NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Obinutuzumab in combination with chlorambucil for treating previously untreated chronic lymphocytic leukaemia

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Key issues for consideration

Clinical effectiveness

- The network meta-analysis includes an RCT of bendamustine that was an open label study. The ERG suggested that this may have biased the progression free survival outcome. In addition, the dose of chlorambucil used in the bendamustine RCT was lower than in clinical practice (112 mg compared with 120 mg). Does the Committee believe that it was appropriate to include the bendamustine RCT in the network meta-analysis?

- The data the company used to calibrate the correlation between the hazard ratio and the percentage of complete responders was based on the sample size calculations of the ongoing MaBLe trial. The ERG believed it would have been more appropriate to use the interim percentage of responding patients from MaBLe instead. Which approach does the Committee believe to be more appropriate?

- The CLL11 trial was an open label study, which may have biased the primary outcome of investigator-assessed progression free survival. CLL11 also used a lower dose of chlorambucil compared to what is used in UK clinical practice. It is uncertain what effect this had on the results of the trial. Does the Committee believe that the results of CLL11 are appropriate for informing their decision making?

- The company believed that standard treatment in the UK for patients with CLL for whom fludarabine therapy is not appropriate is chlorambucil. The ERG believed that the standard treatment for these patients is rituximab plus chlorambucil. What would be the key comparators for obinutuzumab in combination with chlorambucil in clinical practice?

Cost effectiveness

- Health related quality of life data from the CLL11 trial were not provided by the company, who stated that a mapping function to map EORTC QLQC30 to the EQ-5D had not been identified during the development of the submission. The ERG identified a mapping function that could be used. There were limited utility values available in the existing literature so the company undertook a vignette study of a sample of the general public to estimate utility values. The ERG believed that a generic questionnaire such as the EQ-5D should have been used with patients with chronic lymphocytic leukaemia rather than the general public. Which is the most appropriate approach for determining utility values for this model? Does the Committee believe that the health related quality of life data from CLL11 should be provided?

- For the utility value whilst on obinutuzumab treatment after the 1st cycle of treatment, the company used the same utility value as for progression free survival off treatment, which is 0.82. The ERG believed that this should be the same as the utility value for progression free survival on intravenous treatment, which is 0.67. The ERG also noted that the utility value used by the company for progression free survival off treatment (0.82) was higher than the utility value for members of the UK general public at the average age of treatment. The ERG suggested an upper bound of an average of the UK general population mean

utility value at the average age of treatment (0.76). Which utility values does the Committee agree are most appropriate?

- The company assumed a dose intensity of 100% for both bendamustine and rituximab in the bendamustine plus rituximab arm of the model. The ERG suggested that the value for bendamustine in the bendamustine plus rituximab arm should be equal to that for bendamustine alone (90%) and the value for rituximab should be equal to that in CLL11 (98.8%). Which dose intensity values does the Committee consider to be most appropriate?

- The percentage of complete responders in the calculation of the hazard ratio for progression free survival in the comparison of bendamustine plus rituximab and rituximab plus chlorambucil is estimated by the company based on the sample size of the ongoing MaBLe trial. The ERG believed that it would be more appropriate to base the estimate of complete responders on the interim percentage of complete responders from MaBLe instead. Which is the more appropriate approach to use?

- The company used the network meta-analysis to estimate a hazard ratio for progression free survival for obinutuzumab plus chlorambucil and bendamustine (0.40). The ERG believed that it is possible to estimate a progression free survival value for obinutuzumab plus chlorambucil compared with bendamustine in patients aged 65 years or older based on the Knauf et al publication relating to the bendamustine compared with chlorambucil trial and the CLL11 results. Using this method, the ERG estimated a figure very similar to the company's estimate of 0.55 from the fixed effects analysis of the mixed treatment comparison without adjustment for age. Which hazard ratio is more accurate?

- Does the Committee accept the ERG's exploratory analyses, including the adjustments to the model parameters? Which ICER does it consider to be the most plausible?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of obinutuzumab within its licensed indication for previously untreated chronic lymphocytic leukaemia.

1.2 The decision problem is presented in table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable.	Adult patients with previously untreated CLL for whom full-dose fludarabine based therapy is unsuitable.	None	Overall, the population considered is appropriate. However, there is currently a lack of definitive criteria for determining which patients are 'unfit' for treatment with fludarabine combination therapy.
Intervention	Obinutuzumab with chlorambucil	Obinutuzumab	None	None
Comparator	• Chlorambucil, with or without rituximab • Bendamustine, with or without rituximab	• Chlorambucil • Rituximab in combination with chlorambucil • Bendamustine • Rituximab in combination with bendamustine	The main comparator is chlorambucil as this is the treatment used most frequently in patients for whom fludarabine combination therapy is not appropriate. The patient population from	There is no defined standard of care for patients with CLL who are ineligible for full-dose fludarabine-based treatment. The ERG's clinical expert believed the vast majority of patients unsuited to fludarabine are treated with

