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Tuesday 1st December 2009

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BY E-MAIL

Dear Laura,

SINGLE TECHNOLOGY APPRAISAL – Rituximab for the treatment of relapsed/refractory CLL

Thank you for sending us the Appraisal Consultation Document (ACD) for this rituximab technology appraisal.

Roche has several comments to make on the ACD outlined below under the 4 standard headings.

Please do not hesitate to contact us should you require any further information or clarifications.

Yours Sincerely

(1) Do you consider that all of the relevant evidence has been taken into account?

Although included in our original submission and ERG clarification response, data which has now been published by the MD Anderson Cancer Centre (MDACC) since the original Roche submission has not been sufficiently considered with regard to the two sub-groups currently excluded within the ACD; (a) rituximab pre-treated patients and (b) fludarabine-refractory patients.

(a) Rituximab retreated patients demonstrate similar clinical benefits compared with patients who are rituximab naïve and this translates to similar cost-effectiveness estimates for the retreated population. Consequently to not recommend rituximab within this population is not consistent in light of the new available evidence

Phase II data from the MDACC included in our original submission (subsequently presented at the 13th International Workshop on CLL (iwCLL) in October) shows similar response rates for rituximab naïve and pre-treated relapsed/refractory CLL patients salvaged with R-FC between 1999 and 2008 (section 6.8.4.3 of our original submission). Furthermore, long term clinical outcome data from the same study demonstrates no significant difference in TTP (Figure 1) and OS (Figure 2 and Table 1) in R-FC salvaged patients irrespective of whether they had previously received rituximab or not (clarification letter 12th August 2009 pp 92-94).

