-38 negative disease) showed a benefit from R-FC treatment (HR < 1), and this was usually in the same range as for the overall patient population. As shown in Figure 2 below, both patients with and without del17p benefited from the addition of rituximab to FC, with hazard ratios of 0.75 and 0.63 respectively.

Figure 2 Forest Plot of Hazard Ratio for Progression-free Survival by Subgroups (ITT)



Applying a Cox-regression analysis on sub-groups for the secondary endpoint OS, there was a tendency towards a reduced risk of death with R-FC compared to FC for most of the subgroups analyzed. Overall, however, the survival data are not considered mature enough to enable any meaningful interpretation of the subgroup analysis and potential therapeutic effects of R-FC versus FC.

Quality of life

A15. The title of table 39 (p105) suggests that FACT-G sub-scores are available although not presented. If sub-scores are available, please provide these data.

Table 6 Summary Of FACT-G Physical Well-Being Sub-Scores over Time (ITT)

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

FACT-G Parameter/ Timepoint		FC N=276	R-FC N=276
Physical Well-Being Score			
SCREENING	Mean	22.52	22.61
	SD	4.34	4.57
	Median	23.33	23.67
	Min	9.00	5.00
	Max	28.00	28.00
	n	265	266
AFTER CYCLE 3	Mean	21.46	21.93
	SD	4.51	4.78
	Median	22.08	23.00
	Min	7.00	5.00
	Max	28.00	28.00
	n	208	219
AFTER CYCLE 6	Mean	22.79	22.45
	SD	4.78	5.05
	Median	24.00	24.00
	Min	1.00	1.00
	Max	28.00	28.00
	n	168	187
FU MONTH 12	Mean	23.76	23.55
	SD	4.93	5.17
	Median	25.20	25.00
	Min	2.00	3.00
	Max	28.00	28.00
	n	163	185

Table 7 Summary Of FACT-G Social Well-Being Sub-Scores over Time (ITT)

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

FACT-G Parameter/ Timepoint		FC N=276	R-FC N=276
Social Well-Being Score			
SCREENING	Mean	20.78	21.01
	SD	5.38	4.96
	Median	21.00	22.00
	Min	0.00	0.00
	Max	28.00	28.00
	n	266	268
AFTER CYCLE 3	Mean	21.47	20.85
	SD	4.99	5.14
	Median	22.17	21.00
	Min	8.17	2.33
	Max	28.00	28.00
	n	207	219
AFTER CYCLE 6	Mean	21.76	21.39
	SD	4.91	4.86
	Median	22.17	22.00
	Min	7.00	2.80
	Max	28.00	28.00
	n	168	187
FU MONTH 12	Mean	21.12	21.05
	SD	4.82	4.83
	Median	21.00	21.00
	Min	5.83	5.83
	Max	28.00	28.00
	n	163	182

Program : $PROD/cdl1899a/i17072a/et_qol.sas
Output : $PROD/cdl1899a/i17072u/reports/et_qol_I.out
31OCT2008 13:52

Table 8 Summary of FACT-G Emotional Well-Being Sub-Scores over Time (ITT)

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

FACT-G Parameter/ Timepoint		FC N=276	R-FC N=276
Emotional Well-Being Score			
SCREENING	Mean	17.41	17.38
	SD	4.12	4.53
	Median	18.00	18.00
	Min	2.00	0.00
	Max	24.00	24.00
	n	267	268
AFTER CYCLE 3	Mean	18.39	18.73
	SD	4.01	3.88
	Median	19.00	19.00
	Min	5.00	1.00
	Max	24.00	24.00
	n	208	218
AFTER CYCLE 6	Mean	18.68	18.88
	SD	4.06	4.24
	Median	19.00	20.00
	Min	0.00	1.00
	Max	24.00	24.00
	n	166	187
FU MONTH 12	Mean	18.50	18.83
	SD	4.53	4.39
	Median	19.00	20.00
	Min	1.00	3.00
	Max	24.00	24.00
	n	163	184

Program : $PROD/cd11899a/i17072a/et_qol.sas
Output : $PROD/cd11899a/i17072u/reports/et_qol_I.out
31OCT2008 13:52

Table 9 Summary Of FACT-G Functional Well-Being Sub-Scores over Time (ITT)

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

FACT-G Parameter/ Timepoint		FC N=276	R-FC N=276
Functional Well-Being Score			
SCREENING	Mean	17.88	18.62
	SD	5.76	5.21
	Median	18.00	19.00
	Min	0.00	0.00
	Max	28.00	28.00
	n	267	268
AFTER CYCLE 3	Mean	17.90	18.35
	SD	5.54	5.06
	Median	18.00	18.67
	Min	4.00	4.00
	Max	28.00	28.00
	n	208	219
AFTER CYCLE 6	Mean	18.79	19.20
	SD	5.61	5.41
	Median	19.00	20.00
	Min	2.00	5.00
	Max	28.00	28.00
	n	166	187
FU MONTH 12	Mean	18.71	19.60
	SD	6.03	5.61
	Median	19.00	20.00
	Min	0.00	2.00
	Max	28.00	28.00
	n	163	184

Program : $PROD/cd11899a/i17072a/et_qol.sas
Output : $PROD/cd11899a/i17072u/reports/et_qol_I.out
31OCT2008 13:52

A16. Please explain why QoL data was measured for 1 year only and not throughout the trial.

This was the schedule determined by the REACH study group at the time of trial design and was subsequently endorsed by the ethics committee.

Adverse events

A17. Adverse events (AE) may relate to treatment, with more cycles potentially generating more treatment related AEs. On p108 of the submission it states that 67.5% patients in the R-FC arm received 6 cycles of therapy, and 61.4% of patients in the FC arm received 6 cycles of therapy. Please provide information on:

i) the number of patients receiving 0, 1, 2, 3, 4 and 5 cycles of therapy in both arms at the time of the safety analysis.

Table 10 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.

ii) whether patients who restart treatment with rituximab at any time in the follow-up phase are included in the safety analysis.

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. Since only the first subsequent treatment for CLL was collected it is not known how many patients received rituximab at a later date.

Please note, all of these patients are included in the safety analysis (all SAEs considered related to study treatment were reported indefinitely and followed up until resolution, stabilization, or the end of the study, whichever occurred first).

iii) total and average amount of rituximab exposure in the rituximab arm (and those who crossed over to the R arm) in the safety analysis

Table 11 Summary of extent of exposure to rituximab by cycle (SAP)

	Dose Received* (% Of Planned Dose)	FC N=272 No.(%)	R-FC N=274 No.(%)
Cycle 1	<60%	0 (.%)	4 (1%)
	60% - <80%	0 (.%)	0 (0%)
	80% - <90%	0 (.%)	5 (2%)
	>=90%	0 (.%)	262 (96%)
	Missing	0 (.%)	3 (1%)
	n	0 (0%)	274 (100%)
Cycle 2	<60%	0 (.%)	1 (0%)
	60% - <80%	0 (.%)	22 (8%)
	80% - <90%	0 (.%)	4 (2%)
	>=90%	0 (.%)	232 (89%)
	Missing	0 (.%)	3 (1%)
	n	0 (0%)	262 (96%)
Cycle 3	<60%	0 (.%)	0 (0%)
	60% - <80%	0 (.%)	9 (4%)
	80% - <90%	0 (.%)	5 (2%)
	>=90%	0 (.%)	233 (93%)
	Missing	0 (.%)	3 (1%)
	n	0 (0%)	250 (91%)
Cycle 4	<60%	0 (.%)	0 (0%)
	60% - <80%	0 (.%)	3 (1%)
	80% - <90%	0 (.%)	4 (2%)
	>=90%	0 (.%)	218 (96%)
	Missing	0 (.%)	3 (1%)
	n	0 (0%)	228 (83%)
Cycle 5	<60%	0 (.%)	0 (0%)
	60% - <80%	0 (.%)	3 (1%)
	80% - <90%	0 (.%)	5 (2%)
	>=90%	0 (.%)	202 (95%)
	Missing	0 (.%)	2 (1%)
	n	0 (0%)	212 (77%)
Cycle 6	<60%	0 (.%)	1 (1%)
	60% - <80%	0 (.%)	3 (2%)
	80% - <90%	0 (.%)	6 (3%)
	>=90%	0 (.%)	173 (94%)
	Missing	0 (.%)	2 (1%)
	n	0 (0%)	185 (68%)

n represents the number of patients treated with rituximab in the corresponding cycle.
*: Percentages are calculated using the relative dose and are based on n (number of patients receiving rituximab in that cycle).
Planned dose for rituximab: 375 mg/m**2 (cycle 1) / 500 mg/m**2 (cycle 2-6).
Dose reductions are not considered when calculating the planned dose.
Program : $PROD/cdl1899a/i170723/st_doritn.sas

For patients randomized to the R-FC arm, the majority received more than 90% of the planned dose of rituximab (96% in Cycle 1, 89% in Cycle 2, 93% in Cycle 3, 96% in Cycle 4, 95% in Cycle 5 and 94% in Cycle 6) (Table 11). The finding that 96% of patients were able to receive > 90% of the planned dose in Cycle 1 is encouraging. This indicates that despite the well-known risk of infusion reactions with rituximab and the concerns that patients with CLL might be at increased risk of severe reactions because of their high levels of circulating lymphocytes, the great majority of patients were able to successfully complete their first infusion of rituximab. Overall, the great majority of patients received the full planned dose of rituximab at every cycle and there were no obvious trends in rituximab exposure.

Please note, REACH was a parallel group study that did not permit crossover of patients from the control arm to the rituximab arm.

iv) how late (e.g. months, years) after treatment has been completed AEs related to treatment can occur

Long-term follow-up of the use of rituximab in combination with other therapies does not reveal any consistent pattern of adverse events.

The longest follow-up data published to-date is 5-year data for the use of rituximab in the treatment of DLBCL, published by the Group d'Etude des Lymphoma de l'Adulte (GELA) (LNH 98-5)[18]. This study compared the use of 8-cycles of CHOP with rituximab plus CHOP (R-CHOP) in

elderly patients (60-80 yrs) with previously untreated DLBCL. No severe late toxicity was observed in patients treated with R-CHOP and deaths not related to lymphoma did not show any pattern. More recently, Coiffier and colleagues reported 7-year follow-up data for this study in an abstract at the 2007 American Society of Clinical Oncology annual meeting[19]. The authors do not, however, report long term safety and toxicity data in this abstract.

Delayed-onset neutropenia has been reported after administration of rituximab, (>4 weeks after the last dose), with most of these occurring in experimental studies of rituximab in the setting of autologous hematopoietic stem-cell transplantation[20,21,22,23,24,25,26]. In one of the first case series to be reported, delayed-onset neutropenia occurred between 1 and 5 months after rituximab, when administered alone (n = 5) and in combination with chemotherapy (n = 3). All episodes developed after a period of either normal or mildly depressed neutrophil counts following treatment with rituximab, and persisted for between several days and several months, before undergoing spontaneous recovery (n = 4) or recovery after administration of filgrastim (n = 4). More recently reported case series have followed a similar pattern, with several authors reporting neutropenia in patients who received rituximab with high-dose chemotherapy prior to autologous stem cell transplant. All episodes either resolved spontaneously or responded to a few days of treatment with granulocyte colony-stimulating factor. The overall reporting rate of late-onset neutropenia is currently less than 0.02% of all patients worldwide exposed to rituximab[27].

There have also been reports of serious viral infections, either new, reactivated or exacerbated (some of which were fatal), following treatment with rituximab. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoetic stem cell transplant. Examples include infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus[28]. In a recently published systematic review summarizing all the reported data on viral infections associated with rituximab the median time period from the start of rituximab treatment to the diagnosis of the viral infection was 5 months (range 1-20 months)[29].

Interpretation of clinical evidence

A18. Please provide a reference for the methodology of the Q-Twist analysis described on p161.

Q-TWiST is a special QALY endpoint for comparing therapies, which incorporates both length and quality of survival into a single measure, has been developed by Gelber and colleagues[30] in a subject based approach to quality-adjusted survival analysis. The endpoint which they devised, TWiST, is a measure of the 'good' quality time experienced by

the patient. Glasziou and colleagues[31] provide a generalized and more mathematical background to the Q-TWiST methodology introduced by Goldhirsch and colleagues[32]. Gelber et al.[33] and Revicki et al.[34] provide an updated overview of the Q-TWiST method that includes all recent developments and extensions to the method.

A19. Please confirm that the median follow-up time for Q-Twist is 30.75 months, and for the other clinical effectiveness outcomes it is 2.1 years.

This is a reporting error. It should read 25.3 months median follow-up time from the REACH trial.

A20. It states in the submission that a utility of 1 represents a state as good as TWIST (time without symptoms of disease or toxicity of treatment). Does this imply that CLL patients who are in remission and not experiencing side effects are equivalent to people in perfect health?