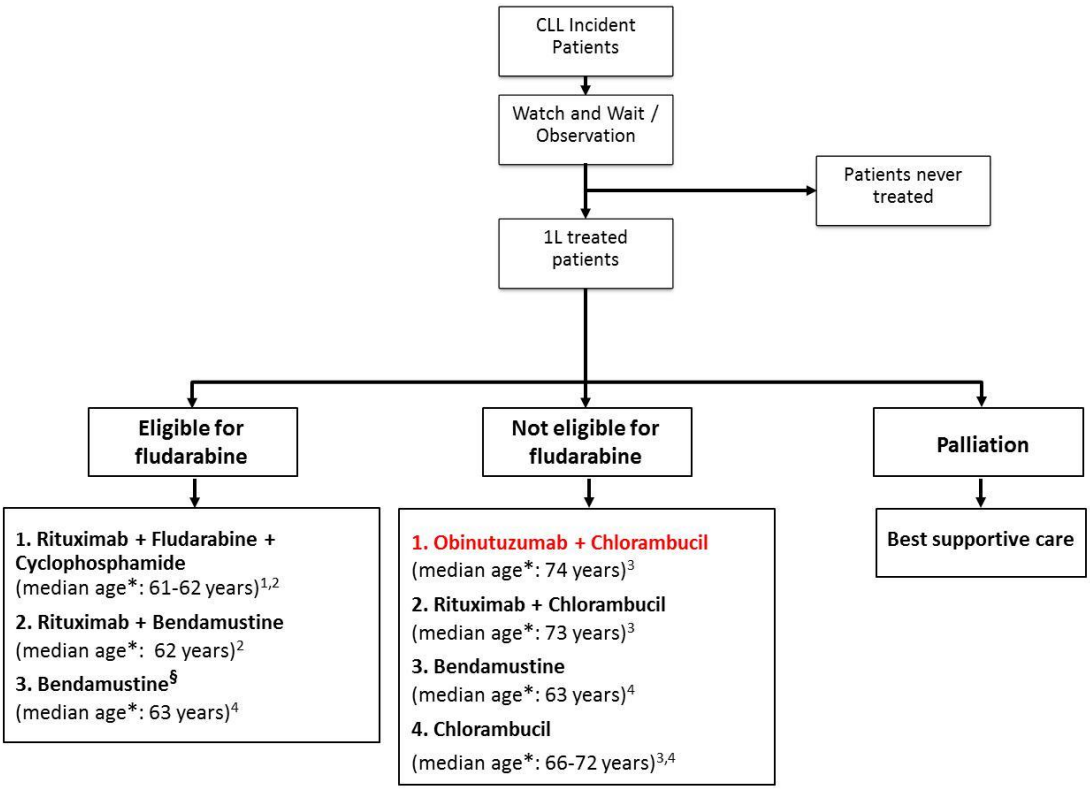
			the pivotal bendamustine trial would be eligible for fludarabine-based therapy, which is outside of the scope of this appraisal.	rituximab plus chlorambucil in the UK. ERG noted further differences of opinion come from commentators to this appraisal and clinicians at the scoping workshop.
Outcomes	• Overall survival • Progression free survival • Response rates • Minimal residual disease negativity • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression free survival • Response rates • Minimal residual disease negativity • Adverse effects of treatment • Health-related quality of life	None	There is an absence of any data for health related quality of life.

2 The technology and the treatment pathway

2.1 Obinutuzumab (Gazyvaro, Roche Products) is a type 2 glycoengineered antibody that binds to the CD20 protein present on B cells, except stem or plasma cells, and causes cell death. It is administered by intravenous infusion.

2.2 A diagram of the treatment pathway for chronic lymphocytic leukaemia including where obinutuzumab would fit is provided in figure 1.

Figure 1. The treatment pathway for chronic lymphocytic leukaemia



SOURCE: Based on Roche internal forecasting assumptions, market research and clinical trials data; CLL8 and CLL10 trials[1,2] (37;38) (37;39)(37;39)(37;39)(37;39)(37;39)(37;39), CLL11 trial [3] (10;27), and Knauf trial[4] (40;40)

2.3 Bendamustine is recommended by NICE for first line treatment of chronic lymphocytic leukaemia in patients for whom fludarabine is unsuitable (NICE technology appraisal guidance 216). In NICE technology appraisal guidance 174, rituximab in combination with fludarabine and cyclophosphamide is recommended by NICE for first line treatment of chronic lymphocytic leukaemia in people for whom fludarabine in combination with cyclophosphamide is considered appropriate.

2.4 The intervention and comparator technologies included in this appraisal are presented in table 2.

Table 2. Technologies

	Intervention	**Comparators**		
	Obinutuzumab	Rituximab	Bendamustine	Chlorambucil
Marketing authorisation	In combination with chlorambucil for adults with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy.	In combination with chemotherapy for treating patients with previously untreated and relapsed/refractory CLL.	For first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine therapy is not appropriate.	For the treatment of CLL.
Administration	Intravenous infusion	Intravenous infusion	Intravenous infusion	Oral
Setting	Hospital	Hospital	Hospital	Hospital
Acquisition cost	£3312 (excluding VAT) per 1000 mg vial	£174.63 per 100mg vial £873.15 per 500mg vial	£69.45 per 25mg vial £275.81 per 100mg vial	£40.51 per 25 x 2mg pack
Number of cycles	6	6	6	6
Total acquisition cost used in the model	£26,496 (£9936 for cycle 1 and £3312 for cycles 2 to 6)	£9953.91	£5809.92 with rituximab £6619.44 without rituximab	£369.45
See Summary of Product Characteristics for details on adverse reactions and contraindications.				

3 Comments from consultees

Current treatment options

3.1 Comments from the professional groups stated that chlorambucil monotherapy was the most widely used treatment for previously untreated chronic lymphocytic leukaemia patients who are unfit for fludarabine-based therapy. The professional groups highlighted that since the publication of NICE guidance on the use of rituximab in these patients (NICE technology appraisal guidance 174), many patients now receive

chlorambucil with rituximab. Some patients are also treated with bendamustine with or without rituximab.

