Obinutuzumab in combination with Chlorambucil for previously untreated chronic lymphocytic leukaemia: a critique of the submission from Roche

Errata

22nd August

In this document, we only include the revised pages that replace those in our original report in response to factual errors identified by Roche. Amendments to the text are in red font for clarity. Deletion, where no text replacement was made, are shown as a tracked change. Page numbering is as per our corrected report (22 August 2014)

[[NB: This document should be used in conjunction with the corrected report; i.e. correction for page numbering and cross references within text]]

of response, time to re-treatment / new anti-leukaemic therapy, overall survival, end of treatment response, best overall response, best overall response within 1 year of start of study treatment, molecular remission, safety assessments (including adverse events, standard laboratory assessments and vital signs), and patient reported outcomes.

The dose of chlorambucil in CLL11, 5mg/kg given on day 1 and 15 of all treatment cycles 1 to 6, is substantially lower than that used in routine clinical practice. We understand that chlorambucil is generally given at a dose of 10mg/m2 for 7 days every month for up to 12 months. Assuming typical body weights and body surface areas, this gives a total dose per cycle in CLL11 of 70mg versus 120mg in general practice. If chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab+chlorambucil versus chlorambucil is uncertain in CLL11. However, we are not aware of any randomised trials comparing chlorambucil at differing doses, and so we cannot be certain of any bias.

Trial results

There are significant improvements in both progression-free survival and overall survival for obinutuzumab+chlorambucil compared to chlorambucil alone and rituximab+chlorambucil. Based on the May 2013 data cut-off, at the end of stage 1, the Kaplan-Meier estimated median PFS was 11.1 months in the chlorambucil arm compared with 26.7 months in the obinutuzumab+chlorambucil arm (HR 0.18 ,95% CI (0.13-0.24), p<0.001). PFS was 11.1 months in the chlorambucil arm compared with 16.3 months in the rituximab+chlorambucilarm (HR 0.44, 95% CI [0.34 – 0.57]), p<0.001). At the end of stage 2, the addition of obinutuzumab to chlorambucil (obinutuzumab+chlorambucil) resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of investigator-assessed PFS compared to rituximab+chlorambucil (stratified HR 0.39 [95% CI: 0.31-0.49]). The Kaplan-Meier estimated median PFS was 15.2 months in rituximab+chlorambucilarm and 26.7 months in the obinutuzumab+chlorambucil arm; an 11.5 month improvement.

Results from the most recent data cut (3rd March 2014; confidential) showed that patients receiving obinutuzumab in combination with chlorambucil had [redacted]

[redacted]

The results of the subgroup analyses of investigator-assessed PFS were consistent with the results seen in the overall ITT population.

Twenty five percent of patients on chlorambucil crossed over to obinutuzumab+chlorambucil on disease progression (Source: Roche Submission, Section 6.3.8, pp58-59). Overall survival (OS) is immature, with most patients still alive at data cut-off. Based on the May 2013 data cut-off, an improvement in OS was observed with obinutuzumab+chlorambucil when compared with chlorambucil alone (HR: 0.41 [95% CI: 0.23 to 0.74], p=0.002). When obinutuzumab+chlorambucil was compared with rituximab+chlorambucil, the hazard ratio was of 0.66 ([95%CI: 0.41 to 1.06], p=0.08).

The most recent confidential results for overall survival (OS) show a [redacted]

In addition, the obinutuzumab+chlorambucil arm had a statistically significant greater event-free survival (p<0.0001 both), end of treatment response (p<0.0001 versus both chlorambucil and rituximab+chlorambucil), MRD-negative rate (26.79 [19.5 - 34.1] versus chlorambucil and 23.06 [17.0 - 29.1] versus rituximab+chlorambucil), best overall response (p<0.0001 versus chlorambucil and p=0.0001 versus rituximab+chlorambucil), disease free survival (p<0.0001 versus chlorambucil and p=0.0475 versus rituximab+chlorambucil), and time to new treatment (p<0.0001 versus chlorambucil and p=0.0018 versus rituximab+chlorambucil) compared to chlorambucil and rituximab+chlorambucil. The significantly prolonged time to new anti-leukaemia therapy with obinutuzumab+chlorambucil compared with rituximab+chlorambucilor chlorambucil means that patients experience a longer period off treatment.

The safety profile of obinutuzumab was generally comparable to that of rituximab+chlorambuciland chlorambucil alone in terms of the severity of AEs and AEs

leading to death. Most AEs were mild to moderate in severity. The incidence of fatal haemorrhagic events was similar between arms, however all such events in obinutuzumab patients occurred in Cycle 1, compared to none in rituximab+chlorambucil patients and 1 in chlorambucil patients. The incidence of IRRs (infusion related reactions), neutropenia, thrombocytopenia and leukopenia was higher (>5% difference) in the obinutuzumab based arm than in the rituximab+chlorambucilor chlorambucil arms of the study. Serious infections, however, were more common in the chlorambucil arm and more people died in that arm, mainly due to progressive disease.

As compared with both patients receiving obinutuzumab+chlorambucil and those receiving chlorambucil alone, patients receiving rituximab+chlorambucilwere less likely to discontinue therapy early owing to adverse events. The imbalance between the obinutuzumab+chlorambucil group and the rituximab+chlorambucilgroup was primarily due to higher incidence of infusion-related reactions in the obinutuzumab+chlorambucil group. The majority of IRR events in the obinutuzumab+chlorambucil arm were low grade in intensity and were clinically manageable by having their treatment regime modified or delayed. However, there were more withdrawals from treatment with obinutuzumab+chlorambucil (7% (ObClb) vs. < 1% (RClb) and more patients were hospitalised (8% (ObClb) vs. 2% (RClb). Most grade 3 or 4 infusion-related reactions occurred in 20% of patients during the first infusion of obinutuzumab, but there were no grade 3 or 4 reactions during subsequent obinutuzumab infusions. The observed effect of rapid and profound B cell depletion by obinutuzumab [3] may explain the intensity of the first episode of IRRs, the high incidence at Cycle 1 and the low incidence of IRRs subsequently as well as the differences in the clinical course compared with rituximab.

We find the CLL11 study to be generally of high quality. The main limitation of the trial's design is that it was open label. Due to the different routes of administration for the intervention and comparators the study lacked blinding for both participants and investigators. It should be noted that awareness of allocation will have introduced the potential for bias in the study, for progression-free survival, and particularly with reporting of adverse events. The primary outcome of this study was progression-free survival (PFS) by investigator review. There is a chance that these results may be biased by additional unscheduled assessments and knowledge of treatment allocation. However, the investigators' assessments of patients' responses were checked by an independent review committee (IRC); members of the IRC were blinded to treatment which should reduce the risk for bias.

Given that the hazard ratios that we estimate for patients <65 and ≥ 65 are so similar, we believe that we should assume that the hazard ratio between bendamustine and chlorambucil for patients aged ≥65 should be assumed to be same as the hazard ratio for all patients in the bendamustine trial, i.e. 0.35.

Given that the hazard ratio between obinutuzumab+chlorambucil and chlorambucil from CLL11 was [redacted], we estimate the hazard ratio between obinutuzumab+chlorambucil and bendamustine simply as [redacted] / 0.353 = [redacted] Table 24 (p92). Henceforth, we assume that the PFS hazard ratio between obinutuzumab+chlorambucil and bendamustine for patients relevant to this HTA is 0.55.

For the indirect comparison to be appropriate, we assume that the PFS hazard ratio of bendamustine versus chlorambucil for patients unsuited to fludarabine can be approximated by the PFS hazard ratio of bendamustine versus chlorambucil in the bendamustine trial for patients aged ≥65. Specifically, the median age in CLL11 was 73 years. Assuming that patients in CLL11 were all unsuited to fludarabine, we therefore assume that the PFS hazard ratio of bendamustine versus chlorambucil for patients aged ≥65 equals that for patients aged 73. We believe these assumptions are reasonable.

We note that the choice of PFS hazard ratio is important, because under Roche's base case, the ICER between obinutuzumab+ chlorambucil and bendamustine is £26,000 per QALY, whereas using a value of 0.55, the ICER increases substantially, to £37,000 per QALY. This constitutes Item 6 in the PenTAG base case (Table 45, p156).

We have two further criticisms of Roche's mixed treatment analysis:

- Many of the trials in the large network include fludarabine-containing treatments. Given that the patients in this HTA are unsuited to fludarabine, Roche are making the assumption that the effect of age estimated from all trials in the network also applies to those trials that do not include fludarabine. If we believe this is an assumption too far and exclude all trials containing fludarabine, it is not possible to estimate an age effect on the hazard ratio because comparisons between all trials are informed by just one trial.

- The mean dose of chlorambucil per cycle was far lower in CLL11 compared to the bendamustine RCT: 70 vs. 112mg, and the mean total dose of chlorambucil was far lower in CLL11 compared to the bendamustine RCT: 329 vs. 549mg. If, as our clinical expert believes, chlorambucil is more effective at higher doses, the relative dosing in the two RCTs would bias the effectiveness of obinutuzumab+chlorambucil vs. bendamustine in favour of

obinutuzumab+chlorambucil . However, we are not aware of any randomised trials comparing chlorambucil at differing doses.

