Single Technology Appraisal – Rituximab for the first line treatment of chronic lymphocytic leukaemia

Clarification Letter

Roche Products Limited
18 December 2008

Section A. Clarification on effectiveness data

Executive Summary

A1. For the outcome end-of-treatment response rate (p16, table 3) the percentage of missing data for the FC arm is 12% and for the R-FC arm 5.7%. Please can you confirm how missing response data was handled for this outcome, and what if any assumptions were made about patients' health status for missing response data? Additionally, were any assumptions subject to sensitivity analysis?

As noted above, for 12% of patients in the FC group and 5.7% of patients in the R-FC group, adequate information to assess response was missing. The main reason for "missing" response assessments was that these patients did not have a confirmation of response at least 2 months after initial response assessment available for the analysis, therefore an end of treatment response (ETR) could not be assigned according to the NCI-WG response criteria. For the main analysis, these patients with missing end-of-treatment analysis were considered as *non-responders*.

Additionally, a worst-case analysis considered patients with missing end-of-treatment responses as responders for both arms and confirmed the robustness of the main analysis of end-of-treatment responses, as provided in Table 1.

Table 1. Summary of End of Treatment Response – Missing ETR Considered as Response (ITT)

	FC (N=407)		FCR (N=403)
Responders$	345 (84.8 %)		370 (91.8 %)
Non-Responders	62 (15.2 %)		33 (8.2 %)
95% CI for Response Rates*	[80.9; 88.1]		[88.7; 94.3]
Difference in Response Rates		7.04	
95% CI for Difference in Response Rates#		[2.5; 11.6]	
p-Value (Chi-squared Test)		0.0018	
Odds Ratio		2.01	
95% CI for Odds Ratio		[1.29;3.15]	

End of treatment response (RSETR2)
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method

$ Responders are defined as patients with ETR assessment CR, nPR, PR or Missing.

Only the primary clinical outcome of progression-free survival from the trial was modelled in the cost-effectiveness analysis. Therefore missing data on other outcome measures such as ETR was not considered from an economic perspective.

Section 6

A2. The submission states the patients had an interim staging after 3 cycles and those with progressive or stable disease, did not continue treatment but were eligible for alternative treatment and followed up for survival analyses (p38). Please can you confirm whether patients were eligible for cross-over into the other treatment arm of the trial? and if so how many patients were crossed-over having experienced either progressive or stable disease between the FC and R-FC arms.

Patients were NOT eligible to cross-over into the other treatment arm of the trial. Any patients who were eligible for alternative treatment because of stable or progressive disease after three cycles were treated with any other treatment deemed appropriate by the individual investigator.

Subsequent data in the submission, presented on page 131 and table 48, infers that patients in the trial were eligible for any 2nd line CLL treatment having experienced progression or stable disease on the treatment to which they were randomised. Please can you confirm if this is correct?

This is correct. Table 48 in the original submission provides a list of the most frequent occurring therapies captured in the trial post-progression. Please note that this subsequent treatment data is only available for a minority of the total trial patients. As also noted above, patients were eligible for any 2nd line CLL treatment subject to their physicians discretion.

A3. Please could you provide the following data:

1. Number of patients for each treatment arm (FC and R-FC) who received 4-, 5-, or 6-treatment cycles.

As noted in Section 6.7.2.1 of the original submission, the safety population in the CLL-8 trial consisted of 793 patients (396 patients in the FC arm, 397 patients in the R-FC arm). This is the group of patients that received at least one cycle of either therapy. Table 30 then goes on to highlight the number of patients receiving at least 1, 2, 3, 4, 5 or 6 cycles. From this table the absolute number of patients who received at least 4, 5 or 6 treatment cycles can be calculated:

Table 2: Number of Patients receiving 4, 5 or 6 cycles

Number of Cycles	FC	R-FC	All
4	**24 (6%)**	**25 (6.3%)**	**49(6.2%)**
5	**16 (4.1%)**	**18 (4.5%)**	**34 (4.3%)**
6	**273 (68.9%)**	**299 (75.3%)**	**572 (72.1%)**

2. The actual (as opposed to planned) mean doses administered for each treatment arm for each treatment cycle.

One way of presenting this data was provided in Table 49 in the original submission. In this table, for rituximab, an average of 5.24 administrations were given (with one administration per cycle as per protocol). For F and C, 15.78 and 15.75 administrations were given in the R-FC arm, and 14.60 and 14.60 administrations were given in the FC arm, respectively. These values were tested in the sensitivity analysis.

There is also further data available for all three drugs (rituximab, fludarabine and cyclophosphamide), highlighting the number of patients who received percentage bands of the actual planned dose. These tables very clearly highlight the mean amounts of dose administered for each cycle as shown in Tables 3, 4, and 5.

Table 3: Summary of Extent of Exposure to Rituximab by Cycle (SAP)

	Dose Received* (% Of Planned Dose)	FC N=396 No.(%)	R-FC N=397 No.(%)
Cycle 1	<60%	0 (.%)	2 (1%)
	60% - <80%	0 (.%)	1 (0%)
	80% - <90%	0 (.%)	16 (4%)
	>=90%	0 (.%)	367 (95%)
	Missing	0 (.%)	0 (0%)
	n	0 (0%)	386 (97%)
Cycle 2	<60%	0 (.%)	0 (0%)
	60% - <80%	0 (.%)	57 (15%)
	80% - <90%	0 (.%)	13 (3%)
	>=90%	0 (.%)	313 (82%)
	Missing	0 (.%)	0 (0%)
	n	0 (0%)	383 (96%)
Cycle 3	<60%	0 (.%)	1 (0%)
	60% - <80%	0 (.%)	30 (8%)
	80% - <90%	0 (.%)	12 (3%)
	>=90%	0 (.%)	320 (88%)
	Missing	0 (.%)	0 (0%)
	n	0 (0%)	363 (91%)
Cycle 4	<60%	0 (.%)	1 (0%)
	60% - <80%	0 (.%)	22 (6%)
	80% - <90%	0 (.%)	14 (4%)
	>=90%	0 (.%)	304 (89%)
	Missing	0 (.%)	0 (0%)
	n	0 (0%)	341 (86%)
Cycle 5	<60%	0 (.%)	1 (0%)
	60% - <80%	0 (.%)	16 (5%)
	80% - <90%	0 (.%)	14 (4%)
	>=90%	0 (.%)	283 (90%)
	Missing	0 (.%)	0 (0%)
	n	0 (0%)	314 (79%)
Cycle 6	<60%	0 (.%)	0 (0%)
	60% - <80%	0 (.%)	17 (6%)
	80% - <90%	0 (.%)	13 (4%)
	>=90%	0 (.%)	268 (90%)
	Missing	0 (.%)	0 (0%)
	n	0 (0%)	298 (75%)

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/m2 (cycle 1) / 500 mg/m2 (cycle 2-6).

The above numbers in Table 3 for rituximab highlight that on average, 90% of patients received greater than 90% of the planned dose of rituximab at each cycle.

The proportion of patients receiving ≥ 90% of their planned fludarabine or cyclophosphamide dose decreased with every subsequent cycle of treatment. Whereas more than 90% of patients received ≥ 90% of the planned dose of F and/or C in Cycle 1, this proportion decreased to approximately 70% in Cycle 6. These findings are expected since dose reductions were not scheduled for the first cycle of therapy and, since dose-escalation was not allowed after a dose-reduction for toxicity, overall exposure to fludarabine and/or cyclophosphamide would be expected to decline progressively with increasing numbers of cycles. The proportion of patients receiving ≥ 90% of their planned dose of F or C was slightly lower in the R-FC group from Cycle 4 onwards. This data is provided in Tables 4 and 5 below.