3.2 The professional groups highlighted that people with a 17p mutation or deletion are treated with alemtuzumab or a steroid based regimen instead of chlorambucil, as chlorambucil is not usually effective in these patients. They stated that regardless of age and comorbidities, these patients tend to have a particularly poor outlook.

Patient experience

3.3 A patient group highlighted that effective treatment for chronic lymphocytic leukaemia is important because quality of life can be badly affected by ongoing symptoms and by concerns over relapse. They stated that many effective treatments are not suitable for the majority of people who have chronic lymphocytic leukaemia as they tend to be older and less fit. They also commented that patients with comorbidities that make more intensive chemotherapy unsuitable would benefit from obinutuzumab. Another patient group highlighted that there is little choice of treatment for patients who are not fit enough for fludarabine based therapy and the existing drugs are old.

3.4 A professional group stated that patients are increasingly choosing bendamustine treatment as it requires 2 trips every 28 days to the day unit rather than a 7 day period of oral chlorambucil treatment.

3.5 A patient group highlighted that some people with chronic lymphocytic leukaemia may be too unfit to attend a day unit on a regular basis to receive obinutuzumab treatment. Another patient group stated that elderly patients with little or no carer support or those living far away from a hospital may have difficulty attending day units for extended treatments.

Clinical challenges

3.6 One professional group stated that the introduction of obinutuzumab as a treatment option would not have a large effect on day units that are

already familiar with the administration of monoclonal antibody treatments, such as rituximab and bendamustine. Another professional group stated that obinutuzumab will require considerably more day unit input for chronic lymphocytic leukaemia patients compared with chlorambucil monotherapy (which is typically administered at home with patients receiving their medication from an out-patients facility) as close monitoring of patients would be required for at least 8 infusions, each taking 4 to 8 hours.

3.7 Patient and professional groups highlighted that obinutuzumab is administered as an intravenous infusion and therefore there is an increased risk of infusion related reactions compared with chlorambucil alone.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company performed a systematic review for clinical trials investigating the efficacy and safety of obinutuzumab in the treatment of chronic lymphocytic leukaemia. One randomised controlled trial (RCT), the CLL11 trial, was identified that was relevant to the decision problem. The company did not present any non-RCT evidence in its submission.

4.2 CLL11 was a multicentre, open-label, 3-arm RCT comparing obinutuzumab plus chlorambucil, rituximab plus chlorambucil, and chlorambucil alone in 781 people with previously untreated chronic lymphocytic leukaemia for whom full-dose fludarabine based therapy was not appropriate.

4.3 People were included in CLL11 if they were aged 18 years or older with previously untreated chronic lymphocytic leukaemia requiring treatment (those with Binet stage C or symptomatic disease). Participants were also required to have a total cumulative illness rating scale (a scale that calculates the number and severity of chronic illnesses in patients with

comorbidities) score greater than 6, a creatinine clearance less than 70 mL/minute, or both; no evidence of bone marrow dysfunction in addition to that caused by chronic lymphocytic leukaemia (determined by an absolute neutrophil count of 1.5 x 10^9/L or greater and platelets of 5 x 10^9/L or greater); and a life expectancy greater than 6 months. People were excluded from the trial if their chronic lymphocytic leukaemia transformed into non-Hodgkin lymphoma or they had inadequate renal function, inadequate liver function, or a history of other malignancies that could have affected compliance with the protocol or interpretation of the results.

4.4 There were 2 stages of recruitment to CLL11. In stage 1, 589 people were randomised in a 2:2:1 ratio to receive obinutuzumab plus chlorambucil, rituximab plus chlorambucil, or chlorambucil alone. In stage 2, an additional 192 patients were randomised to either the obinutuzumab plus chlorambucil group or the rituximab plus chlorambucil group. The stage 1 analysis compared obinutuzumab plus chlorambucil with chlorambucil alone and rituximab plus chlorambucil with chlorambucil alone. The stage 2 analysis compared obinutuzumab plus chlorambucil with rituximab plus chlorambucil.

4.5 The drug regimens used in the 3 treatment groups are presented in table 3.

Table 3. Drug regimens used in CLL11

Group	Drug		
	Obinutuzumab	**Rituximab**	**Chlorambucil**
Obinutuzumab plus chlorambucil	Cycle 1: 1000 mg on days 1, 8 and 15 Cycles 2 - 6: 1000 mg on day 1		Cycles 1 to 6: 0.5 mg/kg body weight* days 1 and 15
Rituximab plus chlorambucil		Cycle 1: 375 mg/m^2 on day 1 Cycles 2 - 6: 500 mg/m^2 on day 1	Cycles 1 to 6: 0.5 mg/kg body weight* days 1 and 15
Chlorambucil			Cycles 1 to 6: 0.5 mg/kg body weight* days 1 and 15
*Patients with a BMI greater than 35 kg/m^2 received a dose no greater than that associated with a BMI of 35. For all treatments, each cycle of treatment lasted 28 days.			

4.6 The median age of participants in CLL11 was 74 years, 72 years and 73 years in the obinutuzumab plus chlorambucil, chlorambucil alone, and rituximab plus chlorambucil groups respectively, with an age range of 39 to 90 years. The majority of participants in the trial were men (from 59% to 64% in each group) and white (from 92% to 96% in each group). The majority of participants (from 72% to 77% in each group) had a vascular disorder comorbidity.