Figure 1. Time to progression for salvage R-FC by rituximab status

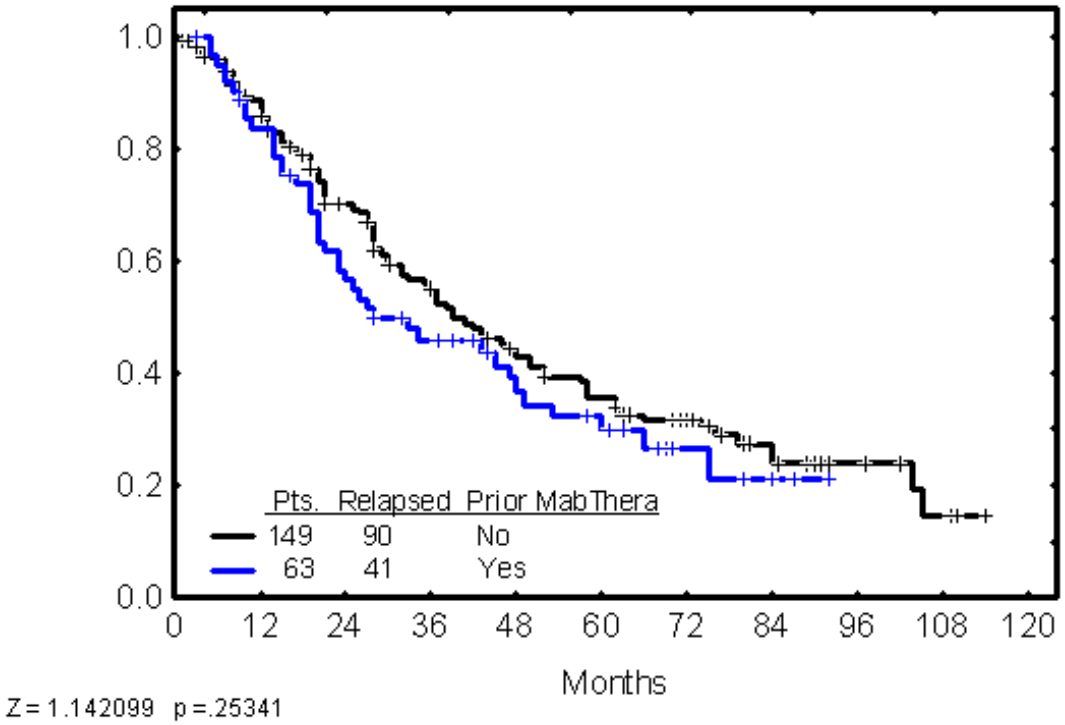

Figure 2. Overall survival for salvage R-FC by rituximab status

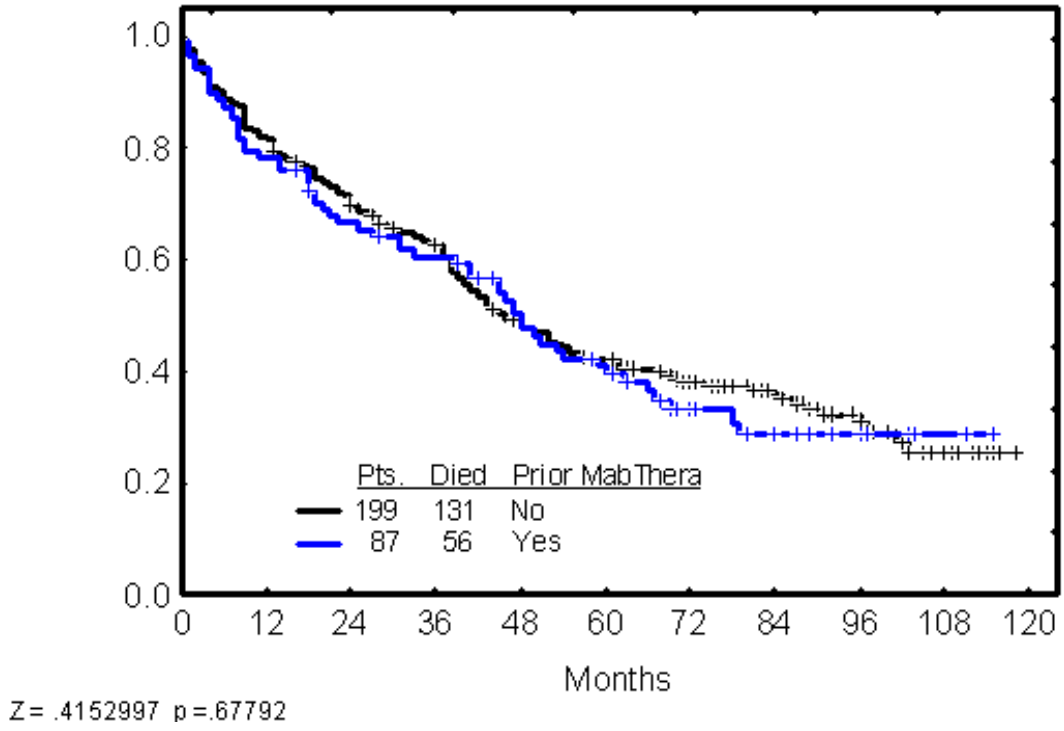

Table 1. Overall survival for salvage R-FC by rituximab status

Variable	Estimate	SE	HR	p-value	Total	Event	Censor
Prior rituximab	0.084	0.156	1.087	0.5916	284	181	103

Statistical analyses confirm no significant difference (p>0.05) in clinical benefit (CR, OR, TTF, and OS) associated with R-FC salvage treatment based on prior rituximab exposure (Table 2). These data were recently presented at the iwCLL conference in Barcelona (Badoux X et al, 2009[1]) and an electronic copy has been supplied with the references associated with this ACD response.

Table 2. R-FC clinical outcomes by prior rituximab status

Risk Factor	Levels	N (%)	CR %	OR %	TTF (mo)	OS (mo)
All		**280 (99)**	**31**	**75**	**21**	**46**
Prior rituximab	**No**	**182 (65)**	**30**	**76**	**21**	**48**
	Yes	**98 (35)**	**32**	**73**	**20**	**45**

A progression-free survival Kaplan-Meier curve has recently been provided by the MDACC for the specific purposes of this ACD consultation. Consistent with data previously supplied, this demonstrates no significant difference in treatment effect in rituximab naïve and pre-exposed patients (p=0.44; Figure 3 and Table 3).