In addition, as in the CLL11 RCT, the bendamustine RCT was open label. This may have biased PFS.

p20 cont.

1.2.3 Bendamustine+rituximab effectiveness

The results of the MaBLe RCT of bendamustine plus rituximab vs. rituximab plus chlorambucil are not yet published. Therefore, in their base case Roche used an indirect method to estimate the PFS hazard ratio between obinutuzumab+chlorambucil and bendamustine + rituximab. This method uses the estimated % of complete responders for the sample size calculations in the MaBLe RCT and assumes perfect correlation between the ratio of complete responders and the PFS hazard ratio.

They estimate the hazard ratio between bendamustine+rituximab and rituximab+chlorambucil as 0.60, and between obinutuzumab+chlorambucil and bendamustine+rituximab as 0.68.

We agree with Roche that patients in MaBLe were relevant to the current decision question, namely unsuited to fludarabine-based therapy, with median age 74.

However, we believe that the assumptions in Roche's method of estimating the hazard ratio between obinutuzumab+chlorambucil and bendamustine+rituximab are highly speculative. Roche provide no evidence to support the key assumptions of their method.

In summary, we believe that the PFS hazard ratio between bendamustine+rituximab and obinutuzumab+chlorambucil is currently unknown. We recommend that this value should be considered when it is made publicly available. Veronique Leblond, lead author of the MaBLe study tells us that results will be available in October 2014. However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015.

However, in the meantime, if Roche's relationship is to be used, we suggest that it is better to base it on the interim % of complete responding patients from MaBLe, rather than from the sample size calculation. This gives a hazard ratio of 0.54 between bendamustine+rituximab and rituximab+chlorambucil, or a hazard ratio of 0.76 between obinutuzumab+chlorambucil and bendamustine + rituximab.

This change alone increases Roche's base case ICER between bendamustine+rituximab vs. obinutuzumab+chlorambucil from £20,000 to £26,000 per QALY.

The PFS HR between bendamustine + rituximab and obinutuzumab + chlorambucil estimated by Roche's mixed treatment comparison is: 0.52 estimated by the fixed effects model, 0.59 estimated by the random effects model and 0.37 from the fixed effects model with age as a covariate (see p288, Appendix 3.3 Roche's report). However, we believe that

little importance should be attached to these estimates, because the two treatments are connected via many other (3) treatments, two of which include fludarabine.

1.3 Summary and critique of cost-effectiveness evidence submitted

In this section, we highlight our key areas of disagreement with Roche's analysis. As a result of our critique of their model, we have developed PenTAG base case ICERs (Table 45, p156) by adjusting the following items in Roche's model:

1. Utility whilst on obinutuzumab+chlorambucil

1.3.2 Model structure

Roche have developed a Markov cohort model where patients can be on or off the principal treatment in the treatment arm and patients can undergo transformation from progression free to progressed disease (PD) and death. This is a standard model structure that has been used in numerous HTAs. The structure is simpler than the existing model of bendamustine for first-line CLL from TA216. In particular, it does not divide PFS into the stable disease, complete response and partial response states. It also does not model second line treatments such as FCR and bendamustine. Therefore Roche's model may not adequately capture the intricacies of the patient pathway. However, given the limited data to inform these complexities, we consider the overall model structure appropriate.

1.3.3 Method of PFS estimation

Progression free survival (PFS) for obinutuzumab+chlorambucil , rituximab+chlorambuciland chlorambucil were modelled using Kaplan-Meier data from the CLL11 trial, with tails from fitted Gamma distributions. The PFS curves for bendamustine+rituximab and bendamustine were estimated by applying the respective HRs to PFS for obinutuzumab+chlorambucil . These hazard ratios were taken from a RCT of bendamustine versus chlorambucil and a RCT of rituximab + bendamustine versus rituximab+chlorambucil.

We consider the patients in CLL11 to be similar to those in clinical practice. Therefore, we consider the PFS hazard ratios for the three treatments in CLL11 as appropriate.

Roche have included appropriate distributions for PFS in their sensitivity analyses and the choice of Gamma in the base case seems justified.

As explained in Section 1.2.2 (p19), we disagree with Roche's estimate of the hazard ratio between obinutuzumab+chlorambucil and bendamustine of 0.40 - we prefer 0.55. Roche's base case ICER between obinutuzumab+chlorambucil and bendamustine then increases from £26,000 to £37,000 per QALY. This constitutes Item 5 in the PenTAG base case (Table 45, p156).

The hazard ratio for bendamustine+rituximab is particularly uncertain given that no PFS results from the MaBLe trial are available at the time of writing (early August 2014). Nonetheless, we disagree with Roche's interim estimate of the hazard ratio between rituximab + bendamustine and obinutuzumab+chlorambucil . We believe the best estimate is 0.76, compared to Roche's estimate of 0.68.

This constitutes Item 4 of the PenTAG base case (Table 45, p156).

1.3.4 Method of OS estimation

OS data from CLL11 is very immature. Instead, Roche estimate post-progression survival from trial CLL5. This was a Phase III RCT conducted in Germany comparing chlorambucil to fludarabine in a previously untreated population. This was an older population, with ages ranging 65-78, at Binet stages A, B or C.

Roche assume no treatment effect on PPS and instead adjusted PPS for age at progression, assuming this would account for the difference in populations between the CLL5 and CLL11 trials. Kaplan-Meier OS data from CLL11 trial was used to validate the estimated OS curves.

We agree that extrapolating from the immature data in CLL11 would be inadvisable, and we believe Roche have used a sensible method of estimating survival whilst in progressive disease, and therefore OS.

The modelled OS does not visually match the current data from CLL11 precisely. However, this does not concern us, given the immaturity of the CLL11 OS data.

1.3.5 Costs

Drug acquisition and administration costs

All drugs are taken over a maximum of 6 x 28-day cycles. Chlorambucil is administered orally. All other drugs are taken intravenously. No vial sharing is assumed for all intravenously administered drugs. Therefore all calculations assume full drug wastage.

The approximate cost of a course of:

- obinutuzumab+chlorambucil is £27,000
- rituximab+chlorambucil £10,000
- bendamustine £16,000
- rituximab+bendamustine £12,000
- chlorambucil £300

Roche estimate the proportions of patients that take obinutuzumab, chlorambucil, and rituximab from the CLL11 trial, and bendamustine from the trial of bendamustine vs. chlorambucil. They also estimate that all patients randomised to rituximab + bendamustine take all of the intended course. We disagree with this assumption. Ideally, we would take the

actual drug dose intensity from the MaBLe trial of rituximab + bendamustine vs. rituximab+chlorambucil. But given that this data is not yet available, we consider that the value for bendamustine should be equal to that for bendamustine monotherapy, and the value for rituximab should be equal to that for rituximab in the rituximab+chlorambucilarm of CLL11. In this case, the:

- ICER for obinutuzumab+chlorambucil vs. bendamustine+rituximab increases from £20,000 to £25,000 per QALY.

This change constitutes Item 3 of the PenTAG base case (Table 45, p156).

Although we disagree with several of Roche's unit costs associated with the administration of drugs, we do not pursue this matter, as we find that the ICERs change only incrementally when we use our values.

Rituximab came off patent in the EU on 12th November 2013.[7] This then opens the market for rituximab biosimilars. However, we currently have no idea of the dates of entry or prices of such biosimilars in the future.

Supportive care costs

Supportive care costs were informed by the CLL5 study and a clinical advisory board. Roche assumed that all participants would receive one treatment with chlorambucil post-progression.

We are satisfied with the assumptions for supportive care costs in the progression-free survival and post-progression states.

Adverse event costs

Adverse event costs in Roche's model are estimated for Grade 3/4/5 events occurring in >2% of people in either treatment arm of CLL11 or any treatment arm of a comparator-related pivotal trial (Knauf et al. and MaBLe). Due to lack of complete data for bendamustine+rituximab from the MaBLe study, the profile and related costs for this combination were assumed to be equal to rituximab+chlorambucilfrom the CLL11 trial.

Roche cites NHS Reference Costs 2012/2013 and HRG codes as the source for the costs. Although we disagree with several of Roche's unit costs, the ICERs are only incrementally affected by this change.

1.3.6 Utilities

The cancer-specific EORTC QLQC30 questionnaire was used in the CLL11 RCT. Roche did not perform a mapping from this instrument to the EQ-5D because they claimed that no validated mapping function exists. We disagree – we find several mapping functions. When we presented Roche with such functions, they said that if the NICE Committee consider the mapping functions to be preferable to existing utility values, they would potentially be able to provide this information in response to consultation.

Roche found two original studies concerning health-related quality-of-life (HRQL) in patients with CLL.[8, 9] However, given that they found limitations with both studies, Roche conducted a utility elicitation study with the UK general public to derive societal preferences for quality-of-life associated with CLL, using the time trade-off method. Health state descriptions (vignettes) were developed to reflect different states or stages of CLL. The utilities used in the model were taken directly from this study. One utility value represents the time whilst taking the drug, one in PFS when off the drug, and one in progressive disease. Disutilities due to adverse events are not explicitly taken into account.