It is important to remember that the objective was to compare treatments in terms of the health states and not to compare across health states. The utilities applied to each health state assessed in any Q-TWiST analysis lie between 0 and 1 [inclusive]. However, the sum of all health state utilities can and most often do exceed 1. TWiST is the health state in which the patient is at their best possible health given their condition. TWiST methodology is extended so that periods spent with toxicity or relapse are included in the comparative analysis but are weighted (with utilities) to represent their quality value relative to TWiST. Thus, overall survival was scaled downwards by arbitrarily giving survival during treatment or symptoms a reduced value. We assess (in sensitivity analyses) the impact on mean overall survival time given various utilities scenarios, with one of the scenarios being when the utility of TWiST = 1. We make no ascertains that patients are equivalent to people with perfect health but rather define a range of clinically plausible values. For instance, given an average relapsed CLL patient, the utilities for the health states could be 0.4 for TOX, .0815 for TWiST and 0.618 for REL. A utility of 1 for either TOX or REL is, in clinical practice, extremely unlikely.

Section B: Clarification on cost-effectiveness data

De novo economic evaluations

B1. To aid the ERG and the committee in the understanding of the economic model (the committee do not see the model-only the submission), please provide a table which expands on table 59 and includes the following information:

- the names of **all** parameters as used in the model
- the values for all parameters
- the range of values they can take
- their function in the model
- the evidence base behind them

Please see Appendix 1 for an exhaustive list of the variables provided in the economic model and their descriptions.

B2. Please clarify in a single table the information given in tables 58, 67 and 68 and on page 47 about dosages and costs for R, F and C. Please highlight any differences between (a) REACH, (b) the economic model inputs and (c) planned licensed dose specifically for the following parameters:

i) single doses in mg/m2

ii) number of doses of each drug in one cycle and total number of doses

iii) mode of administration (iv/oral)

iv) conversion from iv to oral dose

v) costs per dose/cycle of F, C, R

vi) total cost per patient

Following review of the clarification questions, we would like to propose some adjustments to the base case (and subsequently to the sensitivity analysis) of the economic model. This includes the use of the planned dose (including wastage) scenario in the base case as well as the adjustment to the formula for the variable male2female described in question B12. The rational for using the planned dose is explained in

further detail in Section B2 part xii). These results are provided in Appendix 2. These adjustments result in an ICER slightly higher than that provided in the original submission, however it remains highly cost-effective (£15,593 per QALY gained). No new economic model will be provided as these two adjustments are easily made in the version already available to the ERG and NICE.

The below table now reflects the planned dose under the 'Economic model' column. As you will see, due to the nature of the model, the dose used in the analysis is subsequently reduced by the proportion of patients assumed to remain in the progression-free state over the first 6 months of therapy (i.e. the approximate time duration required to complete 6 cycles of therapy). By utilising the 'planned dose' option within the model, this latter adjustment allows for a close approximation of the dose observed in REACH: 864.20mg average dose of rituximab in REACH compared to 866.39mg average dose of rituximab in the economic modelling of REACH. As body surface area is necessary for all dose calculations, we have assumed a body surface area of 1.8636 m^2 as observed in REACH. For simplicity, wastage is not included in the below table so to clearly illustrate the differences in mg doses of rituximab, fludarabine, and cyclophosphamide.

Table 12. Detailed dose information for REACH, the economic model, and the license

	REACH	**Economic model**	**Licensed dose**
Singles Doses in mg/m2 for: a.) R b.) F c.) C	The planned dose according to the protocol is the same as the licensed/accepted dose. Summary statistics indicated that the actual average dose per person was as follows: a.) **864.20** mg per cycle for 6 cycles b.) 43.36 mg in R-FC arm; 43.54 mg in FC arm for 3 days each cycle. Equating to **130**mg in the R-FC arm and **131**mg in the FC arm per cycle. c.) 441.24 mg in R-FC arm; 443.50 mg in FC arm for 3 days each cycle. Equating to **1,324**mg per cycle in the R-FC arm and **1,331**mg per cycle in the FC arm.	The planned dose of rituximab is the same as the licensed/accepted dose. The actual dose in the model is reduced each month by the proportion of patients expected to progress or die in each month. a.) The average dose estimated is **866.39**mg per administration over the 6 cycles. b.) The average dose estimated is 46.06 mg in the R-FC arm; 44.99 mg in the FC arm for 5 days each cycle over the 6 cycles. Equating to **230**mg in the R-FC arm and **225**mg in the FC arm per cycle. c.) The average daily dose estimated is 287.72 mg in the R-FC arm; 273.03 mg in the FC arm for 5 days each cycle over the 6 cycles. Equating to **1,439**mg in the R-FC arm and **1,365**mg in the FC arm per cycle.	a.) 375mg/m^2 in cycle 1; 500mg/m2 in cycles 2-6. 28 days = 1 cycle. This totals to 2875mg/m^2. Assuming m^2 = 1.8636, this is a total dose of 5357.85mg or an average dose of **892.98**mg per administration. In reality, the average dose would be slightly lower to reflect those few patients who died or did not respond to treatment prior to completing their 6 cycles b.) The combination of F and C is not a licensed indication. The accepted dose is 25mg/m^2 for 3 day each cycle over 6 cycles if given by infusion or 24mg/m^2 for 5 days each cycle over 6 cycles if given orally. Equating to **140**mg if provided by infusion and **224**mg if provided orally per cycle. c.) The combination of F and C is not a licensed indication. The accepted dose is 250mg/m^2 for 3 day each cycle over 6 cycles if given by infusion or 150mg/m^2 for 5 days each cycle over 6 cycles if given orally. Equating to **1,398**mg if provided by infusion and **1,398**mg if provided orally per cycle.
# of doses in each cycle and	We have assumed # of doses implies number of administration days per cycle	We have assumed # of doses implies number of administration days per cycle	We have assumed # of doses implies number of administration days per cycle

total number of doses for: a.) R b.) F c.) C	a.) one b.) three c.) three	a.) one b.) five c.) five	a.) one b.) three or five c.) three or five
Model of administration for: a.) R b.) F c.) C	a.) IV b.) IV c.) IV	a.) IV b.) oral c.) oral	a.) IV b.) Oral or IV are accepted. Oral is the standard method in the UK. c.) Oral or IV are accepted. Oral is the standard method in the UK.
Conversion from IV to oral a.) F b.) C	REACH only used the IV administration mechanism for F and C and therefore conversion to IV is not relevant.	The model utilised the standard dose conversion used in established practice. a.) The accepted conversion from IV to oral FC is 24/25 for 5 days instead of 3 days. b.) The accepted conversion from IV to oral FC is 150/250 for 5 days instead of 3 days.	There is no licensed conversion. a.) The accepted conversion from IV to oral FC is 24/25 for 5 days instead of 3 days. b.) The accepted conversion from IV to oral FC is 150/250 for 5 days instead of 3 days.
Total cost per patient	Using the total average dose from REACH a.) Based on 864.20mg per cycle for 6	Based on undiscounted cost results, which is adjusted as described above for those who have progressed prior to completing	a.) Based on an average dose of 892.98mg per cycle for 6 cycles, the

a.) R b.) F* c.) C*	cycles, the approximate cost is **£9,054.66** b.) Based on 130mg in the R-FC arm and 131mg in the FC arm per cycle for 6 cycles, the approximate cost is **£2,433.60** in the R-FC arm and **£2,452.32** in the FC arm. c.) Based on 1,324mg per cycle in the R-FC arm and 1,331mg per cycle in the FC arm for 6 cycles, the approximate cost is **£56.24** in the R-FC arm and **£56.54** in the FC arm.	all 6 cycles. a.) **£9,077.89** b.) **£2,568.79** for R-FC arm; **£2,510.37** for FC arm c.) **£20.72** for R-FC arm; **£19.66** for FC arm	approximate cost would be **£9,356.20.** b.) If provided by infusion, such as in REACH, this would equate to a total of **£2,620.80**. If provide orally, such as in the economic model, this would equate to a total of 1,344mg at a cost of **£2,499.84.** c.) If provided by infusion, such as in REACH, this would equate to a total of **£59.39**. If provide orally, this would equate to a total of 8,388mg at a cost of **£20.13.**

*IV cost of fludarabine and cyclophosphamide differ from the oral dose and were not provided in the original submission. The cost from BNF 57 are as follows: IV fludarabine - Net price 50-mg vial = £156.00; IV cyclophosphamide – Net price 500-mg vial = £3.54

The following points relate to question B2. Please ensure these points are addressed in the table provided in response to the above question or that further explanation is provided.

i) The submission states on p164 that a higher oral dose of FC is required to obtain the equivalent iv dose.

The **iv** doses in REACH (p47 of the submission) are:

F: 25 mg/m2 on 3 days (stated given on days 1,2,3) = 75 mg/m2
C: 250 mg/m2 on 3 days (stated given on days 1,2,3) = 750 mg/m2

The **oral** doses in the economic model are:

F: 24 mg/m2 on 5 days (stated given days 1-5) = 120 mg/m2
C: 150 mg/m2 on 5 days (stated given days1-5) = 750 mg/m2

Please confirm if these calculations are correct and if so why the oral dose of F is higher (as expected) but the oral dose of C is not.

This is the accepted dose conversation as described on page 164 of the original submission, under the heading "Routes of Administration". We have replicated the relevant section below.

"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[35]). 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[36]). 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[37])."

Section 4.5 from the Final Guidance for the 1st line used of rituximab in CLL (TA174) reconfirms these points.

ii) The oral doses of FC were taken from the CLL-4 trial, where patients are previously untreated, as opposed to the population in the decision problem where patients have previously been treated. Please clarify how this difference in patient populations might impact on the dosages used.

As highlighted in Section 6.3.6 of the submission, the approved standard dose of fludarabine as monotherapy in patients with relapsed CLL is 25 mg/m^2/day for the first 5 days of each 28-day cycle (usually 6 cycles). O'Brien and colleagues evaluated the safety and efficacy of combined fludarabine (30 mg/m^2) and cyclophosphamide (300-500 mg/m^2) therapy given daily for three days over 6 cycles (4-6 week cycle duration) (O'Brien et al, 2001). A dose reduction in cyclophosphamide from 500 mg/m^2 to 300 mg/m^2 appeared effective in reducing the severity of myelosuppression. Therefore, to improve the

safety profile further in the REACH study, an even lower dose of fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2/day) was used. This is the same regimen as used in the MDACC phase II studies and the phase III trial in previously untreated CLL patients, CLL-8.

We would like to note that even if different patient populations impacted on the dosages of FC, this would not impact the incremental cost associated with adding rituximab to FC, and therefore does not complicate the decision problem at hand.

iii) Table 67 (p189) states that the actual doses from REACH were 700 mg/m^2 (cycle 1) and 900 mg/m^2 (cycle 2-6) and that this includes rounding up to the nearest vial. Our calculations for the recommended dose of rituximab suggest the dose is 697.5 mg/m^2 (cycle 1) and 930 mg/m^2 (cycle 2-6). Please clarify the actual dose in REACH with no rounding, and the number and size of vials required to provide the actual dose provided in REACH and the dose recommended in the SPC.

We agree with the above calculation for recommended dose of 697.5 mg/m^2 (cycle 1) and 930 mg/m^2 (cycle 2-6). This is reflected in our new proposed base case of 'planned dose (including wastage)'. These figures are implemented in the model and therefore with wastage we estimate 700 mg/m^2 (cycle 1) and 1000 mg/m^2 (cycle 2-6) for those eligible to receive treatment (i.e. those that have not progressed).

The actual dose information from REACH is only provided as summary statistics and provided in the table above. This is 864.20 mg over the 6 cycles. If we assume that the initial planned dose of 375 mg/m^2 was implemented across all patients (therefore 375 mg/m^2 * 1.8636 m^2 = 698.85 mg in cycle 1), this would mean that for the remaining 5 cycles, the average dose was 897.25 mg (or 481.46 mg/m^2). Therefore the actual dose from REACH with wastage based on 700 mg/m^2 (cycle 1) and 900 mg/m^2 (cycle 2-6) is correct. This dosing regimen is reflected in the new sensitivity analysis provided as a result of the following question.

iv) Please complete sensitivity analyses if there are any changes in vial numbers or size

In the new results provided in Appendix 2, we have provided a sensitivity analysis assuming that one fewer 100mg vial of rituximab; and one additional 100mg vial of rituximab is required per cycle based on differences in patients weight. From the base case ICER of £15,593 per QALY, these two sensitivity analysis results in ICERs of £13,803 and £17,383 respectively.

v) Please clarify the calculation of cost of rituximab for cycle 1 and cycles 2-6;

500ml@ £873.15 + 2* 100ml @ 174.63=£1222.41 (not £1328.81)
500ml@ £873.15 + 4* 100ml @ 174.63=£1571.67 (not £1708.47)

These calculations above are correct. The reason these figures were not represented in the table was that they were incorrectly providing the monthly cost (instead of cycle cost) associated with drug treatment using a multiplier of 1.08705 (variable = 'cyc2mon' to convert cycles of 28 days into months).

This means as well that the final cost of rituximab provided in Table 67 (£9871.15) was overestimated as it calculated the cost of 6 months of rituximab rather than 6 cycles of rituximab (the recommended dose).

vi) Please confirm whether the unit cost for a 500mg vial of rituximab is £874.15 or £873.15 (both figures appear in table 67).