Table 4: Summary of Extent of Exposure to Fludarabine by Cycle

	Dose Received* (% Of Planned Dose)	FC N=396 No.(%)	R-FC N=397 No.(%)
Cycle 1	<60%	1 (0%)	0 (0%)
	60% - <80%	6 (2%)	5 (1%)
	80% - <90%	23 (6%)	15 (4%)
	>=90%	365 (92%)	377 (95%)
	Missing	1 (0%)	0 (0%)
	n	396 (100%)	397 (100%)
Cycle 2	<60%	5 (1%)	4 (1%)
	60% - <80%	29 (8%)	28 (7%)
	80% - <90%	19 (5%)	20 (5%)
	>=90%	312 (85%)	331 (86%)
	Missing	1 (0%)	0 (0%)
	n	366 (92%)	383 (96%)
Cycle 3	<60%	14 (4%)	10 (3%)
	60% - <80%	35 (10%)	35 (10%)
	80% - <90%	25 (7%)	22 (6%)
	>=90%	267 (78%)	296 (82%)
	Missing	1 (0%)	0 (0%)
	n	342 (86%)	363 (91%)
Cycle 4	<60%	13 (4%)	22 (6%)
	60% - <80%	34 (11%)	37 (11%)
	80% - <90%	24 (8%)	20 (6%)
	>=90%	242 (77%)	262 (77%)
	Missing	0 (0%)	0 (0%)
	n	313 (79%)	341 (86%)
Cycle 5	<60%	19 (7%)	22 (7%)
	60% - <80%	32 (11%)	48 (15%)
	80% - <90%	22 (8%)	18 (6%)
	>=90%	216 (75%)	226 (72%)
	Missing	0 (0%)	0 (0%)
	n	289 (73%)	314 (79%)
Cycle 6	<60%	25 (9%)	24 (8%)
	60% - <80%	33 (12%)	52 (18%)
	80% - <90%	21 (8%)	17 (6%)
	>=90%	194 (71%)	203 (69%)
	Missing	0 (0%)	0 (0%)
	n	273 (69%)	296 (75%)

n represents the number of patients treated with fludarabine in the corresponding cycle.
*: Percentages are calculated using the relative dose and are based on n (number of patients
receiving fludarabine in that cycle).
Planned dose for fludarabine: 75 mg/m2 (cycle 1-6).
Dose reductions are not considered when calculating the planned dose.

Table 5: Summary of Extent of Exposure to Cyclophosphamide by Cycle.

	Dose Received* (% Of Planned Dose)	FC N=396 No.(%)	R-FC N=397 No.(%)
Cycle 1	<60%	1 (0%)	0 (0%)
	60% - <80%	3 (1%)	5 (1%)
	80% - <90%	26 (7%)	17 (4%)
	>=90%	365 (92%)	374 (94%)
	Missing	1 (0%)	0 (0%)
	n	396 (100%)	396 (100%)
Cycle 2	<60%	7 (2%)	4 (1%)
	60% - <80%	27 (7%)	33 (9%)
	80% - <90%	17 (5%)	17 (4%)
	>=90%	314 (86%)	329 (86%)
	Missing	1 (0%)	0 (0%)
	n	366 (92%)	383 (96%)
Cycle 3	<60%	14 (4%)	11 (3%)
	60% - <80%	34 (10%)	38 (10%)
	80% - <90%	21 (6%)	19 (5%)
	>=90%	271 (79%)	294 (81%)
	Missing	1 (0%)	0 (0%)
	n	341 (86%)	362 (91%)
Cycle 4	<60%	13 (4%)	24 (7%)
	60% - <80%	36 (12%)	38 (11%)
	80% - <90%	19 (6%)	19 (6%)
	>=90%	245 (78%)	259 (76%)
	Missing	0 (0%)	0 (0%)
	n	313 (79%)	340 (86%)
Cycle 5	<60%	18 (6%)	22 (7%)
	60% - <80%	33 (11%)	50 (16%)
	80% - <90%	17 (6%)	15 (5%)
	>=90%	221 (76%)	226 (72%)
	Missing	0 (0%)	0 (0%)
	n	289 (73%)	313 (79%)
Cycle 6	<60%	22 (8%)	25 (8%)
	60% - <80%	35 (13%)	51 (17%)
	80% - <90%	15 (6%)	17 (6%)
	>=90%	200 (74%)	202 (68%)
	Missing	0 (0%)	0 (0%)
	n	272 (69%)	295 (74%)

n represents the number of patients treated with cyclophosphamide in the corresponding cycle.
*: Percentages are calculated using the relative dose and are based on n (number of patients
receiving cyclophosphamide in that cycle).
Planned dose for cyclophosphamide: 750 mg/m2 (cycle 1-6).
Dose reductions are not considered when calculating the planned dose.

A4. Please could you provide the results of significance testing for the difference in proportions for the Grade 3 or 4 adverse events listed in table 31 (section 6.7.2.2).

Table 6: Overview of Adverse Events in Study CLL-8 – Adapted from Table 31 and p-values included (where available)

	Number of Patients (%)		
	FC N = 396	**R-FC N = 397**	**p**
Grade 3 or 4 AE	**246 (62%)**	**304 (77%)**	**<0.0001***
Serious AE	**162 (41%)**	**182 (46%)**	**NA**
AE leading to treatment discontinuation	**70 (18%)**	**71 (18%)**	**NA**
AE leading to dose modification/interruption	**80 (20%)**	**133 (34%)**	**NA**
Treatment-related death	**8 (2%)**	**6 (2%)**	**NA**

*** Hallek et al. ASH 2008**[i]
NA: not available

Section 6.6: Indirect/mixed treatment comparisons

A5. Please could you supply a copy of the following:

1. The search strategy used to identify trials for inclusion in the MTC (none is provided in the appendices)

Table 7. Search Strategy for MTC

No.	Database	Search term	Results
CP		[Clipboard]	0
1	MEZZ	CLL.TI,AB. OR (Chronic ADJ Lymphocytic ADJ Leukemia).TI,AB.	10457
2	MEZZ	Leukemia-Lymphocytic-Chronic-B-Cell.DE.	8010
3	MEZZ	1 OR 2	12952
4	MEZZ	Random-Allocation.DE.	60413
5	MEZZ	Meta-Analysis-As-Topic.DE.	8166
6	MEZZ	Review-Literature-As-Topic.DE.	2291
7	MEZZ	PT=RANDOMIZED-CONTROLLED-TRIAL OR PT=REVIEW	1608467
8	MEZZ	PT=META-ANALYSIS	17878
9	MEZZ	random ADJ allocation OR randomized OR meta-analys$2 OR systematic ADJ review	407174
10	MEZZ	4 OR 5 OR 6 OR 7 OR 8 OR 9	1723377
11	MEZZ	3 AND 10 AND HUMAN=YES	1693
12	MEZZ	Fludara.TI,AB. OR fludarabine.TI,AB.	2408
13	MEZZ	Cyclophosphamide.TI,AB. OR Cyclophosphamide.TI,AB. OR cytoxan.TI,AB. OR neosar.TI,AB.	31243