We consider the data from Roche's study to be low quality as health-related quality-of-life was not elicited from patients, and because vignettes were used, rather than the preferable use of a generic questionnaire, such as the EQ-5D. However, in the absence of better quality of life data, we agree that Roche's study should inform the utility values. However, we disagree with two of Roche's utility values:

- Utility whilst on obinutuzumab treatment after the first cycle of treatment.
- Utility in PFS when off treatment for all comparators.

First, we are satisfied that patients have a utility of 0.55 during the first cycle of obinutuzumab treatment. However, in their model, Roche then assume a utility whilst

Together, this means that Roche's estimates of OS for all treatments are highly uncertain. Nonetheless, we are satisfied with their extrapolation of OS.

- The quality of evidence for utilities is poor as they are based on health state vignettes, and are not based on patient-reported outcomes.

- Roche did not report some secondary outcome measures from the CLL11 trial, particularly HRQL, despite being presented (and commented on) in Goede et al (2014))[4] which reported the results of CLL11.

- Explanation is given in the submission for withdrawals from all treatment arms. The submission states that the safety profile of obinutuzumab was generally comparable to that of rituximab+chlorambucil and chlorambucil alone in terms of the severity of AEs, discontinuations due to AEs, and AEs leading to death. However, there are more discontinuations in the obinutuzumab+chlorambucil arm of the CLL11 study (at stage 2) compared to the rituximab+chlorambucil arm.

- We cannot trace the source of many of the unit costs that Roche state are taken from NHS Reference Costs. However, we find that cost-effectiveness changes only slightly when we use values we find in the NHS Reference Costs.

1.5. Summary of our exploratory and sensitivity analyses

1.5.1 PenTAG base case

A summary of the derivation of our base case ICERs is given in Table 2, Table 3 give the component results of our base case, which can be compared with Roche's base case in Table 1, p29.

All ICERs are uncertain due to uncertainty in mortality in progressive disease, and lack of costs of second-line treatments (with exception of chlorambucil).

The ICER between obinutuzumab+chlorambucil and bendamustine is uncertain because the PFS hazard ratio between these treatments has been estimated by an indirect comparison between the two treatments.

The ICER between obinutuzumab+chlorambucil and rituximab + bendamustine is currently extremely uncertain, additionally because the PFS hazard ratio between rituximab + bendamustine and rituximab+chlorambucil is currently unavailable. However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015.

The total dose per cycle of chlorambucil in CLL11 is substantially lower than that used in routine clinical practice: approximately 70mg versus 120mg (Section 1.2.1, p15). If chlorambucil is more effective at higher doses, but obinutuzumab + chlorambucil is insensitive to the dose of chlorambucil, the estimated effectiveness of obinutuzumab + chlorambucil versus chlorambucil is uncertain in CLL11, and the ICER of obinutuzumab + chlorambucil versus chlorambucil of >£28,000 may therefore be an underestimate. However, our clinical expert believes it is plausible that if chlorambucil is more effective at higher doses, then so too is obinutuzumab + chlorambucil. In this case, any bias in the effectiveness of obinutuzumab + chlorambucil versus chlorambucil in CLL11 is reduced, and the ICER of >£28,000 per QALY is more accurate. However, we are not aware of any randomised trials comparing chlorambucil or obinutuzumab + chlorambucil at differing doses of chlorambucil, so we cannot be certain of any bias.

The mean total dose of chlorambucil was far lower in CLL11 compared to the bendamustine RCT: 329 vs. 549mg (Section 1.2.2, p19). If chlorambucil is more effective at higher doses, the relative dosing in the two RCTs would bias the effectiveness of obinutuzumab + chlorambucil versus bendamustine in favour of obinutuzumab + chlorambucil. The ICER of obinutuzumab + chlorambucil versus bendamustine of >£44,000 may therefore be an underestimate.

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Table 2. Derivation of PenTAG base case ICERs (£ per QALY)

			ObClb vs.			
			RBenda	RClb	Benda	Clb
	Roche base case	**Reference**	**20,000**	**21,000**	**26,000**	**24,000**
1	Utility whilst on obinutuzumab	(p147)	23,000	23,000	28,000	25,000
2	Utility PFS off treatment decreased from 0.82 to 0.76	(p147)	>23,000	>24,000	>30,000	>27,000
3	Mean dose of bendamustine and rituximab in bendamustine+rituximab arm	(p149)	25,000	n/c	n/c	n/c
4	PFS hazard ratio between obinutuzumab+chlorambucil and bendamustine+rituximab increased from 0.68 to 0.76	(p143)	26,000	n/c	n/c	n/c
5	PFS hazard ratio ObinClb vs. Benda from 0.40 to 0.55	(see p94)	n/c	n/c	37,000	n/c
1+2			>25,000	>25,000	>31,000	>28,000
1+2+3+4			>43,000	>25,000	>31,000	>28,000
1+2+3+4+5	**PenTAG base case**		**>43,000[2]**	**>25,000[1]**	**>44,000[3]**	**>28,000[1]**

n/c – Not changed from base case
1 Uncertain due to uncertainty in mortality in progressive disease, and no costs of 2nd-line treatments (with exception of chlorambucil).
2 Extremely uncertain for reasons in 1 and because PFS hazard ratio between rituximab + bendamustine and rituximab plus chlorambucil is currently unavailable.
3 Very uncertain for reasons in 1 and because the PFS hazard ratio between these treatments has been estimated by an indirect comparison.
Shading indicates cost-effectiveness of obinutuzumab: white – ICER < £30,000 per QALY; black ICER > £30,000 per QALY; grey – ICER between £20,000 and £30,000 per QALY

Table 3. Life years, QALYs, costs and net health benefit in PenTAG base case

	ObClb	RBenda	RClb	Benda	Clb
Life years (undiscounted)					
PFS	2.83	2.41	1.68	1.95	1.00
PD	3.86	3.96	4.15	4.08	4.25
Total	**6.68**	**6.36**	**5.82**	**6.02**	**5.24**
Discounted QALYs					
PFS	2.00	1.70	1.20	1.41	0.74
PD	1.84	1.92	2.05	2.00	2.15
Total	**3.84**	**3.62**	**3.26**	**3.41**	**2.88**
Discounted costs					
Drug acquisition	£23,157	£14,021	£9,545	£4,745	£286
Drug administration	£3,736	£4,101	£3,314	£3,991	£1,320
Supportive care PFS	£1,140	£972	£693	£804	£420
Adverse events	£3,579	£2,445	£2,445	£1,675	£1,465
Progressive disease	£4,311	£4,465	£4,756	£4,647	£4,959
Total	**£35,923**	**£26,004**	**£20,753**	**£15,861**	**£8,450**
Net Health Benefit at £20,000 per QALY	**2.05**[1]	**2.32**[2]	**2.22**[1]	**2.62**[3]	**2.46**[1]
Net Health Benefit at £30,000 per QALY	**2.65**[1]	**2.75**[2]	**2.57**[1]	**2.88**[3]	**2.60**[1]

1 Uncertain due to uncertainty in mortality in progressive disease and no costs of 2nd-line treatments (with exception of chlorambucil).
2 Extremely uncertain for reasons in 1 and because PFS hazard ratio between rituximab + bendamustine and rituximab plus chlorambucil is currently unavailable.
3 Very uncertain for reasons in 1 and because the PFS hazard ratio between these treatments has been estimated by an indirect comparison

1.5.2 Key sensitivity analyses

In this section we present one key scenario analysis: reducing the utility whilst patients are off treatment, in PFS. These analyses are applied to both the Roche base case and the PenTAG base case (see Table 4 and Table 5). As explained on page 148, there is an argument for assuming a disutility from that of the general population, for patients in PFS off treatment.

We can identify no other sensitivity analysis for which there is another credible value and for which the ICER changes substantially.

Table 4. Important scenario analysis applied to PenTAG base case ICERs

	ObClb vs.			
	RBenda	**RClb**	**Benda**	**Clb**
PenTAG base case	**>45,000[2]**	**>26,000[1]**	**>£46,000[3]**	**>£29.000[1]**
Utility of 0.71 whilst patients are in PFS off treatment (p147)	49,000[2]	29,000[1]	51,000[3]	31,000[1]

n/c – Not changed from base case
1 Uncertain due to uncertainty in mortality in progressive disease and no costs of 2nd-line treatments (with exception of chlorambucil).
2 Extremely uncertain for reasons in 1 and because PFS hazard ratio between rituximab + bendamustine and rituximab plus chlorambucil is currently unavailable.
3 Very uncertain for reasons in 1 and because the PFS hazard ratio between these treatments has been estimated by an indirect comparison
Shading indicates cost-effectiveness of obinutuzumab: white – ICER < £30,000 per QALY; black ICER > £30,000 per QALY; grey – ICER between £20,000 and £30,000 per QALY

Table 5. Important scenario analysis applied to Roche base case ICERs

	ObClb vs.			
	RBenda	**RClb**	**Benda**	**Clb**
Roche base case	**20,000[2]**	**21,000[1]**	**26,000[3]**	**24,000[1]**
Utility of 0.71 whilst patients are in PFS off treatment (p147)	27,000[2]	£27,000[1]	£34,000[3]	£30,000[1]

n/c – Not changed from base case
1 Uncertain due to uncertainty in mortality in progressive disease and no costs of 2nd-line treatments (with exception of chlorambucil).
2 Extremely uncertain for reasons in 1 and because PFS hazard ratio between rituximab + bendamustine and rituximab plus chlorambucil is currently unavailable.
3 Very uncertain for reasons in 1 and because the PFS hazard ratio between these treatments has been estimated by an indirect comparison
Shading indicates cost-effectiveness of obinutuzumab: white – ICER < £30,000 per QALY; black ICER > £30,000 per QALY; grey – ICER between £20,000 and £30,000 per QALY

1.5.3 Overall cost-effectiveness conclusions

This HTA concerns patients unsuited to fludarabine treatment. Given that our clinical advisor states that some patients are unable to tolerate bendamustine due to toxicities, we identify two subgroups of patients amongst those relevant to this HTA:

- Patients suited to bendamustine.
- Patients unsuited to bendamustine.