4.7 The primary outcome of CLL11 was progression free survival as assessed by the investigator. This was defined as the time from randomisation to the first occurrence of progression, relapse, or death from any cause as assessed by the investigator. The data for this outcome were reported in the company's submission based on a data cut-off on the 3rd March 2014.

4.8 The secondary outcomes in CLL11 were progression free survival as assessed by an independent review committee, overall survival, event-free survival (time before disease progression or relapse, death, or start of a new anti-leukaemic therapy), disease-free survival, duration of response, time to re-treatment or new anti-leukaemic therapy, end of treatment response (response occurring more than 56 days after the end

of treatment), best overall response, best overall response within 1 year of start of study treatment, molecular remission, rate of negative testing for minimal residual disease, adverse events, and patient reported outcomes. The data for the progression free survival and overall survival outcomes were reported in the company's submission based on a data cut-off on the 3rd March 2014. All other outcomes have been reported based on a data cut-off on the 9th May 2013.

4.9 In CLL11, patients were followed up 28 days after the last dose of treatment and then every 3 months for the first 3 years after the last dose of treatment. Further follow ups are planned for every 6 months until 5 years from the date the last patient has entered the study, followed by every year for 8 years after the last patient has entered the study.

4.10 Pre-planned subgroup analyses were performed on the data from CLL11 for age group, race, Binet stage at baseline, total cumulative illness rating scale score at baseline, calculated creatinine clearance, beta2-microglobulin, immunoglobulin variable mutational status, hierarchical model at baseline, time from diagnosis to randomisation, FCγRIIa (CD32), and circulating lymphocyte count at baseline.

ERG comments

4.11 The ERG stated that an open label design may have introduced bias for the primary outcome of progression free survival, however, they acknowledged that the outcome was reviewed by an independent response review panel who were blinded to treatment and similar progression free survival results were found between investigators and reviewers. The ERG acknowledged that the company believed that making the trial double blind would have been prohibitive and unethical because of the number of placebos required for intravenous injections and oral medication.

4.12 The ERG noted that the selection criteria for participants in CLL11 matched those outlined in the final scope. The ERG's clinical expert

believed that the study population in CLL11 was representative of the typical chronic lymphocytic leukaemia patient who would not be eligible for fludarabine-based treatment and of the proposed population of the UK.

4.13 The ERG highlighted that the company did not provide details of which study sites were involved in CLL11 or the number of patients that were recruited from the UK. This may affect the applicability of the trial results to NHS practice.

4.14 The ERG acknowledged that the dosage regimen for obinutuzumab and rituximab used in CLL11 was as stated in the Summary of Product Characteristics. However, they highlighted that the dosage regimen for chlorambucil is subject to uncertainty in clinical practice as there is no clear standard of care dose. The ERG believed that the dose of chlorambucil used in CLL11 is lower than that generally used in clinical practice (typical dose approximately 70 mg in the trial compared with 120 mg in clinical practice). The ERG stated that if chlorambucil is more effective at higher doses and obinutuzumab plus chlorambucil is insensitive to the dose of chlorambucil, the estimated effectiveness of obinutuzumab plus chlorambucil compared with chlorambucil alone was over-estimated in CLL11. However, the ERG acknowledged that obinutuzumab plus chlorambucil may be more effective at higher doses as well.

4.15 The ERG considered the follow up in CLL11 to be adequate.

Clinical trial results

4.16 The median observation time in CLL11 at the May 2013 clinical data cut off was 20.4 months in the chlorambucil alone arm and 23.2 months in the obinutuzumab plus chlorambucil arm and rituximab plus chlorambucil arm for stage 1. For stage 2, the median observation time was 18.6 months for the rituximab plus chlorambucil arm and 18.8 months for the obinutuzumab plus chlorambucil arm. The median observation time at the March 2014 clinical data cut off was [redacted] in the obinutuzumab plus

chlorambucil and rituximab plus chlorambucil arms and [redacted] in the chlorambucil arm in stage 1, and [redacted] for the obinutuzumab plus chlorambucil arm and [redacted] for the rituximab plus chlorambucil arm in stage 2.

4.17 The analysis of the primary endpoint in CLL11 used an intention-to-treat population. Adjustments for multiplicity for the primary endpoint were made using a 3-arm closed-test procedure. Median progression free survival and 95% confidence intervals were estimated using Kaplan-Meier survival methodology.

4.18 The results for the primary outcome for stages 1 and 2 are reported in table 4.

Table 4. Primary outcome for stages 1 and 2

Outcome	Chlorambucil (n=118)	Obinutuzumab plus chlorambucil (n=238)	Rituximab plus chlorambucil (n=233)
Investigator-assessed progression free survival using the May 2013 data cut off (median)			
Stage 1	11.1 months	26.7 months HR 0.18 (0.13 to 0.24) p<0.001*	16.3 months HR 0.44 (0.34 to 0.57) p<0.001*
Stage 2	-	26.7 months HR 0.39 (0.31 to 0.49) p<0.001	15.2 months
HR Hazard ratio, NR Not reported Hazard ratios are reported with 95% confidence intervals in brackets. *p values are compared to chlorambucil alone group in stage 1.			