Figure 3. Progression-free survival for salvage R-FC by rituximab status

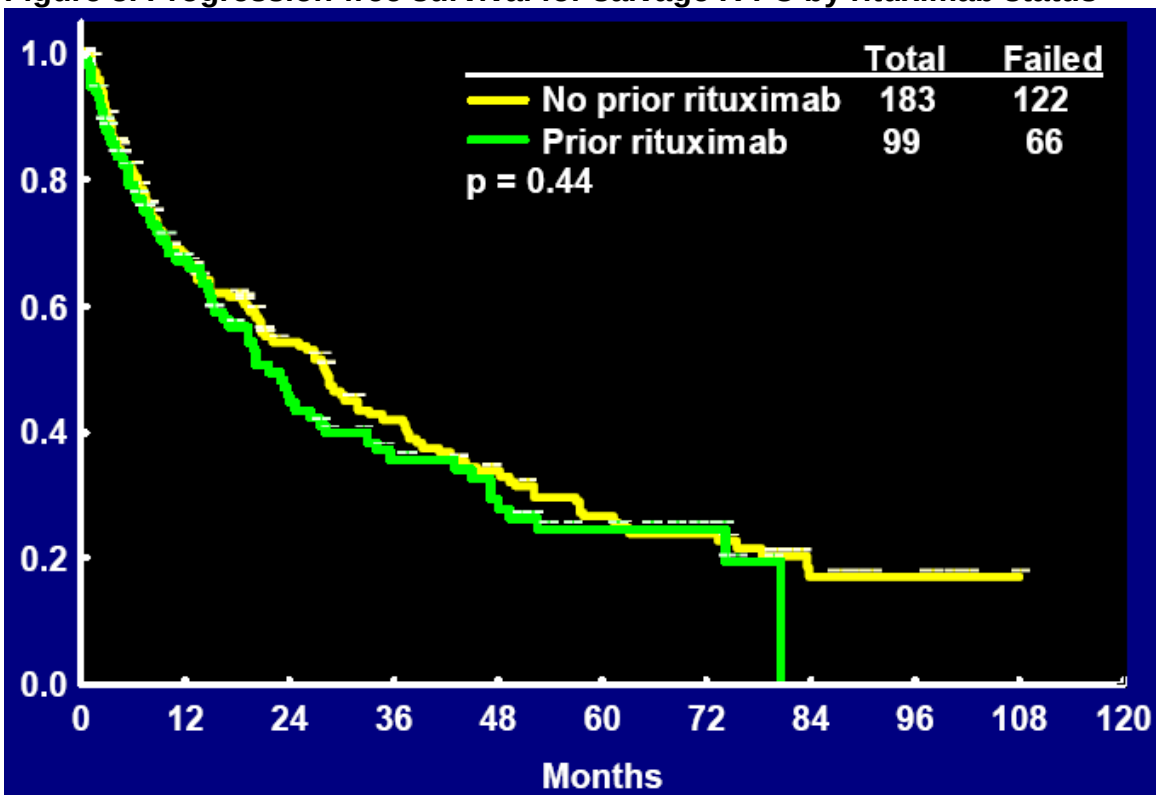

Table 3. Progression-free survival for salvage R_FC by rituximab status

Variable	Estimate	SE	HR	p-value	Total	Event	Censor
Prior rituximab	0.121	0.154	1.13	0.431	282	188	94

As these curves have been generated from non-randomised data, it is important to further understand if the two groups are comparable with regards to patient characteristics. Also if any selection bias is apparent, in which direction this may influence the outcomes. The table below provides details with regards to several known risk factors, stratified by prior rituximab treatment in this population (Badoux X et al [in advance of publication][2]).