Under the PenTAG base case, for patients suited to bendamustine:

- At a willingness to pay of £20,000 or £30,000 per QALY, bendamustine or bendamustine+rituximab provide the best value for money. Obinutuzumab+chlorambucil is poor value.

Under the PenTAG base case, for patients unsuited to bendamustine:

- At a willingness to pay of £20,000 per QALY, chlorambucil or rituximab+chlorambucilprovide the best value for money. Obinutuzumab+chlorambucil is poor value.

- At a willingness to pay of £30,000 per QALY, obinutuzumab+chlorambucil and chlorambucil provide the best value for money, and offer very similar value. Rituximab+chlorambuciloffers slightly worse value.

For patients unsuited to bendamustine, we find a difference of opinion about whether chlorambucil or rituximab+chlorambucilis most widely used on the NHS. Roche believe that most patients currently take chlorambucil, whereas our clinical expert believes that most take rituximab+chlorambucil (Table 44, p142). We repeat that rituximab+chlorambucilwas assessed and not recommended in NICE TA174.[1]

Critical appraisal criterion	Roche assessment	ERG comment
study reflective of patients likely to receive the intervention in UK clinical practice?	previously untreated adults with documented CD20 positive CLL requiring treatment (i.e. those with Binet stage C or symptomatic disease). These patients were also required to have a total cumulative illness rating scale (CIRS) score >6 and/or creatinine clearance,70 mL/minute (Source: Roche Submission, Section 6.3.3, pp44) The median age in all treatment arms at stage 1a and stage 1b was >70 years, with ~ 80% of people in both arms aged more than 65 years. (Source: Roche, Section 6.3.4, pp45)	Our clinical expert believes that the study population of CLL is representative of the typical CLL patient who would not be eligible for fludarabine-based treatment and, overall, the demographics of enrolled participants are considered to be reflective of the proposed population of the UK. These include older patients who typically have multiple co-existing medical conditions that may exclude them from receiving other intensive treatments, such as FCR (Source: Roche Submission, Section 2.1, pp23)
Was the study conducted in the UK (or were one or more centres of the multinational study located in the UK)?	Study CLL11 was an international study conducted in 250 centres in 25 countries including Great Britain (Source: Roche Submission, Section 6.7.2, Table B23, pp80-86; Section 6.10.2, pp123).	In Goede et al (2014), study CLL11 was described as being conducted in 189 centres in 26 countries including Great Britain. No details are reported regarding sites involved or number of patients recruited in the UK. In addition, no analysis by country was performed. Since with any multicentre trial there may be inherent variations in disease management, knowing the proportion of trial participants based in the UK may improve confidence regarding applicability of trial results in this country.
How does the dosage regimen used in the study compare with that detailed in the Summary of Product Characteristics (SmPC)?	All 6 patients entering the safety run-in and all patients randomised to the GCl treatment arm received 1000mg of obinutuzumab as an IV infusion on Day 1, Day 8 and Day 15 of the first treatment cycle (Cycle 1). For each subsequent cycle, patients received obinutuzumab (1000mg) as an IV infusion on Day 1 only (Cycle 2 to 6) (Source: Roche Submission, Section 6.3.2, Table B15, pp43) All patients randomised to rituximab received 375mg/m^2 of rituximab as an IV infusion on Day 1 of the first treatment cycle (Cycle 1). For each subsequent cycle, patients received rituximab (500 mg/m^2) as an IV infusion on Day 1 (Cycles 2 to 6) (Source: Roche Submission, Section 6.3.2, Table B15, pp43)	The dosage regimen used for obinutuzumab is the same as the dosage regimen proposed on the Summary of Product Characteristics (SmPC) and in accordance with the license (Source: Roche Submission, Section 6.10.4, pp126). The dosage regime used for rituximab is the same as the dosage regimen proposed on the Summary of Product Characteristics (SmPC) and in accordance with the licence_.However, the dosage regimen for chlorambucil is subject to uncertainty in clinical practice. As there is no clear standard of care dose, the dose chosen was deemed most suited to the older trial population (and typical of the general CLL population), offering a balance of efficacy and toxicity((Source: Roche Submission, Section 6.3.2, Table B15, pp43). However, we understand that the dose per cycle of chlorambucil is lower than that used in clinical practice, in which it is typically given at 10 mg/m2 on days 1-7, for each 28 day cycle. Given typically body weights and body surface areas, the typical dose of chlorambucil per cycle is approx. 120mg, compared to 70mg in the CLL11 RCT. We understand that there are no clinical studies comparing different doses of chlorambucil. Therefore, it is difficult to say how much the unusually low dose of chlorambucil in CLL11 biases the estimates of effectiveness of obinutuzumab and rituximab in CLL11.

Critical appraisal criterion	Roche assessment	ERG comment
	All patients randomised to chlorambucil received 0.5 m/kg body weight of chlorambucil given orally on Day 1 and Day 15 of all treatment cycles (Cycles 1-6). (Source: Roche Submission, Section 6.3.2, Table B15, pp43)	
Was a justification for the sample size provided?	Yes – (Source: Roche Submission, Section 6.3.6, pp55)	Yes. In the submission, it states that the primary endpoint of investigator-assessed PFS was used to determine the sample size for the study (Roche Submission, Section 6.3.6, pp55). In their submission, Roche were transparent about the limitations encountered during their calculation of the sample size, detailing the limitations of the available trial data and their reliance on clinical opinion in order to justify their sample size calculation.
What randomisation technique was used?	Patients were randomised by computer. The study site obtained the patient's identification number and randomisation to treatment arm was performed from the interactive voice response system (VRS). A complete block randomisation scheme was applied to achieve balance in treatment assignment within each of the strata, as defined by the Binet stage and region.(Source: Roche Submission, Section 6.4.1, Table B19, pp62)	This is an acceptable system of randomisation.
Were patients recruited prospectively?	Yes – (Source: Roche Submission, Section 6.3.2, pp42)	Yes.
Were patients recruited consecutively?	Not reported	Not reported. Roche state in submission that the first six patients entered into the study run-in were not randomized as they were assigned to the GClb treatment arm. All other patients were enrolled and then randomised to a treatment arm (Roche Submission, Section 6.3.2, pp42).
Were the individuals undertaking the outcomes assessment aware of allocation?	Yes – The study was open-label. (Source: Roche Submission, Section 10.4.1, Appendix 5, pp259-269)	Due to the different routes of administration for the intervention and comparator (obinutuzumab and rituximab (i.v. infusion) and chlorambucil (oral)) blinding was not performed. Roche state that the number of placebos required to double blind these studies was considered prohibitive and unethical. The study was therefore open label. (Source: Roche Submission, Section 6.9.2, pp124) but it should be noted that awareness of allocation will have introduced the potential for bias in the study, particularly with reporting of adverse events. Participants or reporters may either over or under report adverse events from the active arm of a trial. The primary outcome of this study was progression-free survival (PFS)

patients" (Goede et al, p 2), while in the Manufacturer's Submission Roche state that study CLL11 was "conducted in 250 centres in 25 countries" (Source: Roche Submission, Section 6.7.2, Table B23, pp80; Section 6.10.2, pp123). There is a further inconsistency in reporting, with Goede et al reporting "this global study was conducted in 269 centres of 26 countries" in their supplementary appendix.[4]

Roche have clarified that this discrepancy is due to differences between centres that enrolled patients and those which opened the study, as well as the number of centres enrolling into different stages of the study. It therefore appears that the figures cited in Goede at al. (2014) were correct and that the study was conducted in 26 countries, with 269 centres (4).

4.1.5 Description and critique of manufacturers outcome selection

There was one primary outcome: investigator-assessed progression free survival (PFS). (Source: Roche Submission, Section 6.3.5, pp49).

Secondary measures include PFS assessed by an independent review committee (IRC), response rates and the rate of negative testing for minimal residual disease, event-free survival, time to new treatment, overall survival, adverse events and patient reported outcomes (HRQL). (Source: Roche Submission, Section 6.3.5, pp49-50)

The outcome measures concur with those specified in the final scope.

4.1.6 Description and critique of statistical approach

Study CLL11, Statistical Analysis: Primary endpoints

The statistical analysis of the primary data was performed from a clinical data cut-off on May 9th 2013. This analysis of the data forms the basis of the Goede New England Journal of Medicine publication March 2014[4] A subsequent analysis of PFS and OS data with a clinical cut-off of 3rd March 2014 has been performed but has not been published in any form and is presented in Roche's submission as data that are commercial in confidence.