The correct figure is £873.15. This is also the figure that has been implemented in the economic model. Therefore this figure in Table 67 is a typographical error.

vii) Table 67 (p189) describes the costs per infusion/cycle. Please confirm that 500ml should be 500mg.

This is a typographical error. This should ready 500mg and 100mg, not ml.

viii) Please confirm the unit cost in table 68 (p190) for 1mg oral F is £1.86 (same as body surface area figure).

Coincidentally, the BNF list price for fludarabine (Fludara®) is £1.86 per mg, coinciding with the body surface area of 1.86 m^2 taken from the REACH trial.

ix) Table 68 (p190) provides the daily dose of cyclophosphamide. Our calculations suggest 150 mg/m^2 equates to 279 mg for a body surface area of 1.86 m^2 which multiplied by an adjustment factor of 150/250, results in 167.4 mg on 5 days (not 265 as stated). Please clarify how the average daily dose for cyclophosphamide is calculated.

The recommended dose should be 279.54 mg for cyclophosphamide, reflecting the recommended dose of 150 mg/m^2 multiplied by 1.8636 m^2. The conversion is only necessary when moving from the IV dose to the oral dose – from REACH, the average administration of cyclophosphamide was 441.24 mg in the R-FC arm and 443.50 mg in the FC arm daily over 3 days. When these figures are converted to oral doses, this results in an average administration of 264.74 mg in the R-FC arm and 266.10 mg in the FC arm daily over 5 days.

The new base case now reflects the planned recommended doses adjusted for proportion of patients progressing who do complete their chemotherapy regimen.

x) Table 68 (p190) provides the daily dose for fludarabine. Our calculations suggest 25mg * 1.86 * (24/25), equates to 44.64 (not 42 as stated). Please clarify how the average daily dose for fludarabine is calculated.

The recommended daily dose should be 44.73 mg for fludarabine, reflecting the recommended daily dose of 24 mg/m^2 multiplied by 1.8636 m^2. The conversion is only necessary when moving from the IV dose to the oral dose – from REACH, the average administration of fludarabine was 43.36 mg in the R-FC arm and 43.54 mg in the FC arm daily over 3 days. When these figures are converted to oral doses, this results in an average administration of 41.64 in the R-FC arm and 41.80 in the FC arm daily over 5 days.

The new base case now reflects the planned recommended doses adjusted for proportion of patients progressing who do complete their chemotherapy regimen.

xi) In table 68 (p190; column headed 'Description'), C is stated to be chlorambucil. Please confirm this should be cyclophosphamide.

This is a typographical error. This should read cyclophosphamide.

xii) On p199 of the submission it states that "the utilisation of actual doses of R-FC and FC from the trial were considered in the base case analysis. The sensitivity analysis explores the planned licensed dose." However, the submission states on p166 that "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."

Please clarify the differences between the dosages used in the REACH trial, the dosages used in the model (and any sensitivity analyses) and the planned licensed doses.

Apologies for the confusion caused by this wording. Our intention is to provide dosing based on the planned dose (which is both that found in the protocol of REACH, in the license for rituximab in 1st line CLL, and used as accepted UK practice for FC). The manner in which the model uses the information on dosing inherently changes these planned doses to reflect potential 'real-world practice'. This is because it is not assumed that 100% of patients in both arms receive their treatment. Instead, the proportion of patients who receive their treatment is the proportion of patients who remain in the progression-free state each month thereby excluding patients who have progressed or died. As a result, even when selecting 'Planned dose (including wastage)' from the model menu, the model will then calculate an observed dose based on those eligible to receive treatment based on treatment-specific PFS curves.

Whilst we accept that this is not straightforward, we hope that the detailed table provided above will provide the ERG and NICE with sufficient confidence that differences in the costs of R, F, and C across REACH, the economic model, and the planned doses, is not large enough to have implications for the cost-effectiveness results.

xiii) Please also clarify whether in the base case analysis the "utilisation of actual doses" (p199) means actual iv dose or adjusted oral dose.

In the base case (and throughout the full analysis) we have used only adjusted oral doses as this is standard of care across the UK. This therefore implies that for FC, the actual IV dose from REACH was converted into the corresponding oral dose prior to use in the model (thereby not truly reflecting an 'actual' dose). In the 1st line CLL submission, Roche provided results on both oral and IV doses which confirms that the incremental costs and benefits of adding rituximab to either mechanism does not result in meaningful changes to the ICER.

B3. The submission describes on p170 the time horizon of the economic model. Please explain why the lifetime time horizon is 25 years, when the previous submission for rituximab as first line treatment assumed 15 years. For relapsed CLL, a shorter rather than longer timeframe might be expected.

We provide below the results of truncation at 15 and 25 years in the relapsed model as well as a recent version of the 1st line model. This model may not correspond directly with the version that NICE retain of

the 1st line model, however, this is for illustrative purposes only as it is not currently being assessed. For a brief explanation, the differences in patients alive at each stage across the two models will be due to the extrapolation of PFS curves as well as the mortality rate assumed in the progressed state. This should however not be the focus of this demonstration.

Table 13. Comparison of 15 v. 25 year truncation in 1st line and relapsed models

	1st line model	Relapsed model
% patients alive at 15 years	2.31%	3.17%
% patients alive at 25 years	1.22%	0.15%
ICER when truncated at 15 years	£13,107	£16,097
ICER when truncated at 25 years	£12,203	£15,593

The NICE reference case requires that models be built to demonstrate *lifetime* costs and benefits and therefore truncation may not be appropriate when a lifetime horizon is undertaken. Sufficient length of time was allowed for the relapsed model to be effectively a lifetime analysis. At the time of model development, it was decided that 3.17% of patients remaining was too much, and therefore the truncation point was extended to 25 years, where effectively all patients had passed. At the time of model development for the 1st line model, the subjective judgement of the modeller allowed for 2.31% of patients still to be alive at time of truncation (15 years). In hindsight, we may have extended the 1st line time horizon out to 30 years to ensure less than 1% of patients were alive when results were truncated.

B4. The submission states on p175 that treatment cycles were given every 28 days but the model uses monthly cycles. Please explain how treatment costs were assigned to the correct month in the model.

By using an adjustment variable entitle 'cyc2mon'. Further detail is provided in Appendix 1. This variable is also described in B2 part v.).

B5. The submission describes on p180 (figure 23) post progression survival. The log rank was non-significant and data considered to be

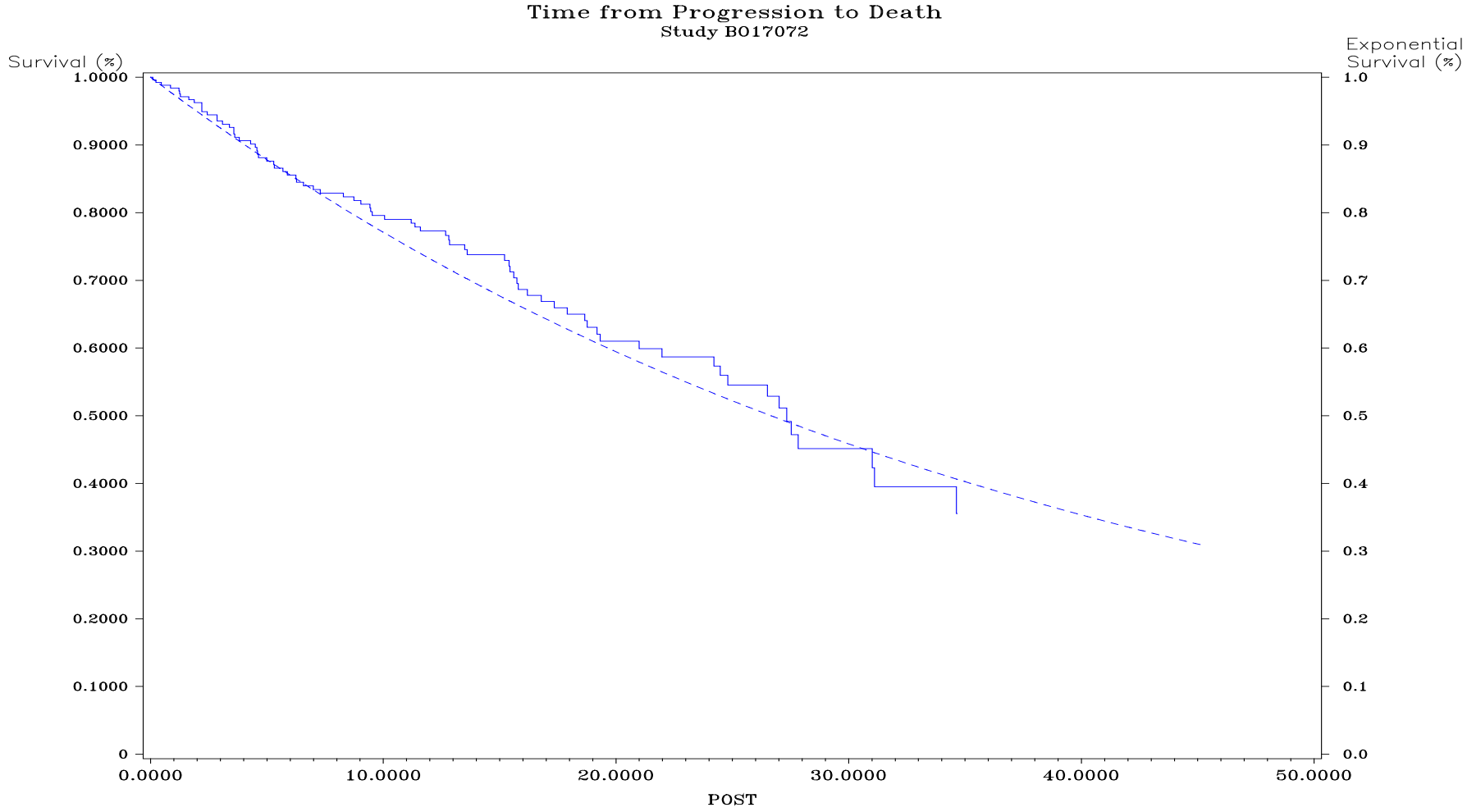
from a single population with assumed exponential distribution. Please provide a Kaplan-Meier (for all patients) with an exponential fit (and scale parameter).

The rationale for this request is due to an error in the text of the original submission on page 180 "*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*.". In fact, the progression to death analysis from which the mortality rates are derived (both using a single population in the base case and by treatment arm in the sensitivity analysis) are based on the log of the progression to death multiplied by time and this logged data is used to arrive at estimates. The KM data is not used in the model to define progression to death rates.

Given that median overall survival has not been reached for both of the 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 modeled as a single population. The log of the progression survival was regressed (linearly) on the time variable with the estimated time probability (slope = -0.2634) serving as the statistic for the single parameter exponential distribution. The slope was then converted into a constant rate of death (= 0.02599) which was then converted to a monthly probability (p = 0.02566) of dying and applied to all progressed patients in the base case analysis. A similar calculation was carried out in the sensitivity analysis by each treatment arm separately.

We have provided below a graphical depiction of these methods. Figure 3 is a composite graph of the non-parametric Kaplan-Meier (KM) and a single parameter exponential whose rate was derived from modeling the log of probability of progression to death versus time for all patients experiencing at least one day of progression using ordinary least squares. As described in the submission and above, progression to death was first analyzed using KM methods stratified by the protocol-defined treatment (R-FC vs. FC) before combining the two arms as a result of the non-significant log-rank.