Table 4. Patient characteristics for salvage R-FC treatment by prior rituximab status

FCR patients (N=284)	No prior R	Prior R	p-value
Number	*184*	*100*	-
> 2 prior treat (%)	22	47	p<0.0001
Median age (y)	59	60	NS
Median B2M (mg/l)	4.5	4.3	NS
Rai stage III or IV (%)	48	41	NS
F-refractory (%)	18	20	NS
Abn 17 or complex (%)[1]	21	27	NS
Bulky disease (%)	27	19	p=0.15
IgVH MS (% unmut) [2]	67	71	NS

Missing values: [1]n= 100 , [2]n=198

As shown in Table 4, patient characteristics, including age, disease stage and chromosome 17 aberrations/complex cytogenetics, were generally well balanced between the rituximab pre-exposed and naïve patient groups, thus minimizing the effect of any selection bias in the efficacy data. Of note, however, a significantly greater number of rituximab pre-treated patients had received 2 or more prior treatments compared to the rituximab naïve patients. Exposure to greater numbers of lines of therapy is a known risk factor correlating with poorer outcomes, as highlighted in the iwCLL poster (Badoux X et al*,* 2009[1]*)* and summarised in Table 5 below. Despite this imbalance, clinical outcomes for rituximab pre-treated patients were not shown to be significantly different to those for rituximab naive patients.

Table 5. R-FC treatment effect by number of prior treatments

Risk Factor	Levels	N (%)	CR %	OR %	TTF (mo)	OS (mo)
All		**280 (99)**	**31**	**75**	**21**	**46**
Number of prior treatments	**1**	**116(41)**	**44**	**82**	**30**	**61**
	2	**78(28)**	**33**	**77**	**28**	**53**
	3	**44(16)**	**18***	**73**	**21***	**39***
	≥4	**42 (15)**	**2****	**57***	**9***	**25***

*** p<0.05, **p<0.001**

Estimated ICER for R-FC in rituximab pre-exposed patients

The cost-effectiveness of R-FC in patients with prior rituximab exposure can be approximated by making one small adjustment to the REACH model already assessed by NICE and the ERG. Univariate analysis from this dataset indicate a non-significant (p=0.431) hazard ratio (HR) of 1.13 for progression-free survival based on rituximab status as noted in Table 3. If one assumes that the proportional hazards is maintained then the HR for PFS of 1.13 can be applied to the lambda element of the R-FC weibull parameter to reflect the impact of R-FC

on a rituximab-retreated population, relative to the REACH rituximab-naïve population. No change is made to the FC curve – thus making the implicit assumption that previous rituximab exposure does not impact the benefit of FC. This can be considered a conservative assumption as it is possible this will reflect an overestimation of the benefits of FC in this setting.

By applying the above hazard ratio to the REACH PFS curve for R-FC, the discounted mean time in PFS has decreased from 3.099 in the base case to 2.818 (a decrease of 0.281 years or 3.4 months of PFS advantage). This model adjustment also decreased the discounted mean life expectancy from 5.207 in the base case to 5.001 (a decrease of 0.206 or 2.5 months of overall survival advantage). These results are provided in Table 6 below.

Table 6. Outcome measures for a rituximab re-treated population

Outcome measure	R-FC	FC	Incremental
Mean Life Years (yrs)	5.001	4.536	0.465
Mean Life Years in PFS	2.818	2.185	0.633
Mean life Years in Progression	2.183	2.351	-0.168
Mean QALYs	3.564	3.158	0.406
Mean QALY in PFS	2.254	1.748	0.506
Mean QALY in Progression	1.310	1.411	-0.101

By applying this non-significant hazard ratio to the REACH PFS curve for R-FC, the cost per QALY increases from £15,593 in the base case analysis to £22,519 for a rituximab pre-treated population (see Table 7). This cost per QALY could be considered an overestimation for several of the potential reasons listed below:

1. The hazard ratio (1.13) used to transform the rituximab-naïve REACH R-FC PFS curve into a rituximab pre-treated curve was not significantly different from 1 (p=0.431).
2. The FC PFS curve from REACH was not altered, therefore implying that FC patients would perform as well as they did in the REACH trial even if they were previously exposed to rituximab.
3. The hazard ratio is based on a non-randomised comparison with more patients in the rituximab pre-exposed arm having received 2 or more prior treatments (a known risk factor for poorer outcomes) than those in the rituximab-naive arm.