Adjustments for multiplicity were done using a three-arm closed-test procedure. (Source: Roche Submission, Section 6.3.6, p53). The first test was for any difference between the three treatment groups at an $\alpha = 5\%$. If the null hypothesis of equal distributions for all three groups was rejected, pairwise tests for each of the three hypotheses (obinutuzumab+chlorambucil versus chlorambucil alone, obinutuzumab+chlorambucil versus rituximab+chlorambucil, and rituximab+chlorambucilversus chlorambucil alone) were

enabled at the 5% alpha level without α -inflation. The closed test procedure was conducted separately for the investigator and IRC assessed PFS.

Treatment comparison was based on PFS using a two-sided stratified (by Binet Stage at baseline) log-rank test. A two-sided non-stratified log-rank test was done to confirm the primary analysis. Median PFS and the 95% confidence limits were estimated using Kaplan-Meier survival methodology. (Source: Roche Submission, Section 6.3.6, p53).

p58 cont.

- The incidence of adverse events, serious adverse events, and adverse events leading to discontinuation of study treatment was higher in the obinutuzumab+chlorambucil arm compared with the rituximab+chlorambucilarm. This difference was mainly due to IRRs.

- The high incidence of IRR's in the obinutuzumab+chlorambucil arm, particularly during the first infusion, was the main driver for the difference in AE rates between each of the treatment and control arms. The majority of IRR events in the obinutuzumab+chlorambucil arm were low grade in intensity and were clinically manageable. No deaths were associated with IRRs.

- Tumour lysis syndrome (TLS) was reported exclusively in patients treated with obinutuzumab+chlorambucil . Of the 14 patients (4%), 1 patient was withdrawn from treatment and 2 patients had dose modifications because of TLS suggesting that TLS is currently manageable with the implemented risk minimisation activities (premedication, hydration and information to investigators). There were no cases of fatal TLS.

- Adverse events leading to death were more frequent in the rituximab+chlorambucil(n=21) and obinutuzumab+chlorambucil (n=15) arms compared with the chlorambucil arm (n=11) (Source: Roche Submission, Section 6.8.2, pp119).

Most AEs were mild to moderate in severity and decreased in frequency after discontinuation of obinutuzumab treatment. IRRs and neutropenia were more common with obinutuzumab+chlorambucil than with rituximab+chlorambucil, but the risk of infections was not increased. The incidence of IRRs, neutropenia, thrombocytopenia and leukopenia, was higher (> 5% difference) in the obinutuzumab based arm than in the rituximab+chlorambucilor chlorambucil arms of the study. Serious infections, however, were more common in the chlorambucil arm and more people died in that arm, mainly due to progressive disease. (Source: Roche Submission, Section 6.9.2, pp120).

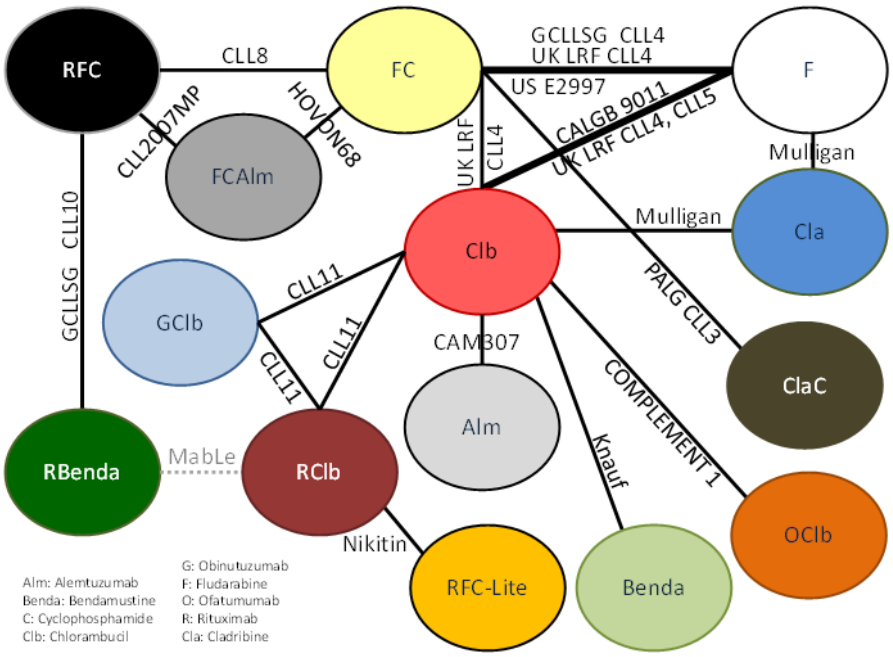
Overall in stage 2 of the CLL11 study, 166/241 patients (69%) in the obinutuzumab+chlorambucil arm and 88/225 patients (39%) in the rituximab+chlorambucilarm experienced an IRR, although the majority of IRRs were Grade 1-2 (20% of patients in the obinutuzumab+chlorambucil arm and 4% of patients in the rituximab+chlorambucilarm had a Grade 3-4 IRR). Of the 221 obinutuzumab+chlorambucil -treated patients with an IRR, 25 patients (7%) were withdrawn from treatment, 121 patients (36%) had their dosage regime of obinutuzumab modified (administration over 2 days) or delayed and 26 patients (8%) were hospitalised. Of the 121 rituximab+chlorambucil-treated patients with an IRR, 3 patients (<1%) were withdrawn from treatment, 67 patients (21%)

The manufacturer sent a revised MEDLINE update search strategy to us following a clarification question about an error in the use of Boolean operators. The revised MEDLINE update search strategy is written correctly and the manufacturer confirmed that, although the original search was reproduced with errors, it was not carried out with errors.

41 studies covering 42 RCTs were identified (Roche Submission, Section 6.7.2, pp80-86). Only 8 studies reported the PFS hazard ratio. The hazard ratio was estimated in another 8 RCTs using published information. This gave a total of 17 studies (including CLL11), encompassing 14 pharmacological interventions. A summary of the RCTs used in the mixed treatment comparison is given in Appendix 2.

Although full results from the MaBLe study have not yet been published, Roche have included the study in the evidence network, as they say that the PFS hazard ratio between rituximab+chlorambuciland rituximab + bendamustine will be publicly available soon. We contacted Veronique Leblond, lead author of the MaBLe study and she said that the results, including the PFS hazard ratio, will be submitted to the ASH conference in October 2014. However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015.

Figure 16. Evidence for large network for mixed treatment comparison. Taken from Roche submission, Figure B22, p99



Key: Alm: Alemtuzumab; Benda: Bendamustine; C: Cyclophosphamide; Cla: Cladribine; Clb: Chlorambucil; F: Fludarabine; G: Obinutuzumab; O: Ofatumumab; R: Rituximab

4.4.1 Quality assessment of bendamustine RCT

Given that the purpose of the mixed treatment comparison is to derive an adjusted estimate of the PFS hazard ratio between obinutuzumab+chlorambucil vs. bendamustine using the RCT of bendamustine vs. chlorambucil, we include a quality assessment (Table 23) of the bendamustine RCT. This is based on our ERG report on the bendamustine STA TA216.[43]

Note that the chlorambucil dose used in the bendamustine RCT was lower and the schedule is different (0.8 mg/kg on days 1 and 15 of each cycle up to 6 cycles) to that used in UK clinical practice, but the dose was higher than in the CLL11 RCT.

Specifically, the total dose per cycle in the bendamustine RCT was approx. 112mg vs. 120mg in UK clinical practice. The mean number of cycles administered was 4.9, giving a total mean dose of 549mg.

By comparison, in CLL11, the dose of chlorambucil was 0.5mg/kg body weight given on Day 1 and 15 of all treatment cycles 1 to 6. This gives a mean dose per cycle of 70mg. The mean number of cycles of chlorambucil in CLL11 was 4.7 (calculated from Roche's model). This gives a total mean dose of 329mg, which is substantially lower than the 549mg in the bendamustine RCT.

If chlorambucil is more effective at higher doses, the relative dosing in the two RCTs would bias the effectiveness of obinutuzumab+chlorambucil vs. bendamustine in favour of obinutuzumab+chlorambucil. However, we are not aware of any randomised trials comparing chlorambucil at differing doses.

Note also that, as in the CLL11 RCT, the bendamustine RCT was open label. This may have biased PFS.

Table 23. Quality assessment of bendamustine trial

Critical appraisal criterion	PenTAG appraisal
Study design	Open label RCT and therefore lacks blinding for both participants and investigators. However, outcomes were reviewed by an independent review team. The study was a Phase III, open-label, multicenter parallel group international study comparing initial treatment of patients with CLL in Binet stage B or C requiring treatment. Patients were randomized to receive either intravenous bendamustine or oral chlorambucil (stratified by centre and Binet stage).
Were selection criteria adequately	Yes, the study eligibility criteria are specified and match those outlined

We agree with Roche that patients in MaBLe were relevant to the current decision question, namely unsuited to fludarabine-based therapy, with median age 74.

As Roche admit, their method of estimating the hazard ratio between bendamustine plus rituximab and rituximab plus chlorambucil assumes perfect correlation between the hazard ratio and the ratio of complete responders in the two treatment arms. Roche supply no evidence to support this assumption.