4.19 The results for the secondary outcomes at the end of stage 1 showed that obinutuzumab plus chlorambucil and rituximab plus chlorambucil were statistically significantly better than chlorambucil alone for most outcomes. At the end of stage 2, obinutuzumab plus chlorambucil was statistically significantly better than rituximab plus chlorambucil for most of the secondary outcomes. Deaths and disease-free survival rate were not statistically significantly different between the groups. See section 6.5.3 of the company's submission for full details of the secondary outcome results.

4.20 In the majority of the subgroups in CLL11, the progression free survival hazard ratios (both assessed by an investigator or independent review committee) favoured obinutuzumab plus chlorambucil and rituximab plus chlorambucil over chlorambucil alone in stage 1, and obinutuzumab plus chlorambucil over rituximab plus chlorambucil in stage 2. In the remaining subgroups ('other' race, cytogenetics 17p deletion and other abnormalities, FCγIIa 131RR and FCγIIIa 158VV) there was no significant difference between treatment groups. The company stated that the number of patients in these subgroups was low and the study was not powered to show significance within subgroups.

ERG comments

4.21 The ERG considered the approach to the statistical analysis of CLL11 to be appropriate.

Network meta-analyses

4.22 No direct evidence comparing obinutuzumab and bendamustine was identified by the company. To compare these 2 treatments, the company created 2 network meta-analyses of RCTs (a large network and a small network) to represent differing scenarios with regard to the suitability of patients for fludarabine based therapy. Evidence from 9 non-RCTs was also identified but not included in the networks because RCT evidence was available.

4.23 The large network included studies regardless of whether full-dose fludarabine therapy was suitable for the enrolled patients (n=17, including CLL11). The results of the large network meta-analysis showed the mean progression free survival hazard ratio statistically significantly favoured obinutuzumab compared with bendamustine (HR 0.399 [95% confidence intervals 0.218 to 0.672], fixed effects model, adjusted for age).

4.24 The small network only included studies of patients ineligible for fludarabine-based therapy (n=3), in line with obinutuzumab's licensed indication. The results of the small network meta-analysis did not provide a comparison of obinutuzumab with bendamustine.

4.25 The company stated that since the network meta-analyses did not allow the calculation of a hazard ratio for the comparison of obinutuzumab plus chlorambucil and rituximab plus bendamustine, it had made an assumption of the value of this hazard ratio to inform the cost-effectiveness model. Based on data from CLL11 at the March 2014 data cut off and the ongoing MaBLe trial that compares rituximab plus bendamustine with rituximab plus chlorambucil, a hazard ratio of 0.68 was calculated and used as the base case in the model. Varying this hazard ratio was explored in the company's sensitivity analysis.

ERG comments

4.26 The ERG stated that the searches and WinBUGS coding conducted for the network meta-analysis were appropriate.

4.27 The ERG noted that the bendamustine RCT included in the network meta-analysis was an open label study, which may have biased the progression free survival outcome. The ERG also noted that the mean dose of chlorambucil used per cycle in the bendamustine RCT (112 mg) was lower than that used in UK clinical practice (120 mg) but higher than in CLL11 (70 mg). The ERG stated that the difference in doses may have affected the results of the network meta-analysis.

4.28 The ERG disagreed with the company's claim that the mixed treatment comparison did not provide a comparison of obinutuzumab plus chlorambucil and bendamustine plus rituximab. The ERG highlighted that the relevant progression free survival hazard ratios were presented in the company's submission (appendix 14). However, the ERG acknowledged that these hazard ratios were of little importance because the 2 treatments are connected via many other treatments and the dose of chlorambucil used differs in each trial.

4.29 The ERG acknowledged 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 the percentage of complete responders. The percentage of complete responders is estimated by the company based on the sample size of the ongoing MaBLe trial. The ERG believed that it would be more appropriate to base this on the interim percentage of complete responding patients from MaBLe instead. The ERG noted that this hazard ratio had an impact on the hazard ratio for obinutuzumab plus chlorambucil and bendamustine plus rituximab.

4.30 The ERG stated that it was possible to estimate a progression free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine in patients aged 65 years or older based on the bendamustine compared with chlorambucil trial (Knauf et al) and the CLL11 results. The ERG's estimate of the hazard ratio based on the Knauf publication and the CLL11 results was very similar to the company's estimate of 0.55 from the fixed effects analysis of the mixed treatment comparison without adjustment for age. The ERG therefore believed 0.55 was a more accurate estimate of the hazard ratio for the comparison of obinutuzumab plus chlorambucil and bendamustine rather than the value of 0.40 from the age adjusted fixed effects analysis of the company's mixed treatment comparison.

Adverse effects of treatment

4.31 Safety analyses were performed on all patients who received at least 1 dose of study medication in CLL11. The most frequent adverse events were infusion-related reactions, neutropenia and nausea. The most frequent adverse events of Grade 3 or higher were infusion-related reactions, neutropenia and anaemia. The most frequent serious adverse events were infection, neoplasm and infusion-related reactions. The statistical significance of the difference in adverse events across groups was not reported by the company.

4.32 Adverse effects as reported at the May 2013 data cut are presented in table 5. The incidence of adverse events, serious adverse events and adverse events leading to discontinuation of study treatment was higher in the obinutuzumab plus chlorambucil arm. This difference was mainly as a result of infusion related reactions.