Table 7. Cost-effectiveness for a rituximab re-treated population

Cost-utility results	R-FC	FC	Incremental
Mean Life Years (yrs)	5.001	4.536	0.465
Mean QALYs	3.564	3.158	0.406
Mean Total Cost	£21,099	£11,964	£9,134
Cost per Life Year Gained			£19,643
Cost per QALY Gained			£22,519

Given that the ICER of £22,519 per QALY may represent an overestimate of the true cost-effectiveness in treating this patient population, it can be inferred with some certainty that treating relapsed/refractory CLL patients with R-FC therefore represents a clinically and cost-effective used of NHS resources, regardless of previous rituximab treatment status.

Clinical practice considerations

Following discussions with leading UK haematologists, it is also widely believed that it would be counterintuitive to prevent rituximab retreatment in patients who achieved a profound and prolonged response to initial rituximab-containing therapy. Indeed, this would contradict current ESMO guidelines which state that "*the first-line treatment may be repeated if the relapse or progression occurs >12 months after the initial therapy*" (Eichhorst et al, 2009[3]).

(b) F-refractory CLL patients represent a difficult to treat, high-risk subgroup for whom rituximab in combination with FC, as well as other chemotherapy regimens, represent effective treatment options, with efficacy comparable to that reported using alternative salvage therapies.

In section 4.15 of the ACD, NICE state that results from the MDACC (included in our original submission) "…*showed a lower response to treatment with rituximab plus fludarabine and cyclophosphamide in CLL that was refractory to fludarabine than in disease that was sensitive to fludarabine*".

Whilst this statement is correct, and indeed whilst updated long term outcome data presented at iwCLL (Badoux X et al, 2009[1]) demonstrated shorter TTF and OS for R-FC salvage therapy in F-refractory versus F-sensitive patients (Table 8), this is maybe not unexpected in such a high-risk, hard to treat subgroup of patients for whom very few viable therapeutic options exist. This reduction in efficacy would also be applicable to an FC treated patient and therefore one can not dismiss the possibility of a treatment effect for rituximab being observed within this population.

In reality, a CR rate of 8% and ORR of 57% with a median OS of 37 months compares more than favourably with data generated using other available treatment options in similar sized studies of fludarabine refractory patients, including alemtuzumab, high-dose methylprednisone, and even newer targeted therapies such as ofatumumab.

Table 8. R-FC treatment effect by fludarabine refractoriness status

Risk Factor	Levels	N (%)	CR %	OR %	TTF (mo)	OS (mo)
All		**280 (99)**	**31**	**75**	**21**	**46**
Fludarabine Refractory	**No**	**227(81)**	**36**	**80**	**27**	**51**
	Yes	**53(19)**	**8****	**57***	**7****	**37***

*** p<0.05, **p<0.001**

To put these numbers into perspective, alemtuzumab is currently licensed in the EU as monotherapy for the treatment of patients who have failed to achieve a complete or partial response or achieved only a short remission (less than 6 months) following fludarabine phosphate therapy *(*Alemtuzumab SmPC[4]). This licence was granted based on data from three small phase II non-comparative studies reporting CR rates ranging between 0 and 2% and OR rates between 21 and 33%. Median OS for all patients in these studies ranged between 16 and 28 months (Keating et al, 2002[5]; EMEA scientific discussion on alemtuzumab[6], 2005; Rai et al, 2002[7]). High-dose methylprednisone (HDMP) is a widely used alternative treatment option for fludarabine refractory patients despite little published data. In a report from the Royal Marsden Hospital, 14 fludarabine-refractory patients treated with HDMP achieved an ORR of 55% with no complete responders (Thornton et al, 1999[8]). Median duration of response

reported in this study was 8 months (range 6-78). Finally, in a recent phase III study, 79 fludarabine refractory patients with bulky disease treated with the human anti-CD20 monoclonal antibody ofatumumab achieved an ORR of 47% (CR 1%), with a median PFS of 5.9 months and median OS of 15.4 months (Osterberg et al, 2009[9]) (summarised in Table 9 below).