We also note that the estimated hazard ratio between bendamustine plus rituximab and rituximab plus chlorambucil depends substantially on the data used to calibrate the correlation between the hazard ratio and % complete responders. For example, in the RCT of bendamustine vs. chlorambucil,[55] 21% of bendamustine patients and 11% of chlorambucil patients achieved a complete response, a ratio of 1.94, with hazard ratio of 0.353. Using Roche's method, this implies that a two-fold difference in % patients with complete response corresponds to a hazard ratio of 1 – 2/1.94 x (1- 0.353) = 0.33. This then gives a hazard ratio between obinutuzumab+chlorambucil and bendamustine plus rituximab of 1.23, i.e. bendamustine plus rituximab is more effective than obinutuzumab+chlorambucil .

Finally, if Roche's relationship is to be used, we suggest that it is better to base it on the interim % of complete responding patients from MaBLe, rather than from the sample size calculation. As stated above, this gives a hazard ratio of 0.54 between bendamustine plus rituximab and rituximab plus chlorambucil, or a hazard ratio of 0.76 between obinutuzumab+chlorambucil and bendamustine plus rituximab. We note that this change alone increases Roche's base case ICER between bendamustine+rituximab vs. obinutuzumab+chlorambucil from £20,000 to £26,000 per QALY. Technically, this is implemented in cells F110 and F112, worksheet "Model Inputs".

In summary, we believe that the PFS hazard ratio between bendamustine+rituximab and obinutuzumab+chlorambucil is currently unknown. We recommend that this value should be considered when it is made publicly available.

4.5 Conclusions of the clinical effectiveness section

The submitted clinical evidence adequately reflects the decision problem defined in the submission. Older patients with previously untreated CLL and comorbidity presently have few treatment options available to them. The submitted clinical trial evidence is relevant to this patient population as trial participant characteristics reflect those encountered in clinical practice.

In addition to the significant improvements in both progression-free and overall survival, the obinutuzumab+chlorambucil arm had a statistically significant greater event-free survival (p<0.0001 both), end of treatment response (p<0.0001 vs. both chlorambucil and rituximab+chlorambucil), MRD-negative rate (26.79 [19.5 - 34.1] vs. chlorambucil and 23.06 [17.0 - 29.1] vs. rituximab+chlorambucil), best overall response (p<0.0001 vs. chlorambucil and p=0.0001 vs. rituximab+chlorambucil), disease free survival (p<0.0001 vs,. chlorambucil and p=0.0475 vs. rituximab+chlorambucil), and time to new treatment (p<0.0001 vs. chlorambucil and p=0.0018 vs. rituximab+chlorambucil) compared to chlorambucil and rituximab+chlorambucil. The significantly prolonged time to new anti-leukaemia therapy with obinutuzumab+chlorambucil compared with rituximab+chlorambucilor chlorambucil means that patients experience a longer period off treatment.(Source: Roche Submission, Section 6.10.1, p131)

The safety profile of obinutuzumab was generally comparable to that of rituximab+chlorambuciland chlorambucil alone in terms of the severity of AEs and AEs leading to death. Most AEs were mild to moderate in severity. The incidence of IRRs, neutropenia, thrombocytopenia, leukopenia,was higher (> 5% difference) in the obinutuzumab based arm than in the rituximab+chlorambucilor chlorambucil arms of the study. Serious infections, however, were more common in the chlorambucil arm and more people died in that arm, mainly due to progressive disease.(Source: Roche Submission, Section 6.10.1, p132)

In summary, the clinical benefits identified for obinutuzumab+chlorambucil are as follows:

Patients receiving obinutuzumab in combination with chlorambucil had [redacted](These results are from the most recent data cut (3rd March 2014) and are confidential).

[redacted]

PFS were modelled using Gamma tails fitted to the Kaplan-Meier data. The tails were fit independently for each arm [redacted] The Gamma distribution was chosen as it had the strongest visual fit and did not produce tails where individuals remain progression free for an amount of time deemed implausible by Roche's clinical experts. The tail of the chlorambucil PFS curve was validated against results from the Knauf trial of bendamustine versus chlorambucil, but for other arms, Roche found no data available for validation.

As MaBLe trial data is not yet available, the HR for rituximab with bendamustine versus rituximab+chlorambucil of 0.60 is estimated using an indirect method, explained in Section 4.5 (p97); the method assumes perfect correlation between the difference in complete responders and the PFS HR. A simple indirect comparison is then used to estimate the HR of obinutuzumab+chlorambucil versus rituximab+bendamustine as 0.68. The HR for obinutuzumab+chlorambucil versus bendamustine of 0.40 is taken directly from Roche's MTC, as explained in Section 4.4.3 (p91). These HRs are then used to model the PFS of bendamustine and rituximab + bendamustine by applying them to the obinutuzumab+chlorambucil PFS curve. Rituximab + bendamustine is expected to be updated when MaBLe trial data is available. A complete listing of the PFS base case and sensitivity analyses is given in Table 27 (p109).

The time when the tail is applied is incorrectly attributed in the model to the median of the KM data, but is implemented as reported in Section 7.3.1.2, p144 of Roche's submission as based on visual inspection, which seems appropriate.

Roche have included appropriate distributions for PFS in their sensitivity analyses and the choice of Gamma in the base case seems justified, given the combination of low AIC, good fit using visual inspection and that it agrees with clinical opinion on PFS.

Discussion of PFS HR estimates for the bendamustine and rituximab+bendamustine arms is reported in Section 4.4 (p83). In summary, both estimates are highly uncertain. The HR for bendamustine and rituximab is particularly uncertain given that no PFS results from the MaBLe trial are available at the time of writing (July 2014)..

As explained in Section 4.4.5, p94, we believe that the best estimate of the hazard ratio between rituximab+bendamustine and obinutuzumab+chlorambucil is 0.76, compared to Roche's estimate of 0.68. This constitutes Item 4 of the PenTAG base case (Table 45, p156).

As mentioned in Section 4.4.4, p92, we disagree with Roche's hazard ratio of 0.40 between obinutuzumab+chlorambucil versus bendamustine. Instead, we prefer the estimate of 0.55. In this case, the ICER between obinutuzumab+chlorambucil and bendamustine increases from £26,000 to £37,000 per QALY (Table B72, p213, Roche's report). This constitutes Item 6 in the PenTAG base case (Table 45, p156).

The transition from PFS to death is calculated differently for bendamustine and rituximab + bendamustine, compared to the other arms. The weekly probabilities from PFS to death for obinutuzumab+chlorambucil ([redacted]), rituximab+chlorambucil ([redacted]) and chlorambucil ([redacted]) are taken directly from the CLL11 trial. However, as data appears not to be available for either of the bendamustine arms, the weekly probability of death in PFS is estimated as using pooled results from the three arms in CLL11 trial ([redacted]). This means that rituximab + bendamustine and bendamustine have a higher transition probability to death from PFS than obinutuzumab+chlorambucil or rituximab+chlorambucil. It also means that both arms with bendamustine have the same weekly probability of moving from PFS to death, despite their different estimates of PFS, which is unlikely. However, we find that that altering this parameter does not substantially affect the overall cost-effectiveness results and therefore consider this approach to calculating the probability appropriate in light of the lack of of evidence to inform it.

Progressive disease and overall survival (OS)

We note that in CLL11, 25% of patients in the chlorambucil arm crossed over to obinutuzumab+chlorambucil (pp64-5, Roche submission). However, this does not affect Roche's modelling of OS.

Given that OS data is very immature in CLL11, Roche estimate PPS from trial CLL5. We agree that extrapolating from the immature data would be inadvisable. However, Roche demonstrate in [redacted] that the current model for OS does not visually match the current data precisely. However, this does not concern us, given the immaturity of the CLL11 OS data.

We note that Roche's implicit assumption is the survival post-progression is approximately equal between treatments. Expressed differently, treatments do not affect survival beyond progression. We agree that this is a reasonable default assumption.

As a matter of interest, the estimated mean OS times for bendamustine and chlorambucil are far lower in this model than those estimated by Napp, the manufacturer of bendamustine in NICE TA216. We discuss this in further detail in Section 5.4, p137.

[redacted]

published paper (Goede et al., 2014[4]), and supplementary appendices report combined Grade 3, 4 or 5 adverse events with an incidence ≥3% whereas the table in the submission reports adverse events by individual Grade (Table 35, p127). Nevertheless, the proportions reported as used in the model are all less than those reported for the amalgamated Grades across treatment, as required.

Estimates reported for the incidence of Grade 3/4 adverse events in the bendamustine arm of the Knauf et al.[54] trial tally with what is reported in the manufacturer's submission.

No adverse event data are available for the MabLe study.[68] This study, published as an abstract, reports that the incidences of adverse events of any grade (bendamustine+rituximab: 98% versus rituximab+chlorambucil: 100%), Grade ≥3 AEs (70% versus 67%), and serious AEs (35% versus 34%) were similar between the two treatment arms. Thus, the manufacturer assumed the incidence of adverse events for rituximab+bendamustine was the same as for rituximab+chlorambucil. We consider this to be an acceptable assumption, but note that the incidence of leukopenia, lymphopenia, and thrombocytopenia in the bendamustine alone arm is higher than for rituximab+chlorambucil, 14.2% vs 0.9% and 6.2% vs 0.6% and 11.7% vs 2.4% respectively. However, clinical opinion indicates that there are no costs associated with treating Grade 3 lymhopenia, and as Grade 3 thrombocytopenia is not treated, there are no associated costs.