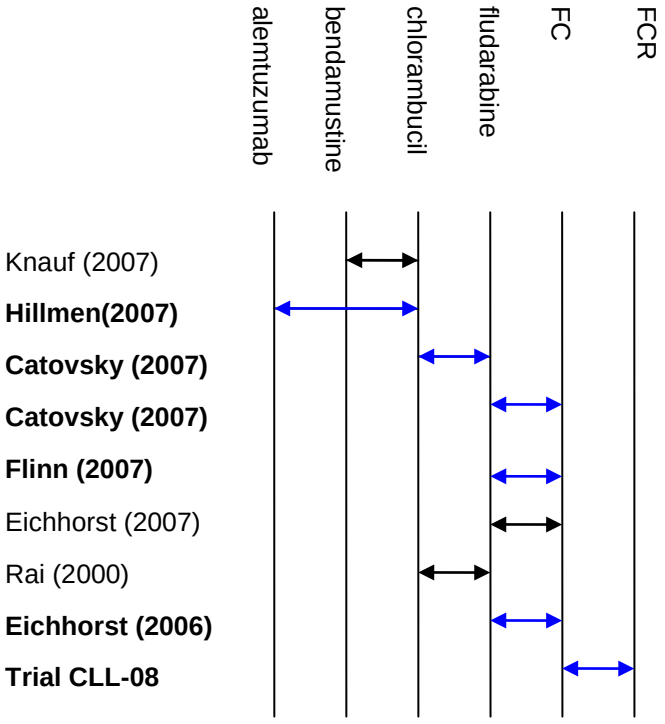
14	MEZZ	Chlorambucil.TI,AB. OR Leukeran.TI,AB. OR Chloraminophene.TI,AB.	2315
15	MEZZ	Rituximab.TI,AB. OR MabThera.TI,AB. OR rituxan.TI,AB.	3598
16	MEZZ	Alemtuzumab.TI,AB. OR Campath.TI,AB. OR MabCambath.TI,AB.	1087
17	MEZZ	Humax-cd20.TI,AB. OR ofatumumab.TI,AB.	10
18	MEZZ	Oblimersen.TI,AB. OR Genasense.TI,AB. OR G3139.TI,AB.	155
19	MEZZ	CHOP.TI,AB.	2736
20	MEZZ	Bendamustine.TI,AB. OR Treanda.TI,AB. OR Cytostasan.TI,AB. OR Ribomustin.TI,AB.	109
21	MEZZ	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20	40312
22	MEZZ	11 AND 21	415
23	EMZZ	CLL.TI,AB. OR (Chronic ADJ Lymphocytic ADJ Leukemia).TI,AB.	9978
24	EMZZ	Chronic-Lymphatic-Leukemia.DE.	11793
25	EMZZ	23 OR 24	13905
26	EMZZ	Randomization.W..DE.	27671
27	EMZZ	Literature.W..DE.	9802
28	EMZZ	Meta-Analysis.DE.	35102
29	EMZZ	random ADJ allocation OR randomized OR meta-analys$2 OR systematic ADJ review	302877
30	EMZZ	AT=REVIEW	808303
31	EMZZ	Randomized-Controlled-Trial.DE.	162310
32	EMZZ	26 OR 27 OR 28 OR 29 OR 30 OR 31	1088836
33	EMZZ	25 AND 32 AND HUMAN=YES	1659
34	EMZZ	Fludara.TI,AB. OR fludarabine.TI,AB.	2388
35	EMZZ	Cyclophosphamide.TI,AB. OR Cyclophosphamide.TI,AB. OR cytoxan.TI,AB. OR neosar.TI,AB.	30060
36	EMZZ	Chlorambucil.TI,AB. OR Leukeran.TI,AB. OR Chloraminophene.TI,AB.	2252
37	EMZZ	Rituximab.TI,AB. OR MabThera.TI,AB. OR rituxan.TI,AB.	3521
38	EMZZ	Alemtuzumab.TI,AB. OR Campath.TI,AB. OR MabCambath.TI,AB.	1091
39	EMZZ	Humax-cd20.TI,AB. OR ofatumumab.TI,AB.	13
40	EMZZ	Oblimersen.TI,AB. OR Genasense.TI,AB. OR G3139.TI,AB.	160
41	EMZZ	CHOP.TI,AB.	2505
42	EMZZ	Bendamustine.TI,AB. OR Treanda.TI,AB. OR Cytostasan.TI,AB. OR Ribomustin.TI,AB.	125
43	EMZZ	34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42	38776
44	EMZZ	33 AND 43	384
45	BIZZ	CLL.TI,AB. OR (Chronic ADJ Lymphocytic ADJ Leukemia).TI,AB.	12961
46	BIZZ	random ADJ allocation OR randomized OR meta-analys$2 OR systematic ADJ review	150086
47	BIZZ	45 AND 46 AND HUMANS#	217
48	BIZZ	PT=LITERATURE-REVIEW	356792
49	BIZZ	46 OR 48	499373
50	BIZZ	45 AND 49 AND HUMANS#	456
51	BIZZ	Fludara.TI,AB. OR fludarabine.TI,AB.	4001
52	BIZZ	Cyclophosphamide.TI,AB. OR Cyclophosphamide.TI,AB. OR cytoxan.TI,AB. OR neosar.TI,AB.	27757
53	BIZZ	Chlorambucil.TI,AB. OR Leukeran.TI,AB. OR Chloraminophene.TI,AB.	2189
54	BIZZ	Rituximab.TI,AB. OR MabThera.TI,AB. OR rituxan.TI,AB.	3778
55	BIZZ	Alemtuzumab.TI,AB. OR Campath.TI,AB. OR MabCambath.TI,AB.	1352
56	BIZZ	Humax-cd20.TI,AB. OR ofatumumab.TI,AB.	6
57	BIZZ	Oblimersen.TI,AB. OR Genasense.TI,AB. OR G3139.TI,AB.	169
58	BIZZ	CHOP.TI,AB.	2945

59	BIZZ	Bendamustine.TI,AB. OR Treanda.TI,AB. OR Cytostasan.TI,AB. OR Ribomustin.TI,AB.	143
60	BIZZ	51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59	37980
61	BIZZ	50 AND 60	224
62	BIZZ EMZZ MEZZ [all]	combined sets 22, 44, 61	1023
63	BIZZ EMZZ MEZZ [all]	dropped duplicates from 62	340
64	BIZZ EMZZ MEZZ [all]	unique records from 62	683

2. A MTC 'network' diagram showing the 8 included trials and their comparators and how they 'link' together to form a network. It would be helpful if this additionally highlighted the 5 trials that were included in the MTC.

Figure 1 below provides the MTC network diagram with the arrows in blue illustrating the studies included in the analysis of the primary outcome, progression-free survival. All eight sudies were used in the analysis of complete response and overall survival.

Figure 1. Network of the included trials and the indirect and direct estimates for the treatment effects.



3. In addition to table 22 which displays the HR for PFS for the 5 trials included in the MTC, it would be helpful if you could provide a table of the PFS rates (numbers, percentages) for each of the 8 trials by comparator for each trial arm.

PFS is generally expressed as a median at a specific point in time, or as an absolute percentage at a given point of follow-up, e.g. x% were progression-free at 3 years of follow up. These numbers are not available for all the trials noted, but we have attempted to provide this data as best we can in Table 8 below. The numbers have been calculated from the percentages where possible. All the trials present the PFS data in slightly different ways, hence the variation in reporting methods seen in the table.

Table 8: PFS rates for all 8 trials included in the MTC

Study	Treatment	PFS rate (n=)	PFS rate (%)
		At Two Years	
CLL-8[+]	FCR	306	76.6%
	FC	241	62.3%
		At Five Years	
Catovsky (2007)	FC	71	36%
	fludarabine	20	10%
	chlorambucil	39*	10%
Hillmen (2007)	alemtuzumab	Median of 14.6 months with 24.5 months follow up	
	chlorambucil	Median of 11.7 months with 24.9 months follow up	
Flinn (2007)	FC	Median PFS 31.6 months	
	Fludarabine	Median PFS 19.2 months	
Rai (2000)	Fludarabine	Not Available	21%
	chlorambucil	Not Available	19%
		At a median follow-up of 22 months	
Eichhorst(2006)	FC	PFS: 48 months	
	Fludarabine	PFS: 20 months	
		At a median follow-up of 18.5 months	
Knauf (2007)	bendamustine	21.7 months	
	chlorambucil	9.3 months	
		At a median follow-up of 22 months	
Eichhorst (2007)	Fludarabine	92	53.8%
	Chlorambucil	115	68.5%

[+]: **These numbers are based on the Hallek abstract (reference number 28 in submission)**

*: **Please note there was a 2:1:1 randomisation between chlorambucil, fludarabine and FC in this trial, hence 10% is a bigger number for chlorambucil than for fludarabine.**

4. Could you provide more details on the methods used to conduct the MTC (e.g. were any assumptions necessary in order to include multi-arm trials and if so how were these handled?). Additionally could you please supply a copy of the WinBUGS code.