Table 9. Summary of efficacy data for treatments in fludarabine-refractory CLL patients

Regimen	N	CR %	OR %	TTF (mo)	Remission duration (mo)	OS (mo)
R-FC	**53**	**8**	**57**	**7**	**-**	**37**
Alemtuzumab[5]	**93**	**2**	**33**	**-**	**4**[#]	**16**
Alemtuzumab[6]	**32**	**0**	**21**	**-**	**5**[#]	**26**
Alemtuzumab[7]	**24**	**0**	**29**	**-**	**7**[#]	**28**
HDMP	**14**	**0**	**55**	**-**	**8**[#]	**-**
Ofatumumab	**79**	**1**	**47**	**-**	**6***	**15**

*Median PFS; [#]Median duration of response

High un-met need in the treatment of fludarabine-refractory CLL patients considering existing NICE guidance

Following the publication of TA174 last July, R-FC will displace FC as a cost-effective first-line treatment for CLL. At the present time, however, FC is still considered standard second-line treatment for CLL patients who are fit enough to receive combination therapy, with approximately 37% of eligible patients receiving treatment. Furthermore, according to market research data, approximately 19% of patients in the UK receive fludarabine monotherapy as a salvage option (Genactis NHL & CLL Patient Case Record Study Q2 2009[10]). For CLL patients who are refractory to either fludarabine monotherapy or FC, salvage with an R-chemotherapy combination regimen is a clinically effective treatment option. As outlined in our original submission (section 6.8.4.2), several of these regimens (including R-FC as discussed above) have demonstrated efficacy in this hard to treat group of patients.

By precluding the use of rituximab in combination with chemotherapies other than FC, some higher-risk patients may be ineligible for treatment due to lack of available options in the choice of chemotherapy partners for rituximab. For example, in F-refractory patients for whom fludarabine-based therapy is contraindicated (e.g. due to renal impairment or previous infection), R-CHOP is a clinically effective option. Rituximab plus HDMP is also an option in F-refractory patients unable to tolerate a more intensive combination regimen. Recommending the use of rituximab with any chemotherapy would increase options to optimally treat this high risk group of patients who currently have limited treatment options. This would also be consistent with current ESMO

guidelines which recommend the use of fludarabine combinations (FC or FCM) ± monoclonal antibodies (R-F, R-FC or F-alemtuzumab) in fludarabine-refractory patients or patients who have relapsed after fludarabine-based therapy (Eichhorst et al, 2009[3]).

Estimating the cost effectiveness of R-FC or R-chemo in F-refractory patients

It is also important to understand if R-FC (or R-chemo more generally) represents a cost-effective treatment option for fludarabine refractory patients relative to their current standard of care. It has not been feasible to conduct an economic analysis on this population to date, due to the lack of evidence to determine the baseline risk or to quantify the treatment effect of adding rituximab to standard chemotherapy in this specific patient population. To this end, we are currently liaising with the MDACC to see if it is feasible to extract such data to build an appropriate health economic model. Whilst it has not been possible to obtain this data for the required ACD response deadline of 1st December, efforts are ongoing. We will certainly share any such findings should they become available prior to the committee meeting on 13th January if considered appropriate by NICE.

(2) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

We would like to highlight some factual inaccuracies in the ACD summary of rituximab retreatment (a). In addition, following correspondence with the ERG, we would like to present corrected ICERs for one of the ERG exploratory analyses (b).

a) Rituximab re-treatment

In section 4.13 of the ACD, NICE suggest that "*…there could be a lower response rate in people who had previously received rituximab*". This is not the case, based on phase II data from the MDACC (included in our clarification response on 12th August 2009 and provided in section (1) above).