Figure 3. Time from Progression to Death



Survival curves

B6. Survival curves are described on page p198 of the submission. It would be helpful for the ERG if a single table were constructed defining:

i) the S(t) function for each of the parametric fits shown on page 198

The survival functions for each parametric fit, asides from Gompertz, were taken from the SAS Online Doc Version 8: LIFEREG Procedure – "Supported Distributions".[38] The Gompertz survival function has been succinctly described in materials elsewhere.[39] We have replicated the relevant section in Appendix 3 of this document.

ii) the parameter values corresponding to each fit that was used for the economic model (base case and sensitivity analyses)

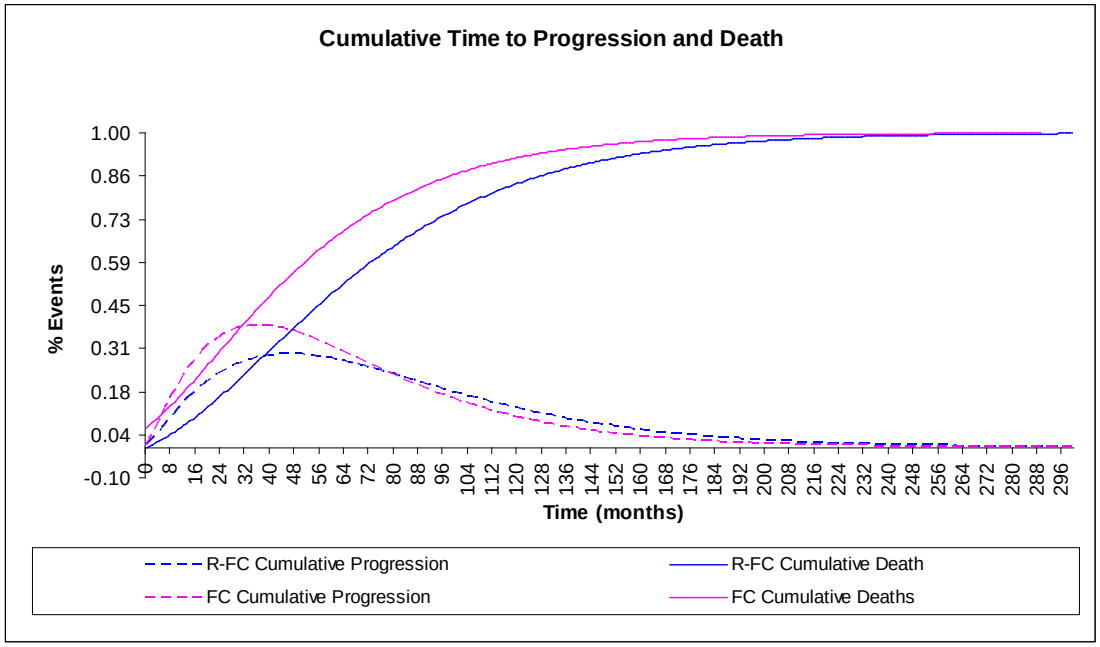
These have all been provided explicitly in Appendix 1.

iii) please also define the time unit to which the parameters apply

The time unit is one month.

B7. The interpretation of figure 26 on p204 of the submission may be confusing. Please plot this figure extended to the life-time of the model (25 years rather than 15 years), and so that the vertical axis starts at 0 and the x axis ticks are only every 8 months.

Figure 4. Figure 26 adjusted:Cumulative time to progression and death for R-FC and FC using REACH trial data



B8. Please provide, if available, a standard survival curve (based on cohort or registry data) for no or standard UK treatment.

We are not aware of a UK cohort or registry where survival data is available for FC or chlorambucil (the two standard UK treatments). There are also no national statistics available for the different stages of CLL or for people treated with different regimens.

In general, for all stages of CLL, on average 44 out of 100 men (44%) and 52 out of 100 women (52%) will live for at least 5 years after being diagnosed but outlook depends largely on disease stage when diagnosed. In the earliest stage (A), survival time is generally 10 years or more. For people diagnosed in the middle stage (B), the survival time is generally from around 5 to 8 years. For people diagnosed in the most advanced stage (C), the survival time is generally around 1 to 3 years. As highlighted in Section 4.1.5 of the submission, it is anticipated that approximately 1/3 of diagnosed CLL patients (usually stage A) will never need any form of treatment for their disease and that they will die with rather than of their disease.

Adverse events

B9. The number of grade 3 and 4 side effects is higher in the R-FC arm (see Table 64, p183). However, the cost of AEs is higher in the FC arm (£554.68) than in the R-FC arm (£504.19). Please clarify these data.

- Number of grade 4 events in R-FC: 222
- Number of grade 4 events in FC: 142
- Number of grade 3 events in R-FC: 511
- Number of grade 3 events in FC: 421

The number of grade 4 events are correct. However, the number of grade 3 events listed above are incorrect. This number reflects the sum total of grade 3 and 4 events.

Table 14. Number of Grade 3 and 4 event in each trial arm of REACH

Number	R-FC	FC
Grade 3 events	289	279
Grade 4 events	222	142
Grade 3+4 events	511	421

The reason the cost of AEs is higher in the FC arm than the R-FC arm is due to the selection of adverse events for which we applied costs. This did not encompass all of the adverse events that occurred. Specifically, a cost was not applied to some adverse events, either due to an assumption of no intervention or where it was assumed that the cost of the intervention required was already captured in the economic modelling (i.e. anemia would require a blood transfusion, and this resource use was already included in the trial and in the model). The list of cost applied to adverse events was provided in Table 71 of the original submission. The adverse events associated with £0 cost are highlighted in the following table (replicating Table 64 of the original submission):

Table 15. Replication of Table 64 from submission. 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

When these highlighted adverse events, assumed to be associated with £0 additional costs, are removed from the list, this results in a new number of AEs provided in the table below:

Table 16. Number of Grade 3 and 4 event in each trial arm of REACH associated with a unit cost in the economic model

Number removing those with no cost	R-FC	FC
Grade 3 events	52	54
Grade 4 events	21	20
Grade 3+4 events	73	74

The associated cost of AEs in each arm (£554.68 for FC and £504.19 for R-FC) was approximately the same due to the nature of this calculation. A brief assessment of the adverse event rates and the costs associated with this suggests that the high cost of pneumonias (assumed to be associated with hospital stay) in the FC arm compared to the R-FC arm (7 more events) was sufficient to result in a slightly higher AE cost for FC patients.

We would however like to stress the low significance of adverse event costs to the ICER due to the small differences in adverse events experience when adding rituximab to chemotherapy. To illustrate this, in a new sensitivity analysis provided in Appendix 2, we arbitrary double the adverse event cost associated with the R-FC arm alone (£1,008.38 compared to the base case (£504.19). The results in a relatively small increase in the ICER from £15,593 to £16,455 per QALY.

B10. Please comment on why, in the sensitivity analysis on p205 of the submission, the adverse events costs are varied by 50%, but the health effects of AEs are not varied.

Health effects were not varied because the base case analysis did not assume any disutility associated with specific adverse events. We chose this route because there were no significant differences in adverse events (see Section 6.7 of the original submission).

Although we admit that this is inconsistent, we chose to provide cost data as it was easily accessible (or easy to approximate) and it was determined that it would be better to provide costs without outcomes, as opposed to providing nothing at all. Collecting meaningful utility decrements across all the adverse events simply wasn't possible, and furthermore, it was not considered that a meaningful difference in adverse events existed across the two arms.

A Q-TWIST analysis was also performed to assess quality of life in the presence of drug-related toxicities. The Q-TWiST endpoint is a natural extension of the Time Without disease Symptoms or treatment Toxicity (TWiST) and an adaptation of the concept of QALYs. TWiST methodology is extended so that periods spent with toxicity or relapse are included in the comparative analysis but are weighted (with utilities) to represent their quality value relative to TWiST. The Q-TWiST analysis

on the REACH study data demonstrated that relapsed or refractory CLL patients receiving R-FC spent less time (mean = 3.45 months) with disease symptoms with no significant increase in treatment toxicity compared with patients who received FC alone. The threshold analysis showed that, whatever the utility weights for toxicity or relapse, the mean Q-TWIST was always greater with R-FC as compared to FC.

B11. Please provide sensitivity analyses that include both the costs and health effects of adverse events.

We have already provided sensitivity analysis regarding costs, including a second analysis where the cost of adverse events in the R-FC arm are arbitrarily doubled to illustrate the low impact these costs have on the ICER. Given the lack of sensitivity of adverse event costs on the ICER, no further analysis will be provided regarding this point.

Here we provide a simple crude analysis using NSCLC adverse event disutility scores.[40] Only 4 adverse events were relevant to CLL. The febrile neutropenia score was therefore used for several serious infection-related adverse events from REACH including: febrile bone marrow aplasia, neutropenic infection, neutropenic sepsis, sepsis, septic shock, and pancytopenia.

Total utility decrements by adverse events and by arm were calculated by summing the number of Grade 3 & 4 events, dividing by the safety population size (269 for R-FC; 268 for FC) and multiplying by the disutility score. These values were then summed for each arm, and the difference in utility value was -0.01187 for the R-FC arm compared to the FC arm.

Table 17. NSCLC adverse event utility scores for sensitivity analysis

Adverse event	Disutility score	Total FC event	Total R-FC event	Total FC utility	Total R-FC utility
Neutropenia	-0.08973	221	253	-0.07399	-0.08439
Febrile Neutropenia	-0.09002	30	34	-0.01008	-0.01138
FEBRILE BONE MARROW APLASIA	*-0.09002*	1	1	-0.00034	-0.00033
NEUTROPENIC INFECTION	*-0.09002*	1	1	-0.00034	-0.00033
NEUTROPENIC SEPSIS	*-0.09002*	5	1	-0.00168	-0.00033
SEPSIS	*-0.09002*	1	3	-0.00034	-0.00100
SEPTIC SHOCK	*-0.09002*	1	1	-0.00034	-0.00033
PANCYTOPENIA	*-0.09002*	6	7	-0.00202	-0.00234
Vomiting	-0.04802	5	6	-0.00090	-0.00107
Diarrhoera	-0.0468	1	3	-0.00017	-0.00052
Total Utility Decrement				**-0.09018**	**-0.10205**
Utility Difference					**-0.01187**

This utility difference was then applied to the base case results (adding the utility score of -0.01187 to the incremental QALYs gained in the model of 0.585). This resulted in a marginal increase to the ICER from £15,593 to £15,916.

Table 18. Results for base case and sensitivity analysis including NSCLC adverse event utility scores

Cost-utility results	Base case	With AE disutility
Mean QALYs	0.585	0.573
Mean Total Cost	£9,128	£9,128
Cost per QALY Gained (£)	£15,593	£15,916

Economic model

B12. On the sheet "Mortality Table UK", the entry in cell J5, named "male2female" is set at 1.6 representing the ratio of males to females. However, it is used in the formulae in cells E6 to E56 as if it were the proportion of males in the population, thus giving an overall death rate that is actually higher than the separate male and female death rates. It would seem that the correct value to use in the formulae in column E is 1.6/2.6. Since background mortality is in practice only used in the later stages of the model, the effect of this error is negligible, as shown in the following table:

Extract from Table 79 (p205) with extra column added

Sensitivity analyses	ICER as claimed	Corrected
Base case (Weibull)	£14,240	£14,236
Gamma function	£13,461	£13,448
Exponential function	£12,007	£11,992
Log logistic function	£13,394	£13,345
Log normal function	£12,122	£12,072
Gompertz function	£15,817	£15,817
Planned dosing including wastage	£15,598	£15,593
Utilities: PFS=0.9; Progressed = 0.5	£11,886	£11,884
Utilities: PFS=0.75; Progressed = 0.65	£15,804	£15,799
Adverse event costs increased by 50%	£14,196	£14,192
Adverse event costs decreased by 50%	£14,283	£14,279

Please confirm that this interpretation is correct.

We confirm that this implementation of this gender-adjustment was incorrect in the model formula, and that the corrected ICERs are

represented in the above table. This change has also been made in the new results provided in Appendix 2.

B13. This model appears to be similar to the model used for the appraisal of rituximab for the first line treatment of chronic lymphoid leukaemia. The ERG for that appraisal highlighted the importance of assumptions about overall survival in the model. There does not appear to be any deterministic sensitivity analysis testing the equivalent assumption in the current submission. Please provide an analysis assuming no overall survival benefit as was done for the previous appraisal.

We did not provide an analysis assuming no overall survival benefit – however, similar to the 1st line CLL appraisal, if this extreme analysis is performed, it results in an ICER of approximately £30-35,000 per QALY. However, the statement above is incorrect as deterministic sensitivity analysis were performed regarding the equivalence assumptions. This was more realistic than simply providing the extreme analysis of no overall survival benefit as it is evidence based (using data from the REACH trial). The final guidance associated with the 1st line CLL treatment with rituximab (TA174 Section 4.3) also suggested that the committee were persuaded by clinical evidence that an overall survival advantage was likely (though it was difficult to quantify).

In the original submission, we had provided two deterministic sensitivity analyses that diverged from the equivalence assumption used in the base case. The description of these two analyses are replicated below:

"Due to the uncertainty associated with the mortality rate post-progression, and the implications this has on overall survival, 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."

It is also worth noting that scenario a) was used as the base model when running the PSA – therefore the probabilistic analysis also takes into account differences in the mortality rates between the R-FC and FC arms (i.e. the assumption of equivalence is absent in the PSA). With reference to the update results provided in Appendix 2, this resulted in the following results:

Sensitivity analyses	**ICER**
Base case (Weibull)	£15,593
Progression to death probability: calculated by arm	£16,138
Progression to death probability: HR=0.874	£19,870

This illustrates that removing the assumption of equivalent mortality rates does increase the ICER, however these results are potentially more realistic than extreme scenario testing that can also be argued to be clinically implausible.

Section C: Additional questions

C1. Please provide a list of abbreviations and definitions used in the submission.