Costs of adverse events

Adverse event costs in the manufacturer's model are estimated for Grade 3/4/5 events occurring in >2% of people (p116). Costs were reportedly taken from NHS Reference Costs (2012/13)[71]; however, we note discrepancies between the figures in the cited source and those presented in the table in the submission (Roche Submission, Table B57, pp187-88. For anaemia, pneumonia, and thrombocytopenia (SA03F, haemolytic anaemia without CC; DZ11C, lobar, atypical or viral pneumonia without CC; and, SA12F, thrombocytopenia without CC respectively), we note that the HRG code stated in Roche's submission is no longer used following amendments to complication and comorbidity (CC) lists. We therefore refer to NHS Reference Costs 2011/2012 for the most recent available value and inflate to 2012/2013 using the inflation indices from the Unit Costs of Health and Social Care.(83)

On advice from Roche we use a weighted average of non-elective inpatient long and short stay costs. While this increases the ICER for the obinutuzumab+chlorambucil vs bendamustine comparison from Roche's base case of £26,000/QALY to £27,000/QALY, it does not alter the base case ICER presented by Roche for the other three comparisons (obinutuzumab+chlorambucil vs rituximab+bendamustine or obinutuzumab+chlorambucil vs

rituximab+chlorambucil or obinutuzumab+chlorambucil vs chlorambucil). As such we do not pursue this any further.

Overall our clinical advisor was satisfied with the resource use as presented by the manufacturer but noted that lymphopenia and Grade 3 thrombocytopenia would incur negligible or no cost. In addition, our clinical advisor considered the cost cited by the manufacturer for anaemia to be an underestimate given that haemolytic anaemia is complex and treatment is often prolonged. Nevertheless, we do not pursue these points any further because we find that these changes affect the ICERs only incrementally.

6. Additional clinical and economic analyses undertaken by the ERG

6.1 Derivation of PenTAG base case

In this section we derive the PenTAG base case (Table 45, 157). The impacts of the individual components of our base case on cost-effectiveness are shown, as well as selected combinations of components and finally the base case, which is composed of all components. All ICERs lie in the first (NE) quadrant (i.e., the obinutuzumab+chlorambucil is more costly and more effective than the comparator).

The results on the cost-effectiveness plane are compared between the Roche and PenTAG base cases (Figure 28 and Figure 29 The component results of the PenTAG base case are given in (Table 45, p157) which is to be compared with the results under Roche's base case (Section 5.3.3, p128).

The ICER between obinutuzumab+chlorambucil and bendamustine is uncertain because the PFS hazard ratio between these treatments has been estimated by an indirect comparison between the two treatments.

The ICER between obinutuzumab+chlorambucil and rituximab + bendamustine is highly uncertain, because the PFS hazard ratio between rituximab+ bendamustine and rituximab plus chlorambucil is currently unavailable. Veronique Leblond, lead author of the MaBLe study tells us that results will be available in October 2014. However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015.

As stated in Section 1.2.1, p15, the dose of chlorambucil in CLL11 is substantially lower than that used in routine clinical practice: total dose per cycle in CLL11 was approximately 70mg versus 120mg in general practice. If chlorambucil is more effective at higher doses, but obinutuzumab + chlorambucil is insensitive to the dose of chlorambucil, the estimated effectiveness of obinutuzumab + chlorambucil versus chlorambucil is uncertain in CLL11, and the ICER of obinutuzumab + chlorambucil versus chlorambucil of >£28,000 may therefore be an underestimate. However, our clinical expert believes it is plausible that if chlorambucil is more effective at higher doses, then so too is obinutuzumab + chlorambucil. In this case, any bias in the effectiveness of obinutuzumab + chlorambucil versus chlorambucil in CLL11 is reduced, and the ICER of >£28,000 per QALY is more accurate. However, we are not aware of any randomised trials comparing

chlorambucil or obinutuzumab + chlorambucil at differing doses of chlorambucil, so we cannot be certain of any bias.

The mean total dose of chlorambucil was far lower in CLL11 compared to the bendamustine RCT: 329 vs. 549mg (Section 1.2.2, p19). If chlorambucil is more effective at higher doses, the relative dosing in the two RCTs would bias the effectiveness of obinutuzumab + chlorambucil versus bendamustine in favour of obinutuzumab + chlorambucil. The ICER of obinutuzumab + chlorambucil versus bendamustine of >£44,000 may therefore be an underestimate.

Table 45. Derivation of PenTAG base case ICERs (£ per QALY)

			Obinutuzumab+chlorambucil vs.			
			Rituximab + bendamustine	Rituximab+chlorambucil	Bendamustine	Chlorambucil
	Roche base case	**Reference**	**20,000**	**21,000**	**26,000**	**24,000**
1	Utility whilst on obinutuzumab	(p147)	23,000	23,000	28,000	25,000
2	Utility PFS off treatment decreased from 0.82 to 0.76	(p147)	>23,000	>24,000	>30,000	>27,000
3	Mean dose of bendamustine and rituximab in bendamustine+rituximab arm	(p149)	25,000	n/c	n/c	n/c
4	PFS hazard ratio between obinutuzumab+chlorambucil and bendamustine+rituximab increased from 0.68 to 0.76	(p143)	26,000	n/c	n/c	n/c
5	PFS hazard ratio ObinClb vs. Benda from 0.40 to 0.55	(p94)	n/c	n/c	37,000	n/c
1+2			>25,000	>25,000	>31,000	>28,000
1+2+3+4			>43,000	>25,000	>31,000	>28,000
1+2+3+4+5	**PenTAG base case**		**>43,000[2]**	**>25,000[1]**	**>44,000[3]**	**>28,000[1]**

Key: n/c – Not changed from base case

Notes: 1 Uncertain due to uncertainty in mortality in progressive disease and no costs of 2nd-line treatments (with exception of chlorambucil).

2 Extremely uncertain for reasons in 1 and because PFS hazard ratio between rituximab + bendamustine and rituximab plus chlorambucil is currently unavailable.

3 Very uncertain for reasons in 1 and because the PFS hazard ratio between these treatments has been estimated by an indirect comparison

Shading indicates cost-effectiveness of obinutuzumab: white – ICER < £30,000 per QALY; black ICER > £30,000 per QALY; grey – ICER between £20,000 and £30,000 per QALY.