In section 4.13 of the ACD, NICE suggest that "*…people who had received first-line rituximab treatment and had relapsed would not be widely observed in clinical practice for a considerable period of time*". Whilst previously untreated CLL patients who receive R-FC can, on average, expect a disease-free period of around 52 months (Hallek et al, 2009[11]) before relapse (based on data from the pivotal CLL-8 trial), NICE appear to be assuming that 1st-line R-FC usage in the UK was negligible prior to publication of positive guidance in July 2009.

Market research commissioned by Roche (see Appendix 1 for details), shows that in Q2 2009 ~24% of patients eligible for rituximab in combination with chemotherapy were treated accordingly[10] (Table 10). Therefore greater numbers of CLL patients relapsing after first-line rituximab can be expected to present significantly earlier than NICE anticipate (see Table 11 below). If the appraisal committee's preliminary recommendations remain unchanged, approximately 232 patients may potentially be ineligible for treatment with the most effective relapse treatment regimen currently available over the next 3 years.

Table 10. First-line R-chemotherapy usage in the UK

	Q4 2006*	**Q4 2007***	**Q2 2008***	**Q4 2008***	**Q2 2009***
1st line rituximab use	4%	9%	14%	6%	24%

*Source: Genactis NHL & CLL Patient Case Record Study 2006-2009[12]

Table 11. Model of 2nd-line CLL patients anticipated to be ineligible for rituximab re-treatment over the next 3 years based on current recommendations

	2008	**2009**	**2010**	**2011**	**2012**
Patients eligible for 1L treatment	1495	1512	1530	1555	1581
% Pts on rituximab (%)[#]	6	24	57	63	65
Actual Pts on rituximab	90	363	872	980	1027
% Relapsed from Yr -1 (%)*	0	0	10	20	10
% Relapsed from Yr 0 (%)*	0	0	0	10	20
% Relapsed from Yr 1(%)*	0	0	0	0	10
No. Relapsed from Yr -1	**0**	**0**	**9**	**18**	**9**
No. Relapsed from Yr 0	**0**	**0**	**0**	**36**	**73**
No. Relapsed from Yr 1	**0**	**0**	**0**	**0**	**87**
2L pts ineligible for rituximab re-treatment	**0**	**0**	**9**	**54**	**169**

Assumptions:

[#] Based on Genactis NHL & CLL Patient Case Record Study 2006-2009[12] and Roche forecast model 2010 onwards[13]

* Based on CLL8 PFS data[14] (approximate 10% relapse at 12 months, 20% at 24 months, 40% at 36 months, and 50% at 48 months) and assuming patients relapsing from R-FC within 12 months would not be considered for re-treatment

In summary, this evidence demonstrates that the impact of negative guidance in the rituximab previous treated population would have an immediate impact on patient access to rituximab in the relapsed setting.

b.) Corrections to the ERG's exploratory analysis on the cost of rituximab

Following the publication of the ACD, Roche sought clarification regarding an ERG analysis on the cost of rituximab. As a result of this dialogue, the ERG confirmed that their analysis of the cost of rituximab contained an error and resulted in an overestimation of their proposed base case ICER. As a result, in section 3.19 and 4.2 of the ACD, it should read that the ERG base case ICER is £16,607. This is approximately £1,000 per QALY higher than the Roche presented base case ICER due to increased precision in the timing of rituximab administration accounted for by the ERG in the economic model. This would replace the incorrect cost per QALY of £18,129 currently reported in the ACD.

(3) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

Roche agrees with the appraisal committee's preliminary recommendations for R-FC as a treatment option for relapsed/refractory CLL patients, however, we believe that the restrictions on the eligible population are too limiting based on the existing evidence base. In summary:

- Rituximab pre-treated patients demonstrate equivalent clinical efficacy to rituximab naive patients when retreated with R-FC. Furthermore, health economic sensitivity analyses demonstrated a cost-effectiveness ratio of approximately £22,000 per QALY for this subgroup, suggesting that rituximab re-treatment would be a cost-effective use of NHS resources (see section 1a above).