AE	**Adverse Event**
AIC	**Akaike Information Criteria**
AIHA	**Autoimmune Haemolytic Anaemia**
ANC	**Absolute Neutrophil Count**
ASCO	**American Society of Clinical Oncology**
ASH	**American Society of Haematology**
BIC	**Bayesian Information Criteria**
BMT	**Bone Marrow Transplant**s
BNF	**British National Formulary**
BOR	**Best Overall Response**
BCSH	**British Committee for Standards in Haematology**
BT	**Blood Transfusions**
CBC	**Complete Blood Count**
CEAC	**Cost-effectiveness acceptability curve**
CHMP	**Committee for Medical Products for Human Use**
CHOP	**Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone**
CI	**Confidence Interval**
CLL	**Chronic Lymphocytic Leukaemia**
CR	**Complete Response**
CRF	**Case Report Form**
CMML	**Chronic Myelomonocytic Leukaemia**
CSR	**Clinical Study Report**
CT	**Computed Tomography**

CVAD	**Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone**
CVP	**Cyclophosphamide, Vincristine, Prednisolone**
DFS	**Disease Free survival**
DOR	**Duration of Response**
DSMB	**Drug Safety Monitoring Board**
DSU	**Decision Support Unit**
ECOG	**Eastern Cooperative Oncology Group**
EFS	**Event Free Survival**
EMEA	**European Medicines Agency**
ESMO	**European Society for Medical Oncology**
ETR	**End of Treatment Response**
F	**Fludarabine**
FACIT	**Functional Assessment of Chronic Illness Therapy**
FACT-G	**Functional Assessment of Cancer Therapy – General**
FAS	**Full Analysis Set**
FC	**Fludarabine, Cyclophosphamide**
FCM	**Fludarabine, Cyclophosphamide, Mitoxantrone**
FISH	**Fluorescence In Situ Hybridisation**
FU	**Follow-up**
GAD	**Government Actuary's Department**
GMCSF	**Granulocyte-macrophage Colony-stimulating Factor**
HCHS	**Hospital and Community Health Services**
HDMP	**High-dose Methylprednisolone**
HR	**Hazard Ratio**
HRG	**Healthcare Resource Groups**
HR-QoL	**Health-related Quality of LIfe**

ICER	**Incremental cost effectiveness ratio**
IgVH	**Immunoglobulin Heavy Chain Variable Region**
IRC	**Independent Review Committee**
ITT	**Intent-to-Treat population**
IV	**Intravenous**
LDH	**Lactate dehydrogenase**
MCL	**Mantle Cell Lymphoma**
MDACC	**MD Anderson Cancer Centre**
MDS	**Myelodysplastic Syndrome**
MRD	**Minimal Residual Disease**
MSD	**Mean Squared Deviations**
NCCN	**National Comprehensive Cancer Network**
NCI-CTC	**National Cancer Institute Common Toxicity Criteria**
NCI-WG	**National Cancer Institute Working Group**
NHL	**Non-Hodgkin Lymphoma**
NHS	**National Health Service**
NICE	**National Institute of Health and Clinical Excellence**
nPR	**Nodular Partial Response**
ORR	**Overall Response Rate**
OS	**Overall Survival**
PbR	**Payment by Results**
PBSCT	**Peripheral Blood Stem Cell Transplant**
PD	**Progressed Diseased**
PFS	**Progression Free Survival**
PH	**Proportional Hazards**
PK	**Pharmakokinetic**
PLL	**Prolymphocytic Leukaemia**

PPS	**Per Protocol Set**
PR	**Partial Response**
PS	**Performance Status**
PSA	**Probabilistic Sensitivity Analysis**
PSSRU	**Personal Social Services Research Unit**
QALY	**Quality adjusted life year**
QoL	**Quality of Life**
Q-TWiST	**Quality adjusted Time Without Symptoms of disease or Toxicity of treatment**
RCT	**Randomised Controlled Trial**
RS	**Richter's Syndrome**
RT	**Richter's Transformation**
SAE	**Serious Adverse Event**
SAP	**Safety Analysis Population**
SD	**Stable Disease**
SLL	**Small Lymphocytic Leukaemia**
SmPC	**Summary of Product Characteristics**
SOC	**System Organ Class**
TNF	**Tumour Necrosis Factor**
Tp	**Transition Probability**
TLS	**Tumour Lysis Syndrome**
UK	**United Kingdom**
ULN	**Upper Limit of Normal**

C2. Please give a breakdown of how the figure of £10,923 was calculated for the budget impact (p213).

The cost is based on the sum of rituximab cost and IV administration costs.

Rituximab cost is based on 700 mg/m2 (cycle 1) and 900 mg/m2 (cycle 2-6), which reflects the REACH dose (as described in question B2 part iii).) adjusted for wastage. Using BNF list price, this equates to £9,081. This was described in section 8.5 of the original submission. If we had excluded wastage, the cost would be £9054.66 – corresponding to the REACH dose described in the first column of the table provided in response to question B2.

The administration cost for rituximab was assumed to be £307 per administration, thus £1,842 over 6 administrations. This was described in section 8.6 of the original submission. It was also explained here that this deviated from the methodology in the cost-effectiveness analysis as it overestimated the administration cost associated with adding rituximab to chemotherapy. In reality, the additional cost incurred will be the difference between £307 and the standard administration cost incurred by the chemotherapy combination (in the cost-effectiveness analysis, the cost of oral chemotherapy was £201 - Deliver exclusively Oral Chemotherapy (HRG Code SB11Z)) thereby resulting in an incremental cost increase of £106 when adding rituximab administration to standard oral chemotherapy in CLL).

Therefore the total cost of £10,923 is the sum of rituximab cost (£9,081) and IV administration £1,842.

C3. Please provide PDFs (where available) or hardcopies of all the references listed in the report (please also indicate where, if any, copyright legalities apply).

See A1 above.

Appendix 1: Table of model variables and descriptions

Name	Base value	Range	Function	Reference
Age	63	NA	Starting age to determine age-specific background mortality	REACH
Alpha_1	*Not used in this version of the model*			
Alpha_2	*Not used in this version of the model*			
Bc	0.072371746	NA	One of 6 parameters that make up the Generalized Gamma function.	SAS version 8.2 Procedure Lifereg and Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995
Bmt_com	£756.02	£629.74 to £1000.84 varied by beta pert	Bone marrow transplants applied to FC arm in PFS health state. Unit cost x Resource use.	REACH; National Reference Costs 2007/08
Bmt_new	£564.91	£470.55 to £747.84 varied by beta pert	Bone marrow transplants applied to R-FC arm in PFS health state. Unit cost x Resource use.	REACH; National Reference Costs 2007/08
Bn	0.053136423	NA	One of 6 parameters that make up the Generalized Gamma function.	SAS version 8.2 Procedure Lifereg and Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995
Bsa_new	1.8636	NA	Body surface area in m2 to determine R, F, C doses	REACH
Bt_com	£497.56	£298.53 to £696.58 varied by beta pert	Blood transfusions applied to FC arm in PFS health state. Unit cost x Resource use	REACH; National Reference Costs 2007/08

Bt_new	£365.74	£219.45 to £512.04 varied by beta pert	Blood transfusions applied to R-FC arm in PFS health state. Unit cost x Resource use	REACH; National Reference Costs 2007/08
C_adm_new	£123.92	£86.96 to £154.36 varied by beta pert	Cost of administering rituximab in cycles 2-6: Incremental administration + pharmacy costs	National Reference Costs 2007/08; PSSRU 2008, Expert opinion
C_adm_new0	£123.92	£86.96 to £154.36 varied by beta pert	Cost of administering rituximab in cycles 1: Incremental administration + pharmacy costs above FC.	National Reference Costs 2007/08; PSSRU 2008, Expert opinion
C_adm_std	£160.34	£126.64 to £198.93 varied by beta pert	Cost of administering fludarabine in cycles 2-6: Administration + clinician consultation + pharmacy costs (half cost, shared with cyclophosphamide)	National Reference Costs 2007/08; PSSRU 2008, Expert opinion
C_adm_std0	£160.34	£126.64 to £198.93 varied by beta pert	Cost of administering fludarabine in cycles 1: Administration + clinician consultation + pharmacy costs (half cost, shared with cyclophosphamide)	National Reference Costs 2007/08; PSSRU 2008, Expert opinion
C_adm_std2	£160.34	£126.64 to £198.93 varied by beta pert	Cost of administering cyclophosphamide in cycles 2-6: Administration + clinician consultation + pharmacy costs (half cost, shared with fludarabine)	National Reference Costs 2007/08; PSSRU 2008, Expert opinion
C_adm_std20	£160.34	£126.64 to £198.93 varied by beta pert	Cost of administering cyclophosphamide in cycles 1: Administration + clinician consultation + pharmacy costs (half cost, shared with fludarabine)	National Reference Costs 2007/08; PSSRU 2008, Expert opinion
C_ae_come	£554.68	£443.74 to £665.61 varied by beta pert	Cost of adverse events = unit cost of selected adverse events x observed event rate in FC arm	REACH; BNF 57; Expert opinion, other references provided in original submission
C_ae_new	£504.19	£403.35 to £605.03 varied by beta pert	Cost of adverse events = unit cost of selected adverse events x observed event rate in R-FC arm	REACH; BNF 57; Expert opinion, other references provided in original submission

C_comtrt	£485.26	£422.57 to £485.26 depending on scenario	Drug cost/month for fludarabine in FC arm. Changes based on planned/actual dose and excluding/including wastage status. Base case: planned dose including wastage.	CLL-4 for oral planned dose and conversion rate oral/IV; BNF 57; REACH for actual dose for FC arm
C_comtrt2	£3.91	£3.47 to £3.91 depending on scenario	Drug cost/month for cyclophosphamide in FC arm. Changes based on planned/actual dose and excluding/including wastage status. Base case: planned dose including wastage.	CLL-4 for oral planned dose and conversion rate oral/IV; BNF 57; REACH for actual dose for FC arm
C_comtrt3	*Not used in this version of the model*			
C_newtrt	£1328.81	£1326.60 to £1328.81 depending on scenario	Cost of rituximab in month 1. Changes based on excluding/including wastage status. Base case: including wastage.	REACH; BNF 57.
C_newtrt1	£1898.32	£1640.52 to £1898.32 depending on scenario	Cost of rituximab in months 2-6. Changes based on planned/actual dose and excluding/including wastage status. Base case: planned dose including wastage.	REACH; BNF 57.
C_pfs	£28.67	£14.33 to £43	Monthly supportive care cost in PFS state. Assumed one consultation every three months.	National Reference Costs 2007/08.
C_progdrugs	£101.60	£71.12 to £132.07 varied by beta pert	Monthly cost of post-progression treatments collected alongside REACH trial. Only includes drugs used in at at least 5% of patients in either arm. Same cost applied to both R-FC and FC progressed state.	REACH; expert opinion on dose level; BNF 57
C_stdtrt	£485.26	£420.83 to £485.26 depending on scenario	Drug cost/month for fludarabine in R-FC arm. Changes based on planned/actual excluding/including wastage status. Base case: planned dose including wastage.	CLL-4 for oral planned dose and conversion rate oral/IV; BNF 57; REACH for actual dose for R-FC arm

C_stdtrt2	£3.91	£3.45 to £3.91 depending on scenario	Drug cost/month for cyclophosphamide in R-FC arm. Changes based on planned/actual dose and excluding/including wastage status. Base case: planned dose including wastage.	CLL-4 for oral planned dose and conversion rate oral/IV; BNF 57; REACH for actual dose for R-FC arm
Comname	"Fludarabine / Cyclophosphamide Alone"		Allows for text appropriate to UK setting	NA
Comname2	*Not used in this version of the model*			
Cost375	£174.63	NA	List price for 100mg rituximab	BNF 57
Cost500	£873.15	NA	List price for 500mg rituximab	BNF 57
Costmg100	£1.75	NA	Unit price per mg of rituximab, based on 100mg vial	BNF 57
Costmg500	£1.75	NA	Unit price per mg of rituximab, based on 500mg vial	BNF 57
Cox	0	0 or 1	1 allows the function of using the cox-model generated hazard ratio (1.14) for the rate of death in the progressed state between FC and R-FC arms. P_dth == 2 in order for this to work.	REACH analysis
cProg	£187.60	£93.80 to £218.39	Monthly supportive care cost in Progressed state. Assumed one consultation per month + c_progdrugs.	National Reference Costs 2007/08.
Currency	"£"	NA	Allows for text appropriate to UK setting	NA
Cyc2mon	1.08705	NA	Number of 28 days cycles per month	NA
Cyclen	28	NA	Cycle length = 28 days	NA

D	0.755785 66	NA	One of 6 parameters that make up the Generalized Gamma function.	SAS version 8.2 Procedure Lifereg and Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995
Day2mon	30.4375	NA	Number of days per month	NA
Disc_c	0.0029	NA	Monthly discount rate (3.5% annual)	NICE Guide to Methods
Disc_u	0.0029	NA	Monthly discount rate (3.5% annual)	NICE Guide to Methods
Distn	1	1 to 7	Selects parametric distribution for PFS curve: choices are Weibull (base case), exponential, gamma, gompertz, log normal, log logistic, kaplan meier	NA
Dose	1	1 to 4	Select dose: choices are planned with wastage (base case), planned excluding wastage, actual with wastage, actual excluding wastage	NA
Dthrate	0.025661	Varied by normal distribution with SE	Constant probability of death across both arms in the progressed state	REACH analysis
Dthrate_fc	0.026761	Varied by normal distribution with SE	Constant probability of death in the progressed state in FC arm (sensitivity analysis; also used in PSA presented)	REACH analysis
Dthrate_fcr	0.027584	Varied by normal distribution with SE	Constant probability of death in the progressed state in R-FC arm (sensitivity analysis; also used in PSA presented)	REACH analysis
Fcmat_e	Variance covariance matrix for Exponential PFS curve		Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data.	REACH analysis