Catovsky (2007) is the only paper evaluating more than 2 treatments at the same time. Because Catovsky (2007) evaluated three treatments, we could have gained power by using a model which takes into account that the three treatments are considered together in one study. Instead, we dealt with Catovsky (2007) as if the results of the comparison of FC versus F and the comparison of F versus Chl are obtained from different studies. By doing this, the final variance is expected to be an overestimation of the true variance of the estimate, given that the fixed effects model is valid (note that this assumption should be reconsidered when more papers are available).

The effect of R-FC with respect to chlorambucil and alemtuzumab is therefore more significantly different than obtained from the analyses, if the fixed effects model holds. The same holds, of course, with respect to the random effects model, where the fact that the comparison is made within one study is more relevant. No bias is introduced by using the approach, as can be obtained from, among others, Rao (Linear statistical inference and its applications, Wiley, 2002).

With the approach we used it is more difficult to show that R-FC is better than chlorambucil and alemtuzumab. Note that, of course, an increase in the variance, for this study, is not a disadvantage, because we may expect some variation due to study variation, which can not be measured at this point of time (too small amount of available papers). Finally, no bias is introduced with respect to the estimates of the effects (only the variance is overestimated).

5. Please provide further explanation as to why the trial by Jaksic et al. (1997) was excluded for consideration in the MTC. It appears from the submission that this was due to heterogeneity in the patient population in terms of baseline ECOG performance status (i.e., not stage 0 to 2) but can this be confirmed, as there are no inclusion/exclusion criteria for consideration in the MTC based on Binet staging as stated in the reasons for trial exclusion.

In the trial by Jaksic et al (1997), the percentages within the Binet stages differed substantially across the arms. This implied that the estimated treatment effect would also be influenced by the difference in severity, and therefore this would not be an appropriate study to include the mixed treatment comparison. This is noted on page 73 and also on figure 9, page 75.

Table 9. Jaksic et al (1997): Comparison of patient characteristics as shown on page 2109

	HD-CLB	CHOP
No. (%)	116 (51)	112 (49)
Sex (M/F)	68/48	74/38
Age		
Mean ± SD	60.7 ± 10.2	60.2 ± 8.5
Median	63	61
TTM		
Mean ± SD	15.2 ± 6.98	15.8 ± 6.14
Median	13	13
Rai		
0	1 (0.9)	0 (0.0)
I	24 (21.4)	13 (11.9)
II	57 (50.9)	48 (44.0)
III	13 (11.6)	23 (21.1)
IV	17 (15.2)	25 (22.9)
Binet		
A	31 (27.7)	15 (13.6)
B	52 (46.4)	46 (41.8)
C	29 (25.9)	49 (44.5)

Section 6.9: Interpretation of clinical evidence

A6. The submission states that the Q-TWIST was based on 2.2 years follow-up data from CLL-8 from 408 and 409 patients in the R-FC and FC arms respectively (p101). Can you confirm these patient numbers are correct or should this read R-FC=403 and FC=407?

Thank you for identifying this minor error, this should indeed read R-FC = 403 and FC = 407 (directly correlating to the intention-to treat population). Out of the 817 patients initially randomised to this study, 7 informed consent forms were not found and these patients were excluded from any analysis.

A7. Were any searches conducted to attempt to identify further studies that had assessed utility for patients undergoing 1st line treatment for CLL? If so, please provide a copy of the relevant identified studies.

A literature search was completed to identify any health economic studies related to CLL, which included studies for utilities. Three articles reported utilities for patients suffering from CLL, of which one was a HTA report, the second was a threshold analysis based on varying utilities for different health states and the third study was a cost effectiveness study based on efficacy data from a double blind RCT.

(1) The Wessex Development and Evaluation Committee (DEC) report number 44, reports an attempt to estimate the impact of fludarabine treatment relative to chlorambucil + prednisone (C+P) and CAP (cyclophosphamide, adriamycin, prednisone) in terms of QoL [ii].

(2) A quality adjusted survival analysis by Levy et al. (2001) compared the quality-adjusted survival in patients receiving one of the following

treatments[iii]: CHOP (cyclophosphamide, doxorubicin, oncovin, and prednisone), CAP or fludarabine.

(3) Weeks et al. (2001) published a cost-effectiveness study using decision-analysis techniques analysing prophylactic intravenous immune globulin in CLL. Utility estimates were used as weights for the calculation of a quality adjusted life expectancy [iv]. The utility estimates were obtained from 10 oncologists experienced in the care of CLL patients.

A8. Will the ERG have access to the revised utility estimates from the study presently being conducted by Oxford outcomes due for completion Q1 2009, and if so, when will they be provided?

This study is still recruiting patients; therefore it is not yet known exactly when the study will recruit an adequate number of patients. We will evaluate patient numbers during January and February to see if there is a meaningful enough sample size to provide interim analysis in advance of the first appraisal committee meeting in March. Roche are happy to share this information with both the ERG and relevant members of the NICE project team.

Section B. Clarification on cost-effectiveness data

Section 7.2: De novo economic evaluation(s)

B1. Please can you provide a copy of the clinical data from the CLL-8 trial for the analysis conducted at a median of 2.2 years on which the CUA is based? This should have the N (%) for both the outcomes of PFS and OS. Additionally, can you clarify whether this data set includes only patients who were classified as having a response at the time of final response assessment, or also those classified as having a 'late response' as per the data set reported in the ASH conference abstract by Hallek et al.

Please find attached the tabulated KM data in Table 10.

Table 10. Duration of PFS: Kaplan Meier Product Limits

Rituximab + Fludarabine / Cyclophosphamide				Fludarabine / Cyclophosphamide Alone			
MONTH	SURVIVAL	FAILED	LEFT	MONTH	SURVIVAL	FAILED	LEFT
0	1	0	408	0	1	0	409
0	0.9975	1	407	0	0.9902	4	405
1	0.9875	5	395	1	0.985	6	381
2	0.98	8	392	2	0.967	13	374
3	0.975	10	390	3	0.954	18	369
4	0.97	12	387	4	0.9385	24	362
5	0.9625	15	384	5	0.9177	32	353
6	0.9499	20	378	6	0.9073	36	349
7	0.9449	22	374	7	0.8968	40	344
8	0.9322	27	368	8	0.8837	45	335
9	0.9221	31	364	9	0.8705	50	330
10	0.9094	36	358	10	0.8519	57	322
11	0.8865	45	349	11	0.8414	61	318
12	0.8764	49	345	12	0.8201	69	308
13	0.8713	51	343	13	0.8041	75	302
14	0.8688	52	342	14	0.7719	87	288