Table 5. Adverse effects in the CLL11 trial

	Stage 1			**Stage 2**	
	O-Clb (n = 241)	**Clb (n = 116)**	**R-Clb (n = 225)**	**O-Clb (n = 336)**	**R-Clb (n = 321)**
At least 1 adverse event of any grade	227 (94%)	96 (83%)	205 (91%)	286 (89%)	315 (94%)
Any adverse event of Grade 3 or higher	175 (73%)	58 (50%)	125 (56%)	235 (70%)	177 (55%)
Any serious adverse event	99 (41%)	44 (38%)	76 (34%)	131 (39%)	102 (32%)
Discontinuation due to infusion related reaction	NR	NR	NR	25 (7%)	3 (<1%)
Discontinuation due to tumour lysis syndrome	NR	NR	NR	1 (<1%)	0
Clb Chlorambucil; NR Not reported; O-Clb Obinutuzumab plus chlorambucil; R-Clb Rituximab plus chlorambucil					

4.33 Obinutuzumab treatment was associated with increases in common chlorambucil-related toxicities (neutropenia, thrombocytopenia, anaemia). These events were mainly mild to moderate in severity, easily managed, and rarely led to discontinuation of all treatment.

4.34 Infusion related reactions occurred in 166 (69%) patients in the obinutuzumab plus chlorambucil arm and 88 (39%) patients in the rituximab plus chlorambucil arm in stage 2 of CLL11. Most infusion related reactions were low grade in intensity and were clinically manageable. No deaths were associated with infusion related reactions.

4.35 There were 21 (6.5%) deaths due to adverse events in the rituximab plus chlorambucil arm, 15 (4.5 %) deaths due to adverse events in the obinutuzumab plus chlorambucil arm and 11 (9%) deaths due to adverse events in the chlorambucil alone arm. The company did not report whether the differences between the groups in the number of deaths due to adverse events was statistically significant.

4.36 The company did not undertake additional searches for safety data because safety was an endpoint in CLL11.

ERG comments

4.37 The ERG stated that the adverse event data suggest that obinutuzumab plus chlorambucil is well tolerated with manageable additional toxicity. The ERG agreed that the adverse event profile reported by the company is consistent with that expected in the patient population of CLL11.

5 Cost-effectiveness evidence

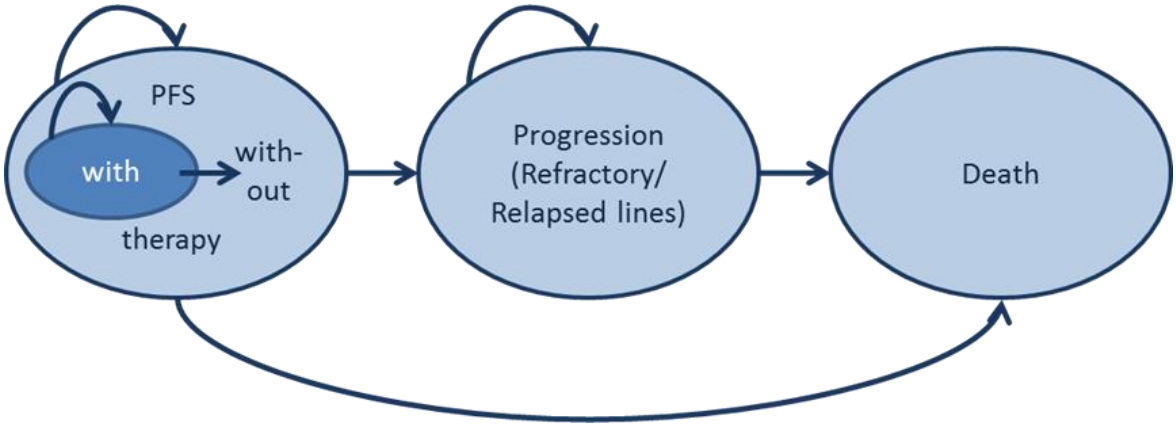
Model structure

5.1 The company identified 1 published cost-effectiveness model of patients with chronic lymphocytic leukaemia (Walzer et al., 2013) that was relevant to this appraisal, which had previously been developed by the same company. The published model was updated by the company for inclusion in this appraisal.

5.2 The company's model evaluated the cost-effectiveness of obinutuzumab plus chlorambucil compared to rituximab plus chlorambucil, bendamustine plus rituximab, bendamustine alone and chlorambucil alone. The model consisted of 3 health states, namely 'progression free survival',

'progressed', and 'death', with the progression free survival health state further divided into 'on therapy' and 'not on therapy', as shown in figure 2. The model had weekly cycles and a half-cycle correction was applied, except to the drug, administration and pharmacy costs. A lifetime time horizon (maximum 20 years) was used. A discount rate of 3.5% per year was used for costs and QALYs. An NHS/PSS perspective was used.

Figure 2. The company's model



ERG comments

5.3 The ERG agreed that there were no other published models that were directly relevant to this appraisal. However, the ERG stated that it would have been useful to look at cost-effectiveness studies for any of the comparators to provide some insight into appropriate modelling approaches.

5.4 The ERG stated that the model structure is appropriate and was adequately validated. They noted that the model is more simple than the model used in a previous appraisal of chronic lymphocytic leukaemia (TA216) which included additional health states and second line treatment such as fludarabine and bendamustine. However the ERG acknowledged that if a more complicated model had been used there would have been limited data to inform these complexities.

Model details

Transitions

5.5 All people in the model started in the progression free survival health state. At the end of each weekly cycle, people in the progression free survival health state either remained there, moved to the progressed health state, or died. People in the progressed health state either remained in the progressed health state or died. Once they moved to a different state in the model, people could not return to their previous state.