Figure 28. Roche base case cost-effectiveness plane

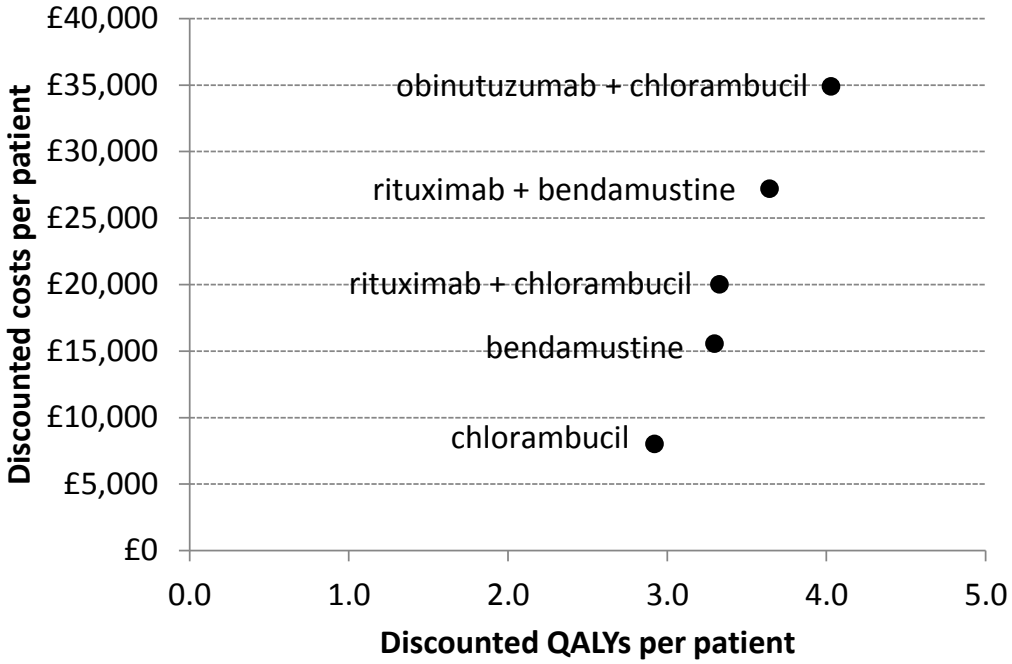


Figure 29. PenTAG base case cost-effectiveness plan

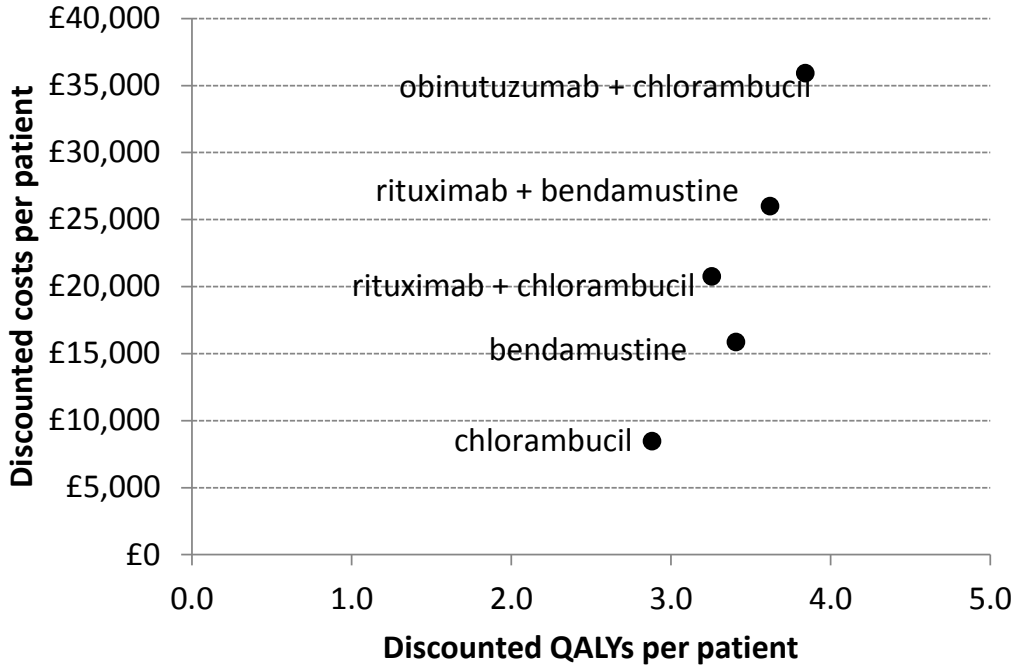


Table 46. Life years, QALYs, costs and net health benefit in PenTAG base case

	Obinutuzumab +chlorambucil	Rituximab + bendamustine	Rituximab+chlorambucil	Bendamustine	Chlorambucil
Life years (undiscounted)					
PFS	2.83	2.41	1.68	1.95	1.00
PD	3.86	3.96	4.15	4.08	4.25
Total	**6.68**	**6.36**	**5.82**	**6.02**	**5.24**
Discounted QALYs					
PFS	2.00	1.70	1.20	1.41	0.74
PD	1.84	1.92	2.05	2.00	2.15
Total	**3.84**	**3.62**	**3.26**	**3.41**	**2.88**
Discounted costs					
Drug acquisition	£23,157	£14,021	£9,545	£4,745	£286
Drug administration	£3,736	£4,101	£3,314	£3,991	£1,320
Supportive care PFS	£1,140	£972	£693	£804	£420
Adverse events	£2,544	£1,694	£1,694	£1,362	£1,036
Progressive disease	£4,311	£4,465	£4,756	£4,647	£4,959
Total	**£34,888**	**£25,253**	**£20,002**	**£15,548**	**£8,020**
Net Health Benefit at £20,000 per QALY	**2.10**[1]	**2.36**[2]	**2.26**[1]	**2.63**[3]	**2.48**[1]
Net Health Benefit at £30,000 per QALY	**2.68**[1]	**2.78**[2]	**2.59**[1]	**2.89**[3]	**2.62**[1]

Notes: 1 Uncertain due to uncertainty in mortality in progressive disease and no costs of 2nd-line treatments (with exception of chlorambucil).
2 Extremely uncertain for reasons in 1 and because PFS hazard ratio between rituximab + bendamustine and rituximab plus chlorambucil is currently unavailable.
3 Very uncertain for reasons in 1 and because the PFS hazard ratio between these treatments has been estimated by an indirect comparison

6.2 Key sensitivity analyses applied to PenTAG and Roche base cases

In this section we select one key scenario analyses: reducing the utility whilst patients are off treatment, in PFS. This analysis is applied to both the Roche base case and the PenTAG base case (see Table 47 and Table 48). As explained (page 146), there is an argument for assuming a disutility from that of the general population, for patients in PFS off treatment.

We can identify no other sensitivity analysis for which there is another credible value and for which the ICER changes substantially.

Table 47. Important scenario analysis applied to PenTAG base case ICERs

	Obinutuzumab+chlorambucil vs.			
	Rituximab + bendamustine	**Rituximab+chlorambucil**	**Bendamustine**	**Chlorambucil**
PenTAG base case	**>43,000[2]**	**>25,000[1]**	**>£44,000[3]**	**>£28.000[1]**
Utility of 0.71 whilst patients are in PFS off treatment (p147**Error! Bookmark not defined.**)	48,000[2]	28,000[1]	49,000[3]	31,000[1]

Key: n/c – Not changed from base case
Notes: 1 Uncertain due to uncertainty in mortality in progressive disease and no costs of 2nd-line treatments (with exception of chlorambucil).
2 Extremely uncertain for reasons in 1 and because PFS hazard ratio between rituximab + bendamustine and rituximab plus chlorambucil is currently unavailable.
3 Very uncertain for reasons in 1 and because the PFS hazard ratio between these treatments has been estimated by an indirect comparison
Shading indicates cost-effectiveness of obinutuzumab: white – ICER < £30,000 per QALY; black ICER > £30,000 per QALY; grey – ICER between £20,000 and £30,000 per QALY

Table 48. Important scenario analysis applied to Roche base case ICERs

	Obinutuzumab+chlorambucil vs.			
	Rituximab + bendamustine	**Rituximab+chlorambucil**	**Bendamustine**	**Chlorambucil**
Roche base case	**20,000[2]**	**21,000[1]**	**26,000[3]**	**24,000[1]**
Utility of 0.71 whilst patients are in PFS off treatment (p147**Error! Bookmark not defined.**)	27,000[2]	£27,000[1]	£34,000[3]	£30,000[1]

Key: n/c – Not changed from base case
Notes: 1 Uncertain due to uncertainty in mortality in progressive disease and no costs of 2nd-line treatments (with exception of chlorambucil).
2 Extremely uncertain for reasons in 1 and because PFS hazard ratio between rituximab + bendamustine and rituximab plus chlorambucil is currently unavailable.
3 Very uncertain for reasons in 1 and because the PFS hazard ratio between these treatments has been estimated by an indirect comparison
Shading indicates cost-effectiveness of obinutuzumab: white – ICER < £30,000 per QALY; black ICER > £30,000 per QALY; grey – ICER between £20,000 and £30,000 per QALY

6.3 Overall cost-effectiveness conclusions

This HTA concerns patients unsuited to fludarabine treatment. Given that our clinical advisor states that some patients are unable to tolerate bendamustine due to toxicities, we identify two subgroups of patients amongst those relevant to this HTA:

- Patients suited to bendamustine.
- Patients unsuited to bendamustine.

Under the PenTAG base case, for patients suited to bendamustine:

- At a willingness to pay of £20,000 or £30,000 per QALY, bendamustine and bendamustine+rituximab provide the best value for money. Obinutuzumab+chlorambucil is poor value.

Under the PenTAG base case, for patients unsuited to bendamustine:

- At a willingness to pay of £20,000 per QALY, chlorambucil or rituximab+chlorambucilprovide the best value for money. Obinutuzumab+chlorambucil is poor value.
- At a willingness to pay of £30,000 per QALY, obinutuzumab+chlorambucil and chlorambucil provide the best value for money, and offer very similar. Rituximab+chlorambucil offers slightly worse value.

For patients unsuited to bendamustine, there is a difference of opinion about whether chlorambucil or rituximab+chlorambucilis most widely used on the NHS. Roche believe that most patients currently taken chlorambucil, whereas our clinical expert believes that most take rituximab+chlorambucil (Table 43, p143). We repeat that rituximab+chlorambucilwas assessed and not recommended in NICE TA174.[1]

6.4 Cost-effectiveness of bendamustine versus chlorambucil: comparison of Roche and Napp estimates

In this section, we compare the estimates of cost-effectiveness of bendamustine versus chlorambucil derived by Roche in the current HTA those of Napp, the manufacturer of bendamustine, in TA216 (Table 28, p119). Although this is not directly relevant to the current HTA, we believe that this comparison sheds light on the methods that Roche have chosen to model the cost-effectiveness of obinutuzumab+chlorambucil in the current HTA. We are able to make this comparison because we, PenTAG, were also the ERG in TA216 and so are familiar with Napp's model of bendamustine versus chlorambucil.

First notice that Napp estimated a lower ICER: £12,000 versus £20,000 per QALY. This is because Napp estimated far higher incremental total QALYs: 1.27 versus 0.38. This factor is of overriding importance, even though they estimated a higher total cost: £15,200 versus £7,500.

Napp predicted a greater PFS benefit of bendamustine over chlorambucil because they did not adjust the hazard ratio for age, from 0.35 to 0.51, as Roche do in the current appraisal.

Next, Napp predicted a [redacted] median overall survival time than Roche: 8.3 versus [redacted] years for bendamustine and 5.8 versus [redacted] for chlorambucil. The manufacturers