15	0.8611	55	338	15	0.7584	92	280
16	0.8509	59	334	16	0.7394	99	273
17	0.8458	61	330	17	0.7259	104	268
18	0.8302	67	319	18	0.7094	110	258
19	0.8143	73	308	19	0.6926	116	247
20	0.8087	75	289	20	0.6718	123	226
21	0.7875	82	260	21	0.6651	125	201
22	0.7749	86	245	22	0.6405	132	182
23	0.7681	88	227	23	0.6256	136	168
24	0.746	94	203	24	0.6092	140	149
25	0.7422	95	193	25	0.6005	142	137
26	0.7256	99	175	26	0.6005	142	137
27	0.7034	104	158	27	0.5539	151	107
28	0.6985	105	145	28	0.5378	154	100
29	0.6931	106	128	29	0.5258	156	88
30	0.6872	107	116	30	0.5258	156	88
31	0.6679	110	104	31	0.512	158	74
32	0.6543	112	96	32	0.4903	161	68
33	0.6543	112	96	33	0.4514	166	58
34	0.6465	113	83	34	0.4431	167	53
35	0.612	117	71	35	0.4253	169	48
36	0.594	119	66	36	0.4253	169	48
37	0.5838	120	57	37	0.4024	171	35
38	0.5838	120	57	38	0.3898	172	31
39	0.5465	123	44	39	0.3898	172	31
40	0.5185	125	37	40	0.3898	172	31
41	0.5185	125	37	41	0.3898	172	31
42	0.5012	126	29	42	0.3898	172	31
43	0.4773	127	20	43	0.3654	173	15
44		127	12	44	0.3322	174	10
45		127	11	45		174	6
46		127	8	46		174	5
47		127	6	47		174	3
48		127	3	48		174	1
49		127	1	49		174	0
50		127	0				

The data used for the CUA is the ITT population and is not related explicitly with responders. Patients were restaged at cycle 3 and if they crossed over to alternative (2nd-line) therapy, they were censored at this time for the purposes of estimating PFS, otherwise they continued to contribute to PFS until they progressed. All patients with PFS information were analysed.

B2. In the base case analysis (R-FC vs. oral FC) for cycles 2-6 for R-FC it appears that only the administration cost for R (£430) has been added, please can you clarify whether an additional cost for FC (£280) should also be added (p129)? The additional cost (£280) for oral chemotherapy in the first cycle is justified by an extra appointment. Can you please explain **why** an extra appointment is necessary and why it is not possible to combine the costs with the administration of rituximab (as for cycles 2-6 in R-FC arm)?

In the trial, for cycle 1 only, the rituximab was given on day 0, followed by the i.v. fludarabine and cyclophosphamide on days 1, 2, and 3. Therefore, in the base case we attempted to model this accurately, with rituximab administered on day 0, and then an extra visit on day 1 to pick up and start the oral FC. This assumption is described in greater detail in Section 7.2.9.2, following Table 46.

The trial was designed in this way because there was a concern that at cycle 1 there would potentially be a risk of severe infusion-related reactions +/- tumour lysis syndrome due to the high circulating tumour burden typically seen in CLL. Therefore this was reflected in the costs given. The safety data from the trial indicates that infusion-related reactions were actually very low in the R-FC arm and pragmatically speaking, when R-FC is used in the United Kingdom, oral FC will be given with IV rituximab, so even if in cycle 1 the rituximab is given 24 hours before FC is initiated, because FC will be given as an oral prescription, an extra day visit will not be required – i.e. rituximab will be given on day 0 and the oral chemotherapy prescription picked up and started on day 1. We therefore agree that our base case over estimates R-FC hospital visit costs and the extra £280 for the appointment to pick up oral FC on day 1 of cycle 1 will not be required and that the costs for all 6 cycles will be the same.

The below provides the cost-effectiveness results assuming that in cycle 1, only one chemotherapy administration visit will occur, where IV rituximab will be administered and oral FC will be collected for self-administration on the subsequent 5 days. This results in a cost per QALY estimate of £12,867, a 2.4% decrease from the base case ICER of £13,189 in the original submission.

Table 11. Base case result assuming 1 administration visit in Cycle 1

Cost-utility results	**RFC**	**FC**	**Incremental**
Mean Life Years (yrs)	5.73	4.65	1.07
Mean QALYs	4.26	3.38	0.88
Mean Total Cost	£25,312	£13,978	£11,334
Cost per Life Year Gained (£)			**£10,562**
Cost per QALY Gained (£)			**£12,867**

B3. The submission states that a higher oral dose of fludarabine is required to obtain equivalent bioavailability as IV administration (page 103). However the oral dose used in the model are lower than the IV dose (table 36). Please can you confirm the appropriate dosing when switching from IV to oral administration, and comment on how this has been accounted for in the analysis?

As noted in section 6.9.2 of the submission, bioavailability studies identify that a higher oral dose is required to obtain the equivalent iv dose (55% bioavailability, Foram et al., 1999[v]). 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 (e.g. Rossi et al., 2004[vi]). Thus, when adjusting for oral fludarabine from an i.v. formulation, one should aim to increase the cumulative dose by around 55%. This was done in the UK CLL-4 study, and the economic analyses reflect this:

5 days of 24mg/m^2 orally gives a total of 120mg/m^2. Assuming a bioavailability of 55%, the cumulative i.v. dose required would be 66mg/m^2, which is very similar to the 75mg/m^2 given in CLL-8.

From Table 36 in the original submission, fludarabine does have an overall higher dose as an oral formulation, as 24mg/m^2 will be given for 5 days of each cycle (a total of 120mg/m^2 per cycle) whilst as an infusion, fludarabine will be provided as 25 mg/m^2 for 3 days of each cycle (totally to 75 mg/m^2). The cyclophosphamide doses for IV and oral are equivalent (bioavailability close to 100% - see B4 below). These doses have been taken into account in the analysis by applying the appropriate costs associated with the oral and IV formulations from the BNF into the model. These calculations are provided in Table 12 below.

Table 12. Calculation of total doses of FC for oral and IV

Therapy	Daily dose (mg/m^2)	Days of Therapy per cycle	Total dose per cycle
Fludarabine (oral)	24	5	120
Fludarabine (IV)	25	3	75
Cyclophosphamide (oral)	150	5	750
Cyclophosphamide (IV)	250	3	750

B4. Can you confirm that the bioavailability of cyclophosphamide is the same regardless of administration of the dose orally or intravenously? If not, how has this been accounted for in the analysis?

It is well established that the bioavailability of cyclophosphamide is virtually the same, regardless of IV or oral administration, and it is close to 100%.

Supporting publications:

1. **Wagner T, Fenneberg K. Pharmacokinetics and bioavailability of cyclophosphamide from oral formulations. Arzneimittelforschung. 1984;34(3):313-6.[vii]**
2. **Wagner T, Fenneberg K. Bioavailability of cyclophosphamide from oral formulations. Eur J Clin Pharmacol. 1984;26(2):269-70. [viii]**

B5. The submission states (pages 29 and 99) that chlorambucil would be considered in a subgroup of patients (frail/elderly patients with comorbidities) in clinical practice.

1. Please comment on the likely use of R-chlorambucil in this population?

The combination of rituximab and chlorambucil as the initial treatment of CLL is being intensively investigated (see B5, question 3), in a UK only study, led by Professor Peter Hillmen. Anecdotally, Roche are aware of centres that have used this combination in CLL. R-chlorambucil is also used in advanced stage III/IV follicular lymphoma (in the lymphoma population it is used as an alternative to R-CVP (rituximab, cyclophosphamide, vincristine and prednisolone), and falls within the marketing authorisation for this indication. There is some Phase II data (Martinelli et al, 2003[ix]), that highlights the efficacy and safety of R-chlorambucil in other low-grade lymphoproliferative disorders (not CLL).

Following the publication of the pivotal, randomised Phase III UK CLL-4 study (Catovsky et al, 2007), the superior efficacy seen with the FC combination (fludarabine and cyclophosphamide) over chlorambucil has led to a greater number of patients being treated with the FC regimen, compared to chlorambucil (see section 4.5 of the original submission). However there will always be a number of poor-performance patients who will be deemed unsuitable for fludarabine-based therapy, and this is where a chlorambucil based regime will be used. At the current time it would mainly be used as a monotherapy, however combining it with rituximab is potentially a very attractive option to considerably improve the efficacy of chlorambucil, without adding to toxicity, which is of paramount importance to the group of patients with poor performance status, who are often older.

As we are expecting the first efficacy data from this study to be published within the next 12 months, we anticipate that if R-chlorambucil was made available for use, there would be considerable usage in this poor-performance group.