5.6 The overall survival distribution was modelled using data from the CLL5 trial (an RCT that compared fludarabine to chlorambucil in previously untreated patients with chronic lymphocytic leukaemia) because the overall survival data from CLL11 was very immature. The overall survival distribution in the model was validated using the Kaplan-Meier overall survival data that was available from CLL11.

5.7 The number of people in the progression free survival health state was calculated using data from the CLL11 trial for the obinutuzumab plus chlorambucil, rituximab plus chlorambucil, and chlorambucil alone arms and data from the network meta-analysis for the bendamustine and rituximab plus bendamustine arms. The transition from the progression free survival health state was modelled using data from the CLL11 trial and background mortality.

5.8 The proportion of people in the progressed health state in each cycle was the difference between the proportion of people that were alive and the proportion of people that were progression free.

Costs

5.9 The drug costs used in the model are presented in table 6 and administration, health state and adverse event costs are presented in table 7.

Table 6. Drug costs used in the company's cost-effectiveness model

	Obinutuzumab	Rituximab	Bendamustine	Chlorambucil
Technology cost	£3312 per 1000 mg vial	£174.63 per 100 mg vial £873.15 per 500 mg vial	£69.45 per 25 mg vial £275.81 per 100 mg vial	£40.51 per 25 x 2 mg pack
Cost per mg	£3.31	£1.75	£2.76	£0.81
Cost per treatment course	£26,496	£9953.91	£5809.92	£369.45

Table 7. Administration, health state, and adverse event costs used in the company's cost-effectiveness model

Administration costs	
Initial dose of obinutuzumab, rituximab, or bendamustine	£514
All subsequent doses of obinutuzumab, rituximab, or bendamustine	£343
All doses of chlorambucil	£136
Clinical haematologist cost of first cycle consultation (30 mins)	£134
Clinical haematologist cost of subsequent cycles consultations (30 mins)	£53
Pharmacy costs per dispensing for obinutuzumab, rituximab or bendamustine (15 minutes)	£16.75
Pharmacy costs per dispensing for chlorambucil (5 minutes)	£5.58
Health state costs	
Supportive care costs per week for progression free survival	£8.13
Supportive care costs for progressed disease (including post-progression treatments) per week	£24.38
Post-progression treatment costs	£369.45
Adverse event costs	
Anaemia	£2088
Febrile neutropenia	£3894
Infusion-related reaction	£359
Leukopenia	£942
Lymphopenia	£942
Maculo-papular rash	£500
Neutropenia	£3894
Pneumonia	£1353
Thrombocytopenia	£1847

5.10 Resource use in the progression free and progressed health states was informed by European Society of Medical Oncology guidelines and validated with clinical experts at an advisory board. The progression free survival health state assumed 1 outpatient appointment lasting 60 minutes every 3 months and the post-progression state assumed 1 outpatient appointment every month.

Adverse events

5.11 Adverse events were included in the model if they were grade 3, 4 or 5 and occurred in 2% or more people in CLL11 (obinutuzumab plus chlorambucil, rituximab plus chlorambucil or chlorambucil), the Knauf trial (bendamustine and rituximab plus bendamustine), or the MaBLe trial (bendamustine and rituximab plus bendamustine). As there was a lack of complete data for bendamustine plus rituximab from the MaBLe study, the frequency and cost of adverse events was assumed to be the same as those of rituximab plus chlorambucil in stage 2 of CLL11. The total cost of all adverse events in each arm was applied as a one-off event in the first cycle of each Markov state.

5.12 The estimated total adverse event costs per patient for each treatment arm are presented in table 8.

Table 8. Total adverse event cost by treatment arm used in the company's cost-effectiveness model

Treatment arm	Total adverse event cost per patient
Obinutuzumab	£2544
Rituximab plus chlorambucil	£1694
Chlorambucil	£1036
Bendamustine	£1362
Bendamustine plus rituximab	£1694

Utility values and health related quality of life

5.13 The company identified 9 potentially relevant studies that provided utility values. However, the company believed that the utility values from these studies were not applicable to this appraisal for the following reasons: the utility values were originally derived from expert opinion and may not reflect societal preferences, the utility values were not related to progression free survival or progressed disease, the study used a standard gamble methodology rather than time trade off methodology, the utility values were related to 3rd line treatment, or the line of treatment was not clear.

5.14 To determine relevant utility values, the company conducted a utility elicitation study with a sample of 100 members of the UK general public. The utility elicitation study used vignettes to explore societal preferences for quality of life associated with chronic lymphocytic leukaemia. The utility values elicited in the study and used in the model are presented in table 9.

Table 9. Utility values used in the company's cost-effectiveness model

Factor	Utility value
Progression free survival under oral treatment (chlorambucil)	0.71
Progression free survival under IV treatment (rituximab, bendamustine)	0.67
Progression free survival on initial therapy with increased hospital visits (1st dose of obinutuzumab)	0.55
Progression free survival after initial treatment is completed (all arms)	0.82
Progressed disease (all arms)	0.60

5.15 Health related quality of life was assumed to be constant over time within each health state in the model.

ERG comments

5.16 The ERG believed that, in general, the modelling in the company's base case is acceptable. The ERG noted that the inputs and assumptions of the model were adequately validated. The ERG stated that the programming of the company's model is generally appropriate, with no serious errors. The ERG stated that the time horizon was sufficient to

account for all costs and benefits and that the discounting was appropriate.