- F-refractory patients are a difficult to treat population incorporating F-monotherapy, FC, and R-FC refractory patients
    - We would agree that R-FC is not a viable treatment option for R-FC refractory patients.
    - F-mono refractory and FC-refractory patients do, however, derive clinical benefit from rituximab in combination with several different baseline chemotherapy regimens, with efficacy data comparing more than favourably with that generated using other available treatment options for this high risk group. We have requested a feasibility count from the MDACC to explore the viability of demonstrating cost-effectiveness within this patient population. Unfortunately, despite our best efforts, it has not been possible to acquire this data within the timelines for the ACD response.

(4) Are there any equality related issues that need special consideration that are not covered in the ACD?

Two specific patient groups would currently be excluded from rituximab treatment given the current guidance as they are not eligible for FC, these include (a) older, frailer patients and (b) younger, fit patients with renal impairment. These are different to the F-Refractory patient group and therefore Roche consider may warrant further consideration by the committee, as currently these are excluded from receiving rituximab within the ACD.

(a) It is well established that a significant proportion of relapsed CLL patients requiring treatment will not be suitable for a fludarabine-containing regimen* and chlorambucil-based treatment would be much more suitable and tolerable (*market research data shows that 40% of relapsed/refractory patients are treated with non-fludarabine based chemotherapy +/- rituximab - Genactis NHL & CLL Patient Case Record Study Q2 2009[10]). Roche accept that that there are no large multi-centre phase III studies of rituximab plus chlorambucil compared to chlorambucil alone in previously treated CLL patients, however, the combination of rituximab and chlorambucil in first-line CLL is currently being actively investigated in a UK only phase II clinical trial (UK CLL208), led by Professor Peter Hillmen.

Since the original Roche submission this study has now fully recruited (100 patients) with efficacy and safety data for the first 50 patients due to be presented at ASH in December of this year. Results from this planned interim analysis demonstrate an overall response rate of 84%. When compared with a well matched subset of chlorambucil patients from the UK LRF CLL4 study, the overall response rate was 17.3% higher (95% CI 4.7% - 30.0%), indicating that the rituximab plus chlorambucil patients have improved responses (Hillmen et al, 2009[15]). Extrapolating results from this 1st-line trial, R-chlorambucil would allow the opportunity for a relapsed CLL patient who is too fit for chlorambucil monotherapy, but not fit enough for fludarabine based treatment due to age/performance status to obtain a deeper remission and longer progression-free survival than offered by chlorambucil alone.

(b) For younger CLL patients who are renally impaired (thereby restricting eligibility of fludarabine-based treatments) rituximab plus chlorambucil may be preferred in an attempt to maximize clinical benefit whilst minimizing systemic toxicity due to delayed drug excretion. Rituximab in combination with regimens such as CHOP or bendamustine are additional treatment options for these patients. As already discussed in our submission (section 6.8.4), both of these combinations have demonstrated efficacy in previously-treated CLL patients (Eichhorst et al, 2005[16]; Fischer et al, 2008[17]).

Appendix: Background on Genactis NHL & CLL Patient Case Record study

The Genactis NHL & CLL Patient Case Record Study is a market research study commissioned by Roche and conducted by Genactis, an independent market research agency.

The study has been conducted once a year since 2002 and twice per year since 2008. Each wave runs for a 3-month period. Since 2006 the Genactis survey has collected information from 811 CLL patient records, 475 of which were treated with first-line therapy (see detailed breakdown below).

Survey Period	Total CLL Patient Records	1st-line CLL Patient Records
Q4 2006	141	75
Q4 2007	138	68
Q2 2008	182	102
Q4 2008	185	115
Q2 2009	165	115

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