In summary, with the wealth of the data that has been generated over the last decade highlighting the efficacy and safety of rituximab combined with any number of chemotherapy regimes in low grade lymphomas, there is widespread acceptance by the haematology community that combing rituximab with chlorambucil will significantly improve its efficacy in CLL without compromising safety. It will therefore become a potentially useful tool for managing CLL in the frail/elderly population, allowing a longer progression-free time before relapse. However we accept that for many clinicians they will be waiting for this first data to be published before using the combination considerably, and this is anticipated within 12 months.

2. Please comment on the clinical and cost effectiveness of the combination of R-chlorambucil in comparison with chlorambucil?

Clinical Effectiveness:
As discussed in B5, question 1, we are still waiting for definitive data. The best guide to the clinical effectiveness of chlorambucil comes from reviewing the UK CLL-4 study (Catovsky et al, 2007)

and extrapolating. In this study, treatment with chlorambucil was associated with an overall response rate of 72%, a complete response rate of 7%, and a progression-free survival of 10% at 5 years, considerably inferior to the FC regimen. The major advantage of using chlorambucil is that it is usually well tolerated, and has a favourable safety profile.

One can only estimate the potential clinical effectiveness of R-chlorambucil, but given that a doubling in CR rates was observed in the CLL-8 trial when rituximab was added to FC (from 17.2% to 36.0% as detailed in Table 14 of the original submission), it is not unreasonable to suggest that adding rituximab to chlorambucil would result in a similar improvement in CR rate (i.e. from 7% (as demonstrated in the pivotal CLL-4 trial) to approximately 15%)). With respect to PFS, in the Tam et al. phase II trial 60% of patients were observed to be progression-free at 6 years median follow-up following treatment with R-FC. In contrast, 36% of FC patients were progression free in the pivotal CLL-4 trial at 5 years. Assuming therefore, that the addition of rituximab to chemotherapy results in an approximate doubling of PFS rate, it is again not unreasonable to suggest that approximately 20% of R-chlorambucil patients would be expected to be progression-free at 5 years (compared to 10% of chlorambucil monotherapy patients as reported in the CLL-4 study).

Of note, the R-chlorambucil UK trial (UK CLL201), uses exactly the same chlorambucil schedule as in the UK CLL-4 study, together with the standard, to be licensed rituximab dose schedule (see below).

Extrapolating to what has been seen in other low-grade lymphoproliferative disorders, addition of rituximab to any number of chemotherapy regimes leads to an additive clinical benefit without a significant increase in adverse events.[x] It is likely that R-chlorambucil in CLL would be similar.

Cost-effectiveness:
Because rituximab is an additive treatment, the ICERs are associated with the additional costs and outcomes that rituximab is expected to provide. This was explored briefly in the scenario analysis entitled "Considerations for R-chemo" in the original submission.

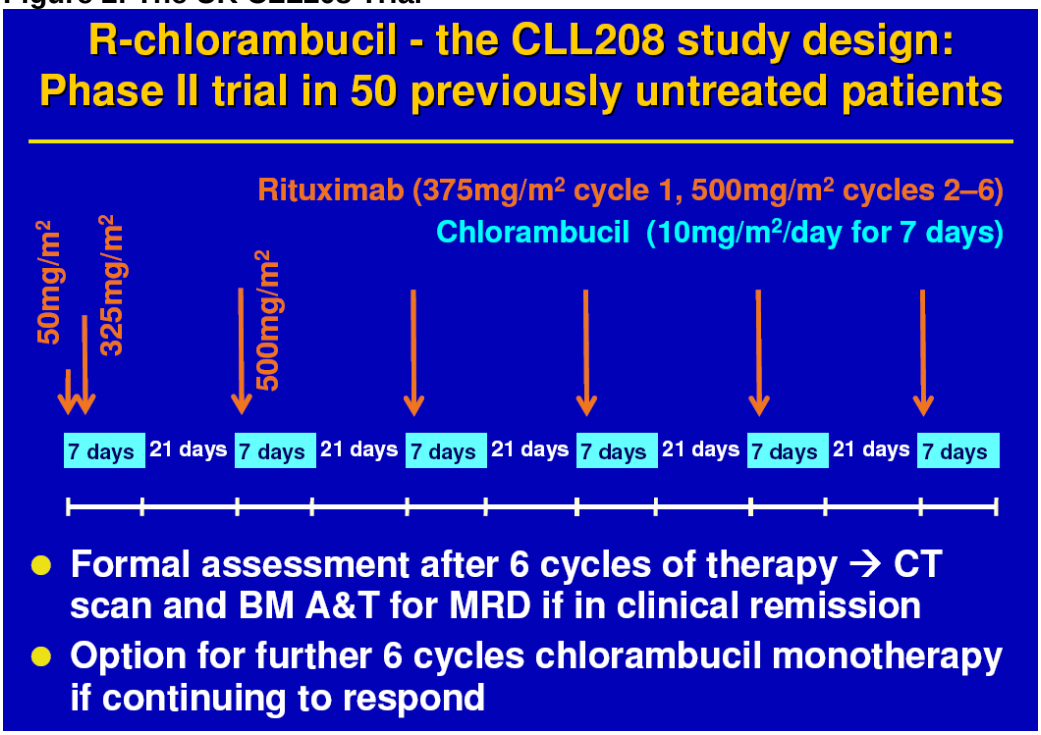
Incremental costs: The base case analysis of R-FC versus FC provides an estimate of the incremental costs of adding rituximab to FC, which would not change significantly if rituximab were added to a different chemotherapy regimen. Various adjustments to the cost components of the base case illustrates that the results are not sensitive to changes to such costs, even when alternative adverse event profiles and large changes in supportive care costs are considered.

Incremental outcomes: Incremental differences in the outcome measure is driven by expected differences in PFS between the two arms. According the scenario analysis provided in Figure 26 of the original submission, given the current cost structure, the improvement in PFS would need to decrease by more than 50% in order to no longer be cost-effective (as illustrated in Figure 26 from the original submission). According to clinical opinion, this is unlikely. Furthermore if the treatment effect of adding R to Chlorambucil was similar to adding R to FC; given a higher baseline risk of progression for Chlorambucil compared to FC, the absolute incremental benefit could be greater for R-Chlorambucil. Given comparable costs in such circumstances it may be reasonable to assume the ICER could conceivably be lower than that estimated for R-FC versus FC.

3. Please confirm when the results of trial UK CLL201 will be available?

The overall design of this trial is highlighted below:

Figure 2: The UK CLL208 Trial



Please note that this is the CLL208 trial, it was incorrectly written in as the CLL201 study in the original submission.

As of 8th December 2008, 64/100 patients have signed informed consent and 54 patients have initiated treatment. The first interim safety analysis in imminent, and is due when 25 patients have completed 3 cycles of treatment. A further clinical interim analysis is planned when 50 patients have completed 6 cycles of treatment. It is hoped that this clinical analysis will be presented for the first time at the 2009 meeting of the American Society of Haematology

(December). At current recruitment rates it is anticipated that the last patient will sign their informed consent (100/100), at the end of Q1 2009.

4. Please provide further justification that the assumption in the model of similar adverse effect profile for chlorambucil as for FC?

The randomised comparative evidence to substantiate a similar adverse profile is not available. Chlorambucil is commonly known to be much less toxic than FC, therefore a sensitivity analysis was performed where the adverse events profile in the chlorambucil arm (for the analysis of R-FC versus chlorambucil) was significantly reduced relative to the FC arm. This was described in the methods as follows:

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

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

This increased the ICER against chlorambucil comparator by 5.2%, from £6,422 to £6,756 per QALY gained.

Section 7.3.3 Sensitivity analysis

B6. Please complete a one-way sensitivity analysis to show changes in the incremental cost-effectiveness ratio based on the differential mortality rates assumed between PFS and Progressed health states?