Fcmat_ga	Variance covariance matrix for Gamma PFS curve	Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data. .	REACH analysis
Fcmat_go	Variance covariance matrix for Gompertz PFS curve	Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data. .	REACH analysis
Fcmat_ll	Variance covariance matrix for Log Logistic PFS curve	Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data. .	REACH analysis
Fcmat_ln	Variance covariance matrix for Log normal PFS curve	Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data. .	REACH analysis
FCmat_w	Variance covariance matrix for Weibull PFS curve	Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data. .	REACH analysis
Fcr_chl	*Not used in this version of the model*		
Fpest_e	Parametric estimates full data for Exponential PFS curve	Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Fpest_ga	Parametric estimates full data for Gamma PFS curve	Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis

Fpest_go	Parametric estimates full data for Gompertz PFS curve		Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Fpest_ll	Parametric estimates full data for Log Logistic PFS curve		Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Fpest_ln	Parametric estimates full data for Log normal PFS curve		Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Fpest_w	Parametric estimates full data for Weibull PFS curve		Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ful_mfu	*Not used in this version of the model*			
G	1.050071891	NA	One of 6 parameters that make up the Generalized Gamma function.	SAS version 8.2 Procedure Lifereg and Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995
Gamma	*Not used in this version of the model*			
Gd	0.793629277	NA	One of 6 parameters that make up the Generalized Gamma function.	SAS version 8.2 Procedure Lifereg and Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995

Hr	*Not used in this version of the model*			
Hr_fcr_chl	*Not used in this version of the model*			
Hr_rfc	*Not used in this version of the model*			
K	1.750663612	NA	One of 6 parameters that make up the Generalized Gamma function.	SAS version 8.2 Procedure Lifereg and Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995
Lcl	*Not used in this version of the model*			
Male2female	1.6	NA	Ratio of Male to Female incidence of CLL	Watson 2008
Maxcycle	6	NA	Maximum number of cycles of rituximab	REACH
Maxcycle2	*Not used in this version of the model*			
Mcmat_e	*Not used in this version of the model*			
Mcmat_ga	*Not used in this version of the model*			
Mcmat_go	*Not used in this version of the model*			
Mcmat_ll	*Not used in this version of the model*			
Mcmat_ln	*Not used in this version of the model*			
Mcmat_w	*Not used in this version of the model*			
Moadm_new_com	0	NA	Average number of administration months for rituximab in the FC arm	REACH

Moadm_new_new	4.87	NA	Average number of administration months for rituximab in the R-FC arm	REACH
Moadm_std_com	4.52	NA	Average number of administration months for fludarabine in the FC arm	REACH
Moadm_std_new	4.80	NA	Average number of administration months for fludarabine in the R-FC arm	REACH
Moadm_std2_com	4.52	NA	Average number of administration months for cyclophosphamide in the FC arm	REACH
Moadm_std2_new	4.80	NA	Average number of administration months for cyclophosphamide in the R-FC arm	REACH
Mpest_e	*Not used in this version of the model*			
Mpest_ga	*Not used in this version of the model*			
Mpest_go	*Not used in this version of the model*			
Mpest_ll	*Not used in this version of the model*			
Mpest_ln	*Not used in this version of the model*			
Mpest_w	*Not used in this version of the model*			
Mu	0.025996	NA	Constant rate of death across both arms in the progressed state	REACH analysis
N_com	276	NA	Number of patients in FC arm in trial (ITT population)	REACH

N_new	276	NA	Number of patients in R-FC arm in trial (ITT population)	REACH
Newname	“Rituximab + Fludarabine / Cyclophosphamide”		Allows for text appropriate to UK setting	NA
Newname2	“Parametric Distribution”		Allows for text appropriate to UK setting	NA
Nr_simulate	1000	0 -10000	Desired Nr. of Iterations for the Monte Carlo Simulation. This is changed by selecting the Run PSA option in the Model dropdown menu.	NA
Ofcmat_e	Variance covariance matrix for Exponential OS curve		Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofcmat_ga	Variance covariance matrix for Gamma OS curve		Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofcmat_go	Variance covariance matrix for Gompertz OS curve		Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofcmat_ll	Variance covariance matrix for Log Logistic OS curve		Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofcmat_ln	Variance covariance matrix for Log normal OS curve		Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data.	REACH analysis

Ofcmat_w	Variance covariance matrix for Weibull OS curve	Is the named reference of the var-covariance matrix used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofpest_e	Parametric estimates full data for Exponential OS curve	Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofpest_ga	Parametric estimates full data for Gamma OS curve	Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofpest_go	Parametric estimates full data for Gompertz OS curve	Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofpest_ll	Parametric estimates full data for Log Logistic OS curve	Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofpest_ln	Parametric estimates full data for Log normal OS curve	Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis
Ofpest_w	Parametric estimates full data for Weibull OS curve	Is the named reference of the matrix of parameter estimates (e.g. Intercept, treatment effect, shape parameter, etc.) used by the model when running PSA on the ITT untruncated data.	REACH analysis

Ogce	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Ogcga	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
ogcl	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Ogcn	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Ogcw	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Ogne	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Ognga	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Ognl	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Ognn	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Ognw	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Olce	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Olcga	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Olcl	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Olcn	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Olcw	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Olne	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Olnga	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*

Olnl	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Olnn	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Olnw	*Placeholder for overall survival parameter not used in this model. Overall Survival is not modelled parametrically.*
Omcmat_e	*Not used in this version of the model*
Omcmat_ga	*Not used in this version of the model*
Omcmat_go	*Not used in this version of the model*
Omcmat_ll	*Not used in this version of the model*
Omcmat_ln	*Not used in this version of the model*
Omcmat_w	*Not used in this version of the model*
Ompest_e	*Not used in this version of the model*
Ompest_ga	*Not used in this version of the model*
Ompest_go	*Not used in this version of the model*
Ompest_ll	*Not used in this version of the model*
Ompest_ln	*Not used in this version of the model*
Ompest_w	*Not used in this version of the model*

P_dth	1	1 or 2	Single versus Treatment specific Monthly Probability of Death in the progressed state. 1 = Combined probability, 2 = Treatment Specific probabilities	NA
Pbc	Pbc is the probabilistic version of the variable "bc" described above. Its value changes randomly for every PSA iteration. The range of this parameter is restricted to uncertainty seen in the var-covariance matrix when PSA.		One of 6 probabilistic parameters that make up the Generalized Gamma function. This parameter is derived from the Intercept and treatment effect parameters and the var-covariance matrix obtained from the analysis of the PFS data under the assumption of a gamma function.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995; Andrew Briggs, Karl Claxton, Mark Sculpher, Decision modelling for health economic evaluation, Oxford Unversity Press (2006)
Pbn	Pbn is the probabilistic version of the variable "bn" described above. Its value changes randomly for every PSA iteration		One of 6 probabilistic parameters that make up the Generalized Gamma function. This parameter is derived from the intercept parameter and the var-covariance matrix obtained from the analysis of the PFS data under the assumption of a gamma function. The range of this parameter is restricted to uncertainty seen in the var-covariance matrix when PSA.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995; Andrew Briggs, Karl Claxton, Mark Sculpher, Decision modelling for health economic evaluation, Oxford Unversity Press (2006)
Pc_pfs	£28.67	£20.07 to £37.27 varied by beta distribution	Cost of supportive care cost in the PFS health state. C_pfs +/-30%.	See variable c_pfs
Pc_prog	£28.67	£131.32 to £243.87 varied by beta distribution	Cost of supportive care cost in the PFS health state. cProg +/-30%.	See variable cProg

Pd	Pd is the probabilistic version of the variable “d” described above. Its value changes randomly for every PSA iteration. The range of this parameter is restricted to uncertainty seen in the var-covariance matrix when PSA.		One of 6 probabilistic parameters that make up the Generalized Gamma function. This parameter is derived from the shape parameter and the var-covariance matrix obtained from the analysis of the PFS data under the assumption of a gamma function.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995; Andrew Briggs, Karl Claxton, Mark Sculpher, Decision modelling for health economic evaluation, Oxford Unversity Press (2006)
Pdcga	0.793629277	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pdcga is the PFS delta parameter of the gamma function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pdnga	0.793629277	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pdnga is the PFS delta parameter of the gamma function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pfsdth_com	0.004741	NA	Monthly death rate in FC arm	REACH
Pfsdth_new	0.004721	NA	Monthly death rate in R-FC arm	REACH

Pgce	1	NA	The gamma parameter of the PFS exponential function for the comparator arm. This value is always 1	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pgcga	1.750663612	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgcga is the PFS gamma parameter of the gamma function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pgcgo	0.009632453	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgcgo is the PFS gamma parameter of the gompertz function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pgcl	1.439731176	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgcl is the PFS gamma parameter of the log logistic function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;

Pgcn	1.26999224	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgcn is the PFS gamma parameter of the log normal function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pgcw	1.168851232	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgcw is the PFS gamma parameter of the weibull function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pgd	Pgd is the probabilistic version of the product of the variables "g" and "d" described above. Its value changes randomly for every PSA iteration The range of this parameter is restricted to uncertainty seen in the var-covariance matrix when PSA.		Two of 6 probabilistic parameters that make up the Generalized Gamma function. This parameter is derived from the shape and scale parameters and the var-covariance matrix obtained from the analysis of the PFS data under the assumption of a gamma function.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995; Andrew Briggs, Karl Claxton, Mark Sculpher, Decision modelling for health economic evaluation, Oxford Unversity Press (2006)
Pgne	1	NA	The gamma parameter of the PFS exponential function for the new therapy arm. This value is always 1	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;

Pgnga	1.750663612	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgnga is the PFS gamma parameter of the gamma function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pgngo	0.009632453	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgngo is the PFS gamma parameter of the gompertz function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pgnl	1.439731176	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgnl is the PFS gamma parameter of the log logistic function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Pgnn	1.26999224	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgnn is the PFS gamma parameter of the log normal function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;

Pgnw	1.168851232	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Pgnw is the PFS gamma parameter of the weibull function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Phr	*Placeholder for ITC hazard ratio. Not used in this model.*			
Pk	Pk is the probabilistic version of the product of the variable "k" described above. Its value changes randomly for every PSA iteration. The range of this parameter is restricted to uncertainty seen in the var-covariance matrix when PSA.		One of 6 probabilistic parameters that make up the Generalized Gamma function. This parameter is derived from the shape (1/shape^2) parameter and the var-covariance matrix obtained from the analysis of the PFS data under the assumption of a gamma function.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995; Andrew Briggs, Karl Claxton, Mark Sculpher, Decision modelling for health economic evaluation, Oxford Unversity Press (2006)
Plce	0.032648063	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plce is the PFS lambda parameter of the exponential function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;

Plcga	0.535570302	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plcga is the PFS lambda parameter of the gamma function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Plcgo	-0.028526053	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plcgo is the PFS lambda parameter of the gompertz function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Plcl	0.012562418	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plcl is the PFS lambda parameter of the log logistic function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Plcn	3.033729 45	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plcn is the PFS lambda parameter of the log normal function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;

Plcw	0.019089139	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plcw is the PFS lambda parameter of the log normal function for the comparator arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Plne	0.021538853	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plne is the PFS lambda parameter of the exponential function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Plnga	0.093024002	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plnga is the PFS lambda parameter of the gamma function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Plngo	-0.018423665	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plngo is the PFS lambda parameter of the gompertz function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;

Plnl	0.007234917	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plnl is the PFS lambda parameter of the log logistic function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Plnn	3.43910477	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plnn is the PFS lambda parameter of the log normal function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Plnw	0.012247453	The range of this parameter when running PSA is restricted to the degree of uncertainty seen in the var-covariance matrix.	Plnw is the PFS lambda parameter of the weibull function for the new therapy arm.	SAS version 8.2 Procedure Lifereg; Allison, Paul, D, Survival Analysis Using the SAS System, A Practical Guide, Gary, NC: SAS Institute Inc. 1995;
Prob_est	0.025661138	0.025100698 – 0.02689073569.	Probabilistic constant probability of death in the progressed state across both arms	REACH analysis
Psa	0	0 or 1	Also PSA functionality to turn on or off	NA
Psa_sw	FALSE	FALSE or TRUE	Corresponds to ‘Psa’ variable	NA
Psa1	0	0 or 1	Also PSA functionality to turn on or off	NA
Psa1_sw	FALSE	FALSE or TRUE	Corresponds to ‘Psa1’ variable	NA