The base case analysis does assume differential mortality rates in PFS and Progressed health states. These values were determined by the mortality rates observed in CLL-8. The mortality rates in the R-FC and FC arms were modelled separate for the PFS state (Monthly probability of death: R-FC = 0.00119627 and FC = 0.00138823) while the progressed state used an aggregated approach for mortality rates estimates by assuming a single population and summing across to the two arms. The single monthly probability of death obtained was 0.0405144 and this was applied to both arms of the study.

The below table provides the requested one-way sensitivity analysis considering different mortality rates between the PFS and Progressed health states. Here the base case values have been

systematically increased and decreased by 50% for both health states, summing to 8 sensitivity analyses. From this table, it is clear that the mortality rates do not have a large impact on the ICERs.

Table 13. Sensitivity analysis on alternative mortality rates

Scenario	PFS to death (monthly probability)	Progression to death (monthly probability)	Incre-mental costs	Incre-mental utilities	Cost per QALY gained
Base case	Maximum value from either background mortality or CLL-8 mortality for the R-FC and FC arms independently during PFS R-FC = 0.00119627 FC = 0.00138823	CLL-8 mortality derived across both arms of the trial post-progression Both = 0.0405144	£11,617	0.88	£13,189
New SA #1	+50% of base case	No change	£11,618	0.88	£13,188
New SA #2	-50% of base case	No change	£11,615	0.88	£13,191
New SA #3	No change	+50% of base case	£11,788	0.91	£13,013
New SA #4	No change	-50% of base case	£11,022	0.79	£13,886
New SA #5	+50% of base case	+50% of base case	£11,789	0.91	£13,012
New SA #6	-50% of base case	-50% of base case	£11,019	0.79	£13,890
New SA #7	+50% of base case	-50% of base case	£11,024	0.79	£13,883
New SA #8	-50% of base case	+50% of base case	£11,787	0.91	£13,014

A further sensitivity analysis may be to consider the possibility of different mortality rates in the two arms of the trial from within the progressed state. This was not feasible for the base case analysis due to the very high survival rate in the trial and the long duration of life expectancy anticipated for this patient population. Therefore there was no clinical basis to assume that the R-FC and FC arms would experience differential mortality rates in the post-progression state. This is further illustrated by the overlapping KM curve for post-progression survival by treatment provided in Figure 16 in the original submission.

However, we have considered the potential change in the ICER given a calibrated increase in the mortality rate for the R-FC arm only in the progressed health state, to the point where there is no expected increase in life years (thereby forcing the model to consider only the quality of life benefit provided by rituximab by prolonging PFS). The result is as follows:

By increasing the post-progression monthly mortality rate experienced in the R-FC arm by 315% of that experienced in the FC arm (FC monthly mortality = 0.0405144, therefore R-FC monthly mortality = 0.12762036), an outcome is reached where the life years gained in R-FC relative to FC is 0.00. This is presented in the table below.

Table 14. Outcome results for increased mortality in the R-FC arm to remove all gain in life expectancy

Outcome measure	R-FC	FC	Incremental

Mean Life Years (yrs)	4.66	4.65	0.00
Mean Life Years in PFS (yrs)	4.11	2.93	1.18
Mean life Years in Progression (yrs)	0.55	1.73	-1.18
Mean QALYs	3.62	3.38	0.24
Mean QALY in PFS	3.29	2.34	0.95
Mean QALY in Progression	0.33	1.04	-0.71

Despite this clinically implausible increase in mortality for the R-FC arm relative to the FC arm in the progressed health state, the resulting cost per QALY estimate is £30,336 per QALY gained.

Table 15. Outcome results for increased mortality in the R-FC arm to remove all predicted gain in life expectancy

Cost-utility results	RFC	FC	Incremental
Mean Life Years (yrs)	4.66	4.65	0.00
Mean QALYs	3.62	3.38	0.24
Mean Total Cost	£21,204	£13,978	£7,226
Cost per Life Year Gained (£)			**£3,473,529**
Cost per QALY Gained (£)			**£30,336**

B7. In the listed model weaknesses (page 156; item d), the assumption of aggregation in the PFS state is defended by reference to sensitivity analysis on the cost and utility differences, however, as the main impact of this assumption is caused by the differential mortality rates between PFS and progressed states, please clarify, how is this accounted for in the analysis?

For clarification, a weakness we considered related to the Progressed health state; where monthly costs, utilities and mortality rates from subsequent therapies are averaged across one single health state. These are also assumed equivalent across both arms. Whilst sensitivity analyses were provided on the impact of costs and utilities on the ICERs, we had neglected to include such analyses on the mortality rates. The above analysis addressed in Question B6 provides evidence that despite changes in the mortality rates used in the analysis, estimated ICERs are still robust.

Subgroups

B8. People with the p53 deletion/mutation were noted as a subgroup in the scope but are not analysed as a subgroup in the clinical effectiveness or economic analysis. Were such participants included in the trial and what was their outcome? Please provide a rationale for their exclusion as a subgroup in the submission.

This subgroup was discussed in section 6.4.2 (results). Quoting directly from the text:

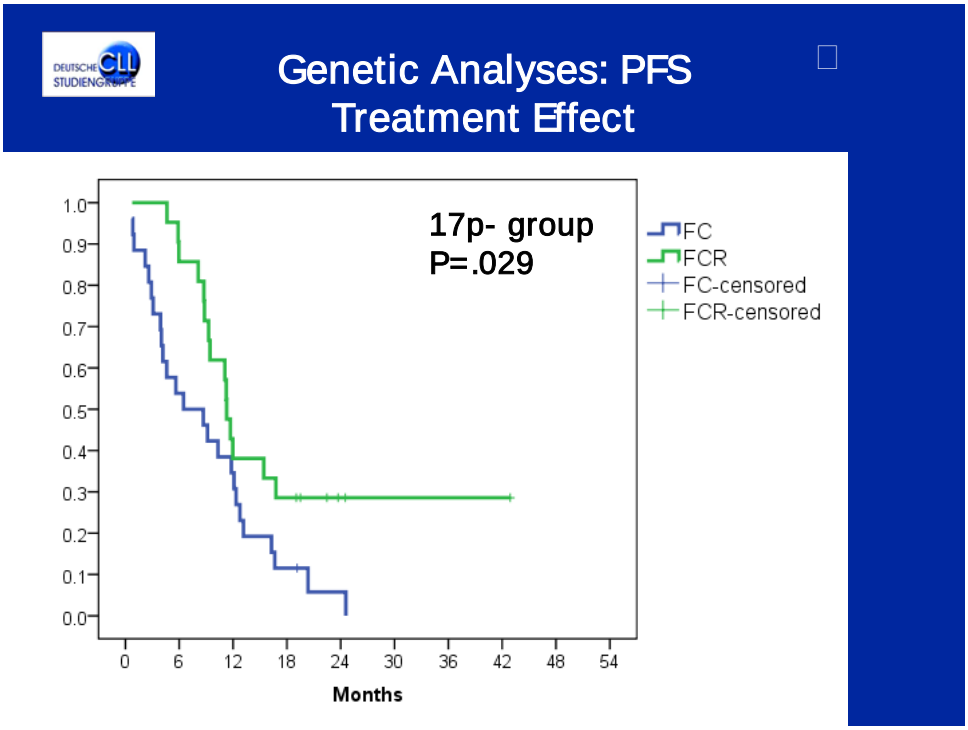
"Subgroup Analysis based on Cytogenetics at Baseline (specifically 17p deletion)

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

This subgroup made up approximately 8.2% of the total population who had cytogenetics tested for. Further analysis had not been undertaken and included in the document because at the time of submission, extra data was not available from this subgroup. Following the 2008 American Society of Haematology meeting, further data is available from this subgroup following the oral presentation by Dr Stephan Stilgenbauer (Abstract #781)[xi].

The results for the 17p- group are as follows: (FC and FCR); CR (4.5% and 19.0%), CR+PR (45.5% and 71.4%), PFS (at 24 months: 0.0% and 29.6%), and OS (at 24 months: 41.0% and 53.3%). The PFS curve is provide below, in Figure 3.

Figure 3: PFS for 17p- subgroup



The results highlight that PFS for the R-FC arm is significantly better than for FC alone, and at 2 years the addition of rituximab to FC led to 30% being progression-free at 2 years compared to 0% with FC. However it must be appreciated that the median PFS for both groups is very poor (8 months for FC and 13 for R-

FC). This highlights the well-known poor prognosis of patients in this subgroup. The optimal treatment for this group of patients has yet to be established and the clinical consensus suggests that an alemtuzumab-containing regime together with an early allogenic transplant may still an the optimal approach, although R-FC is clearly a superior option to FC alone.

An economic analysis was not performed as the PFS curves highlighted above were not available at the time of submission, **and with such a small non-randomised subgroup (n=46), any analysis would have very limited value.**

Costs

B9. Does the use of rituximab entail additional costs for testing CD-20 status of malignant cells?

No. All patients diagnosed with CLL would have white cell immunophenotyping on peripheral blood done as part of their initial work-up as this is core to confirming that the disease is CLL, rather than another malignant lymphoproliferative disorder. Thus the immunophenotype reveals the characteristic markers of CLL cells, and testing for CD20 is always part of this work-up.

B10. Please can you explain why the cost for FC and chlorambucil administration in table 37 (£371 per cycle) is different from that in tables 46 & 47(£280)? The difference in the figures not seem to be explained by adjusting for cycle length of one month in model versus the 28 day cycle in trial

This is a typographical error on our part in Table 37. The value should read £304.38 which is the value used in the model for both FC and chlorambucil administration costs per month (equal to £280 * 1.08707 cycles/month).

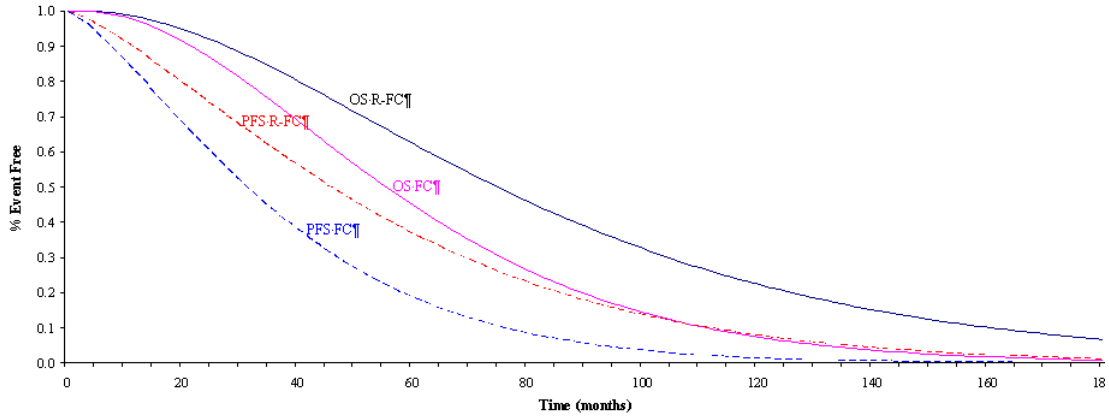
Textural issues

B11. Please clarify the following in the submission?

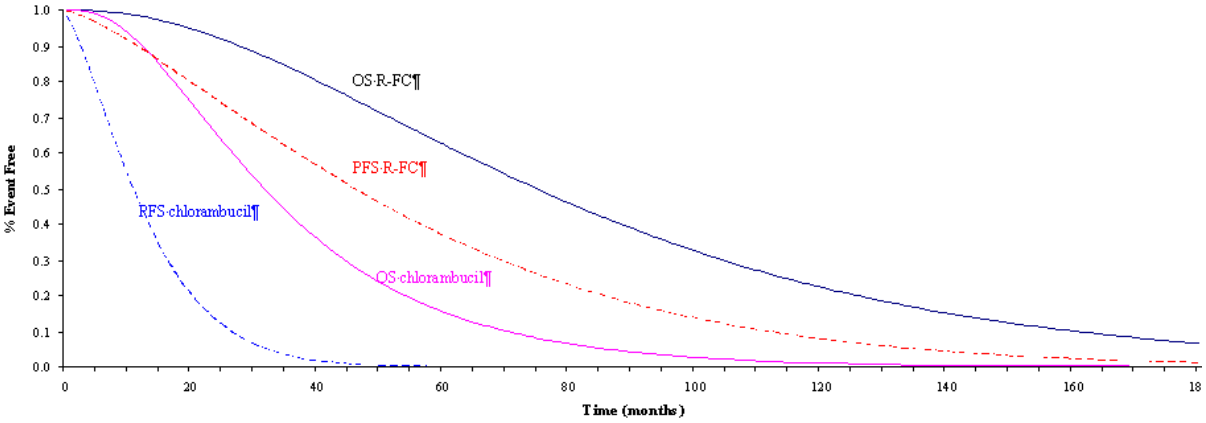
1. The labelling of curves in figures 17 and 18 (p121, 122) and the keys underneath the figures do not appear to match.

Please disregard the labelling in these previous figures and consider instead the figures provided below. Apologies for this confusion.

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



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



2. The text on p130 states that there were 5 and 3 bone marrow transplant events in R-FC and FC arms, while on p131, table 48, states 4 and 1 stem cell transplants in the R-FC and FC arms.

Bone-marrow transplants (BMTs) are the same as stem cell transplants (SCTs) in this context and we apologise for not using consistent wording. This issue has also brought a 'double-counting' error to our attention. A review of the data indicates that there are, in fact, 5 and 2 bone marrow transplants for the R-FC and FC arm captured from initiation of treatment to end of trial follow-up. In order to account for these errors, in the FC arm, the 3 BMTs have been replaced by 2 BMTs (which are accounted for in the supportive care cost in PFS) and the 4 and 1 SCTs (for R-FC and FC respectively) have been removed from the '2nd line and subsequent treatment costs' aggregated in the Progressed-health state (reducing this value from to £257.66 to £189.80 per month). Compared to the base case in the original submission, this increases the ICER from £13,189 to £13,428 per QALY gained.

Table 16. Base case result assuming cost of 5 and 2 BMTs included in PFS (for R-FC and FC respectively) and no SCTs double-counted in 2nd-line treatment costs

Cost-utility results	RFC	FC	Incremental
Mean Life Years (yrs)	5.73	4.65	1.07
Mean QALYs	4.26	3.38	0.88
Mean Total Cost	£24,278	£12,450	£11,828
Cost per Life Year Gained (£)			**£11,022**
Cost per QALY Gained (£)			**£13,428**

If we consider that the proposed change in Question B2 (removing the additional administration visit in cycle 1 for R-FC) should also be incorporated into the new base case ICER, then the values in Table 17 would apply. The net change in the ICER from the original submission is thereby minimal, as these two changes offset one another, with a final ICER of £13,107 per QALY gained.

Table 17. Base case result assuming cost of 5 and 2 BMTs included in PFS (for R-FC and FC respectively), no SCTs double-counted in 2nd-line treatment costs, and 1 administration visit in Cycle 1 for R-FC

Cost-utility results	RFC	FC	Incremental
Mean Life Years (yrs)	5.73	4.65	1.07
Mean QALYs	4.26	3.38	0.88
Mean Total Cost	£23,995	£12,450	£11,545
Cost per Life Year Gained (£)			**£10,758**
Cost per QALY Gained (£)			**£13,107**

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