Pu_pfs	0.8	0.76 – 0.84	Probabilistic value for PFS utility	See variable 'U_pfs'
Pu_prog	0.6	0.545 – 0.649	Probabilistic value for Progressed utility	See variable 'U_prog'
S_com	268	NA	Number of patients in trial that received FC (safety population)	REACH
S_new	269	NA	Number of patients in trial that received R-FC (safety population)	REACH
Study	"Study ML17072 in CLL"		Allows for text appropriate to UK setting	NA
T_horizon	25	Any value with max of 25	Years in time horizon	NA
U_pfs	0.8	0.75 to 0.9	Utility value for PFS state	Hancock 2002
U_prog	0.6	0.5 to 0.65	Utility value for Progressed state	Hancock 2002
Ucl	*Not used in this version of the model*			
VAR	*Not used in this version of the model*			
wtp	£30,000	NA	Willingness to pay Threshold	Assumption

Appendix 2: New cost-effectiveness results

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

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

Base case results

Costs

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

Table 19: Total average per-patient cost for the two compared treatment groups over a lifetime period (deterministic analysis) using REACH trial data

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

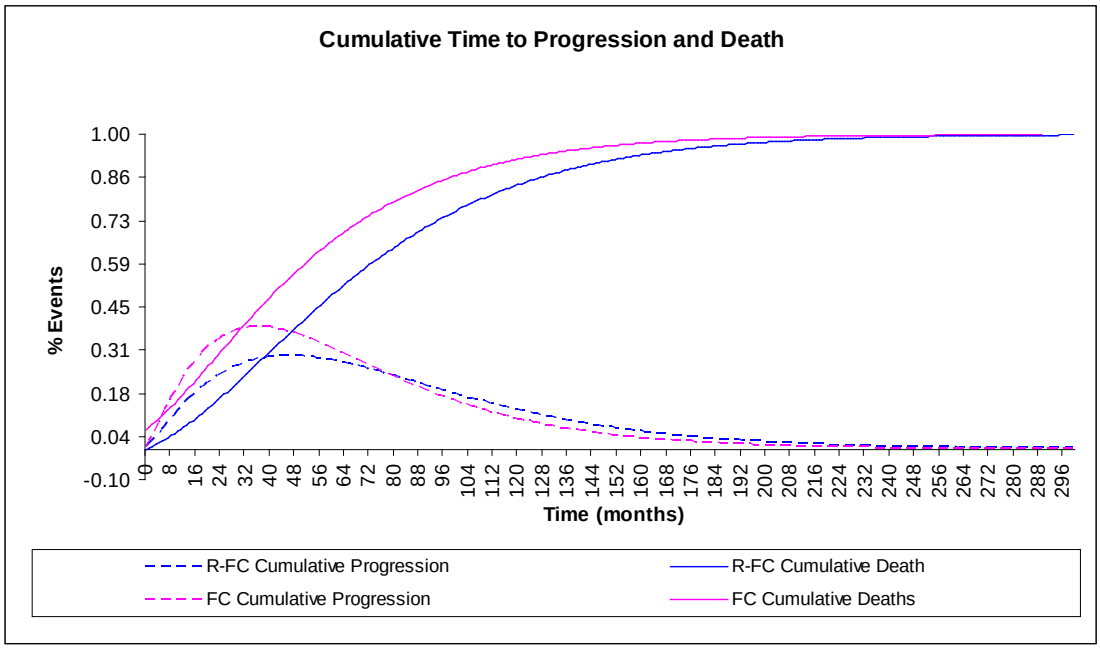
Life Years and Quality-Adjusted Life Years

Table 20 shows that the combination of rituximab plus fludarabine and cyclophosphamide results in a mean gain of 0.671 life years and 0.585 quality-adjusted life years (QALYs) when compared to Fludarabine and Cyclophosphamide alone over the analyzed lifetime period. This finding is related to a QALY gain due to a longer stay in the health state of progression-free survival (PFS) for the patients assigned R-FC than that observed for patients assigned FC alone. This is further illustrated in Figure 5 where patients in the FC arm progress quicker and have a shorter time to death than R-FC patients.

Table 20: Total mean QALYs per patient for the two compared treatment groups over a lifetime period (deterministic analysis) using REACH trial data

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

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



Incremental Cost-Utility Ratio

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

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

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

Sensitivity analyses

Overview of one-way sensitivity analysis results

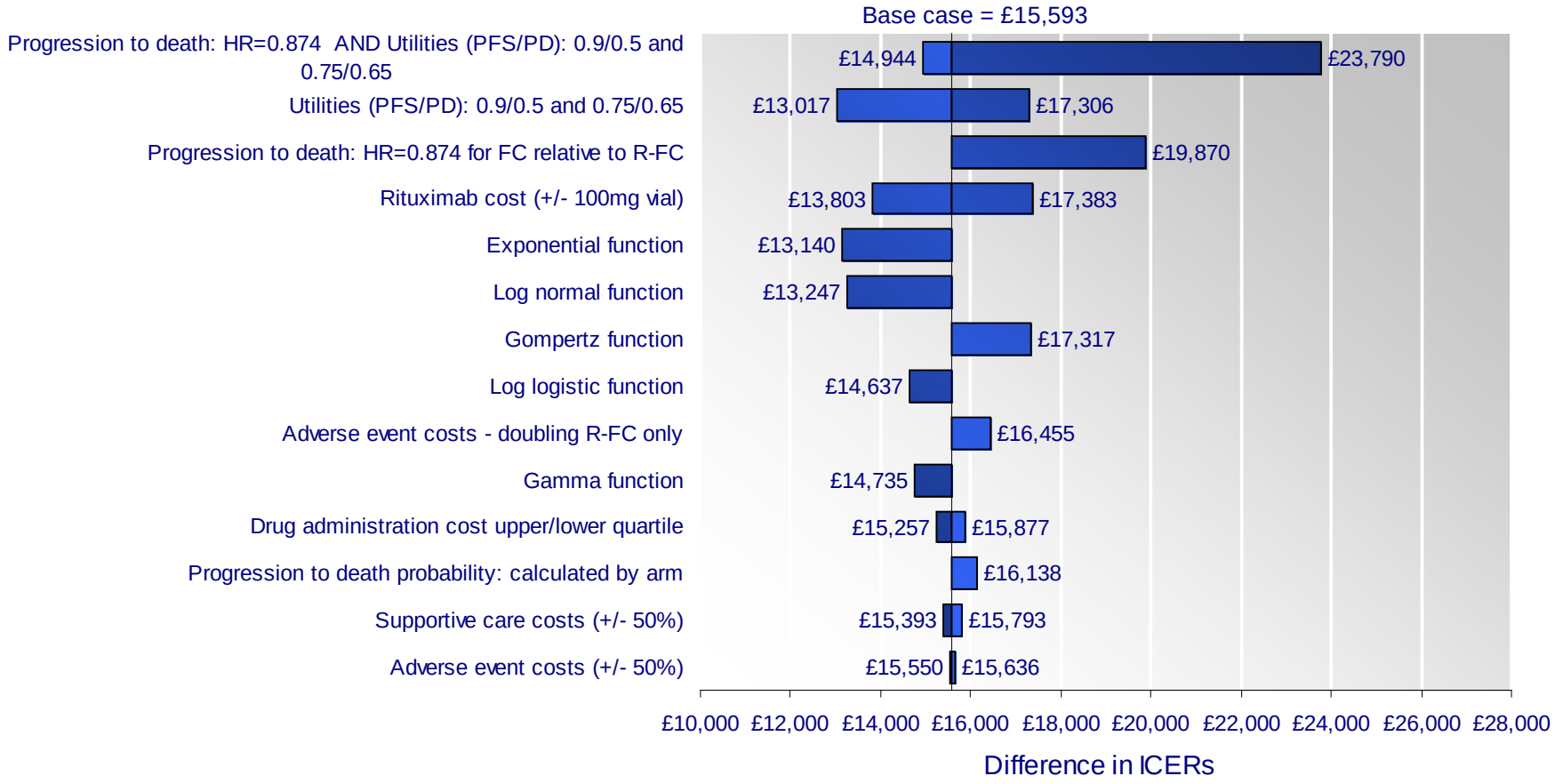
The following table provides the incremental cost-effectiveness results for a selection of one-way sensitivity analyses for the comparison of R-FC versus FC.

Table 22. One-way sensitivity analyses: R-FC versus FC

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

* PSA results are also based on this scenario

Figure 6: Tornado diagram of one-way sensitivity analyses: R-FC v. FC



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

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

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

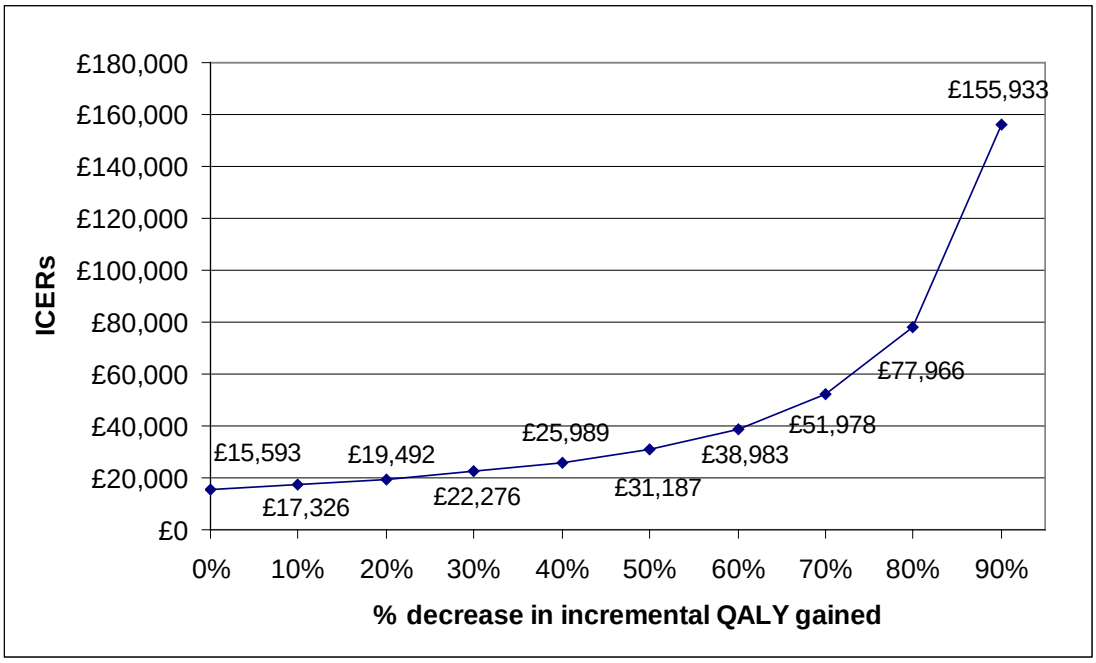
The results from the Phase II trials (section 6.8) describe the assessment of efficacy and tolerability of other rituximab combination chemotherapy. This included R-CHOP (34 patients), R-PC (rituximab, pentostatin and cyclophosphamide – 17 patients) and R-FCM (R-FC and mitoxantrone – 52 patients). The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

Without a comparator arm to represent baseline risk, it would not be possible to perform a reliable and comprehensive cost-effectiveness analysis of these alternative rituximab based combinations. However, in order to assess the potential differences in cost-effectiveness when utilising alternative background chemotherapies with rituximab compared to FC, scenario and threshold analysis may be informative for the purposes of decision making.

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

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

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



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

R-CHOP is a potential option for patients refractory to fludarabine. In Section 6.8.4.1 of the original submission, a simple comparison of the overall response rates among fludarabine-refractory patients from the phase II R-CHOP study was compared to CHOP patients from unpublished follow-up data from the phase III CLL-4 study. The comparison confirmed that the overall response rates (and subsequently the potential duration of progression-free and overall survival) may be improved for R-CHOP treated fludarabine-refractory patients. The absolute magnitude of the improvement of efficacy cannot be measured in a manner suitable for the economic evaluation, however from the threshold analysis we can be certain that the incremental QALYs associated with this comparison could be half that observed for R-FC versus FC and still remain cost-effective.

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

observational data from Badoux et al confirms that the incremental QALYs is likely identical for a rituximab re-treated relapsed CLL population, resulting in a highly cost-effective ICER.

Probabilistic Sensitivity Analyses (PSA)

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

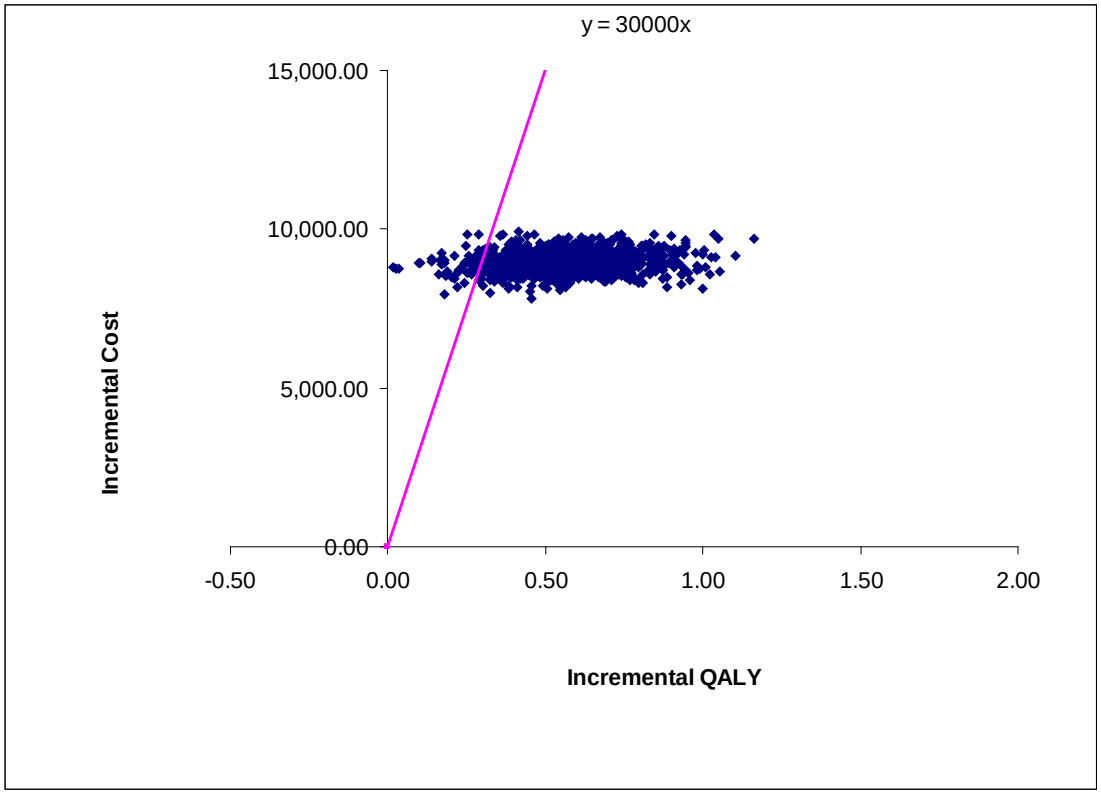
Table 23. Mean Cost Effectiveness results for R-FC versus FC (1000 runs)

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

Scatter plots

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

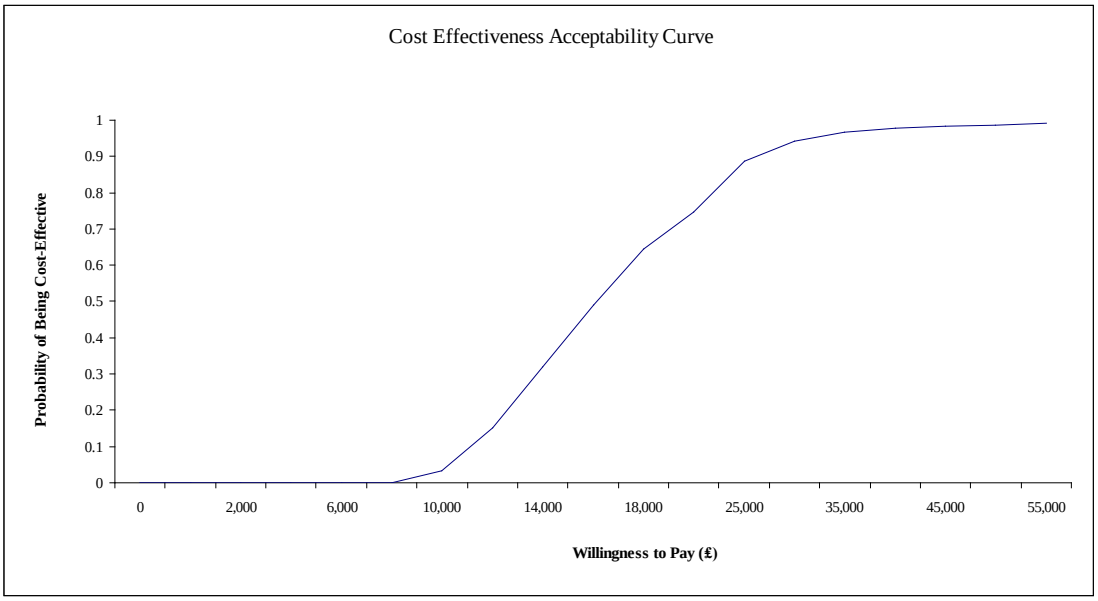
Figure 8: Scatter plot of cost per QALY for R-FC vs. FC (example:1,000 Monte Carlo simulations)



Cost-effectiveness acceptability curve (CEAC)

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

Figure 9: Cost-effectiveness acceptability curve of R-FC vs. FC (example: 1,000 Monte Carlo simulations)



Appendix 3: Survival analysis distributions described

Source 1: SAS Online Doc Version 8: LIFEREG Procedure

For each distribution, the baseline survival distribution function (*S*) and the probability density function(*f*) are listed for the additive random disturbance. These distributions apply when the log of the response is modeled (this is the default analysis). The corresponding survival distribution function (*G*) and its density function (*g*) are given for the untransformed baseline distribution. For example, for the WEIBULL distribution, *S*(*w*) and *f*(*w*) are the baseline survival distribution function and the probability density function for the extreme value distribution (the log of the response) while *G*(*t*) and *g*(*t*) are the survival distribution function and probability distribution function of a Weibull distribution (using the untransformed response).

The chosen baseline functions define the meaning of the intercept, scale, and shape parameters. Only the gamma distribution has a free shape parameter in the following parameterizations. Notice that some of the distributions do not have mean zero and that σ is not, in general, the standard deviation of the baseline distribution.

Additionally, it is worth mentioning that, for the Weibull distribution, the accelerated failure time model is also a proportional-hazards model. However, the parameterization for the covariates differs by a multiple of the scale parameter from the parameterization commonly used for the proportional hazards model.

The distributions supported in the LIFEREG procedure follow. μ = Intercept and σ = Scale in the output.

Exponential

$$
\begin{aligned}
S(w) &= \exp(-\exp(w-\mu)) \\
f(w) &= \exp(w-\mu)\exp(-\exp(w-\mu)) \\
G(t) &= \exp(-\alpha t) \\
g(t) &= \alpha \exp(-\alpha t)
\end{aligned}
$$

where $\exp(-\mu) = \alpha$.

Generalized Gamma

(with $\mu = 0$, $\sigma = 1$)

$$S(w) = \begin{cases} \frac{\Gamma\left(\delta^{-2}, \delta^{-2}\exp(\delta w)\right)}{\Gamma(\delta^{-2})} & \text{if } \delta > 0 \\ 1 - \frac{\Gamma\left(\delta^{-2}, \delta^{-2}\exp(\delta w)\right)}{\Gamma(\delta^{-2})} & \text{if } \delta < 0 \end{cases}$$

$$f(w) = \frac{|\delta|}{\Gamma\left(\delta^{-2}\right)} \left(\delta^{-2}\exp(\delta w)\right)^{\delta^{-2}} \exp\left(-\exp(\delta w)\delta^{-2}\right)$$

$$G(t) = \begin{cases} \frac{\Gamma\left(\delta^{-2}, \delta^{-2}t^{\delta}\right)}{\Gamma(\delta^{-2})} & \text{if } \delta > 0 \\ 1 - \frac{\Gamma\left(\delta^{-2}, \delta^{-2}t^{\delta}\right)}{\Gamma(\delta^{-2})} & \text{if } \delta < 0 \end{cases}$$

$$g(t) = \frac{|\delta|}{t\Gamma\left(\delta^{-2}\right)} \left(\delta^{-2}t^{\delta}\right)^{\delta^{-2}} \exp\left(-t^{\delta}\delta^{-2}\right)$$

where $\Gamma(a)$ denotes the complete gamma function, $\Gamma(a, z)$ denotes the incomplete gamma function, and δ is a free shape parameter. The δ parameter is referred to as Shape by PROC LIFEREG. Refer to Lawless, 1982, p.240 and Klein and Moeschberger, 1997, p.386 for a description of the generalized gamma distribution.

Loglogistic

$$
\begin{aligned}
S(w) &= \left(1 + \exp\left(\frac{w-\mu}{\sigma}\right)\right)^{-1} \\
f(w) &= \frac{\exp\left(\frac{w-\mu}{\sigma}\right)}{\sigma\left(1 + \exp\left(\frac{w-\mu}{\sigma}\right)\right)^2} \\
G(t) &= \frac{1}{1+\alpha t^{\gamma}} \\
g(t) &= \frac{\alpha\gamma t^{\gamma-1}}{(1+\alpha t^{\gamma})^2}
\end{aligned}
$$

where $\gamma = 1/\sigma$ and $\alpha = \exp(-\mu/\sigma)$.

Lognormal

$$
\begin{aligned}
S(w) &= 1 - \Phi\left(\frac{w-\mu}{\sigma}\right) \\
f(w) &= \frac{1}{\sqrt{2\pi}\sigma}\exp\left(-\frac{1}{2}\left(\frac{w-\mu}{\sigma}\right)^2\right) \\
G(t) &= 1 - \Phi\left(\frac{\log(t)-\mu}{\sigma}\right) \\
g(t) &= \frac{1}{\sqrt{2\pi}\sigma t}\exp\left(-\frac{1}{2}\left(\frac{\log(t)-\mu}{\sigma}\right)^2\right)
\end{aligned}
$$

where Φ is the cumulative distribution function for the normal distribution.

Weibull

$$
\begin{aligned}
S(w) &= \exp\left(-exp\left(\frac{w-\mu}{\sigma}\right)\right) \\
f(w) &= \frac{1}{\sigma}\exp\left(\frac{w-\mu}{\sigma}\right)\exp\left(-\exp\left(\frac{w-\mu}{\sigma}\right)\right) \\
G(t) &= \exp\left(-\alpha t^{\gamma}\right) \\
g(t) &= \gamma\alpha t^{\gamma-1}\exp\left(-\alpha t^{\gamma}\right)
\end{aligned}
$$

where $\sigma = 1/\gamma$ and $\alpha = \exp(-\mu/\sigma)$.

If your parameterization is different from the ones shown here, you can still use the procedure to fit your model. For example, a common parameterization for the Weibull distribution is

$$
\begin{aligned}
g(t;\lambda,\beta) &= \left(\frac{\beta}{\lambda}\right)^{\beta}\left(\frac{t}{\alpha}\right)^{\beta-1}\exp\left(-\left(\frac{t}{\lambda}\right)^{\beta}\right) \\
G(t;\lambda,\beta) &= \exp\left(-\left(\frac{t}{\lambda}\right)^{\beta}\right)
\end{aligned}
$$

so that $\lambda = \exp(\mu)$ and $\beta = 1/\sigma$.

Again note that the expected value of the baseline log response is, in general, not zero and that the distributions are not symmetric in all cases. Thus, for a given set of covariates, **x**, the expected value of the log response is not always $\mathbf{x}'\beta$.

Some relations among the distributions are as follows:

- The gamma with Shape=1 is a Weibull distribution.
- The gamma with Shape=0 is a lognormal distribution.
- The Weibull with Scale=1 is an exponential distribution.

Source 2: Stanford Short Course

Gompertz Mortality

Gompertz (1825) suggested that a "law of geometric progression pervades" in mortality after a certain age

Gompertz mortality can be represented as

$$\mu(x) = \alpha e^{\beta x}$$

α is known as the baseline mortality, whereas β is the senescent component

Makeham (1860) extended the Gompertz model by adding a constant γ

Note that since the Gompertz model is for a mortality hazard, we can integrate it to give us the the survival function:

$$h(x) = \alpha e^{\beta x}, \qquad S(x) = \exp\left[\frac{\alpha}{\beta}(1 - e^{\beta x})\right]$$

Appendix 4: Supplemental clinical data

Supplemental evidence to support the efficacy of rituximab-containing regimens in patients with fludarabine-refractory CLL

To further support the data outlined in section 6.8.4.2 of the submission document, which demonstrates that R-FC has clinical activity and is a useful therapeutic option for patients whose disease is refractory to prior fludarabine-containing therapy, we now have access to long term-outcome data for R-FC in previously treated patients with CLL from the MD Anderson Cancer Center (MDACC). These data are unpublished and have been kindly shared with Roche ahead of publication.

Together, these data demonstrate that R-FC is a useful therapeutic option for CLL patients whose disease is refractory to prior fludarabine-containing therapy. These data are also supported by data on other rituximab-containing regimens in fludarabine-refractory CLL (see Section 6.8.4.2 of submission).

Re-iterating the original submission document, 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.

Supplemental Evidence to Support Rituximab Re-Treatment

Further to the data presented in section 6.8.4.3 of the submission, which demonstrate that rituximab-containing regimens are a viable and useful therapeutic option for CLL patients whose initial treatment contained rituximab, the MDACC have since carried out statistical analyses on the TTP and OS curves highlighted in Figures 17 and 18.
These updated analyses further support the wealth of data in CLL (and follicular lymphoma) outlined in the submission suggesting that patients previously treated with rituximab can be successfully re-treated on disease progression.

Again, re-iterating the original submission document, 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.

Summary

Together, these data support the anticipated licence for rituximab plus chemotherapy in both rituximab naïve and pre-treated patients who have relapsed after or are refractory to chemotherapy.

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