5.17 The ERG highlighted that the transition from progression free survival to death is calculated differently for bendamustine and rituximab plus bendamustine than in the other arms. The ERG did not find that altering the transition substantially affected the overall cost effectiveness results and considered the approach taken by the company to be appropriate in light of the lack of evidence to inform it.

5.18 The ERG believed that the population in CLL5 was not generalizable to the population in which the drug would be used in clinical practice, as they could be treated with fludarabine. In addition, CLL5 was conducted in Germany and may not be applicable to a UK population. The ERG noted that the company adjusted the mortality rate in the progressed disease state with age as a covariate, with the assumption that age would account for the impact of comorbidities. The ERG's clinical expert believed this was an appropriate approach. The ERG stated that the company's assumption that post progression survival is approximately equal between treatments is a reasonable assumption.

5.19 The ERG believed that the company's approach to modelling the costs of adverse events was appropriate. The ERG disagreed with some of the company's unit costs, including the unit cost of administration of the first dose of an intravenous drug, the administration of subsequent doses of an intravenous drug, administration of an oral drug, first visit with a haematologist per hour, and subsequent visits with a haematologist per hour. The ERG also noted some discrepancies between the adverse event costs presented in the company's submission and in the sources that the company cited. However, the ERG noted that the ICERs changed only marginally if their preferred values were used.

5.20 The ERG highlighted that the company did not perform a mapping of the EORTC QLQC30 questionnaire to the EQ5D. The ERG identified several mapping functions that could have been used.

5.21 The ERG believed that a generic questionnaire such as the EQ-5D should have been used instead of vignettes in the company's utility study. They also noted that the vignette approach would have been more useful if utility values had been elicited from chronic lymphocytic leukaemia patients rather than the general public.

5.22 The ERG disagreed with 2 of the company's utility values. The ERG argued that the utility value whilst on obinutuzumab treatment after the 1st cycle of treatment should be the same as the utility value for progression free survival on intravenous treatment (0.67) rather than progression free survival off treatment (0.82). In addition, the ERG noted that the utility value used by the company for progression free survival off treatment (0.82) is higher than the utility value of members of the UK general public at the average age of treatment. The ERG noted that there is no reliable data to give a more accurate figure, however, they suggest the use of 0.76 as an upper bound, which is an average of the UK general population mean utility value at the average age of treatment. These are amended in the ERG's base case (see sections 5.32 and 5.33).

5.23 The ERG highlighted that disutilities from adverse events were not explicitly taken into account in the company's model. The ERG's clinical expert suggested that health related quality of life is lowest whilst on bendamustine due to the incidence of fatigue, nausea and vomiting. However, the ERG noted that using a further disutility of 0.05 for patients taking bendamustine or bendamustine plus rituximab causes only a small decrease in the ICERs compared to obinutuzumab plus chlorambucil.

5.24 The ERG disagreed with the company's assumed dose intensity of 100% for both bendamustine and rituximab in the bendamustine plus rituximab arm. The ERG highlighted that the dose intensity used in the MaBLe trial

is not yet available. In the absence of this data, the ERG suggested that the value for bendamustine in the bendamustine plus rituximab arm should be equal to that for bendamustine alone (90%) and the value for rituximab should be equal to that in CLL11 (98.8%). These are amended in the ERG's base case (see sections 5.32 and 5.33).

Company's base case results and sensitivity analysis

5.25 The company's base case and incremental results are presented in tables 10 and 11. These include the company's base case and the results of the company's incremental analysis.

Table 10. Company's base case ICERs

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Obinutuzumab plus chlorambucil	£34,888	4.03	-	-	-
Rituximab plus bendamustine	£27,215	3.65	£7673	0.38	£20,076
Rituximab plus chlorambucil	£20,002	3.33	£14,886	0.70	£21,275
Bendamustine	£15,557	3.30	£19,331	0.73	£26,463
Chlorambucil	£8020	2.92	£26,868	1.11	£24,256
ICER Incremental cost effectiveness ratio, QALY Quality adjusted life year					

Table 11. Company's incremental analysis versus chlorambucil

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER versus chlorambucil (£/QALY gained)	ICER Incremental (£/QALYs)
Chlorambucil	£8020	2.92	-	-	-	-
Bendamustine	£15,557	3.30	£7536	0.38	£19,983	£19,983
Rituximab plus chlorambucil	£20,002	3.33	£11,982	0.41	£29,369	Extendedly dominated*
Rituximab plus bendamustine	£27,215	3.65	£19,195	0.73	£26,458	Extendedly dominated*
Obinutuzumab plus chlorambucil	£34,888	4.03	£26,868	1.11	£24,256	£26,463
ICER Incremental cost effectiveness ratio, QALY Quality adjusted life year *A treatment is extendedly dominated when its ICER is higher than that of the next, more effective, option when compared with a common baseline.						

5.26 The company undertook deterministic sensitivity analyses on a range of parameters around the base case ICER from the simultaneous comparison compared with chlorambucil, namely progression free survival values, post-progression death rate, hazard ratios from the mixed treatment comparison, significant costs, utility values, and the discount rate for both costs and outcomes for the incremental cost-effectiveness results. The ICERs from the deterministic sensitivity analyses for obinutuzumab plus chlorambucil compared with chlorambucil ranged from £18,402 to £36,527 per QALY gained. The ICERs over £30,000 per QALY gained were from using:

- a lower utility value of progression free survival off treatment
- a higher hazard ratio for progression free survival when comparing obinutuzumab plus chlorambucil and rituximab plus bendamustine,
- a higher hazard ratio for progression free survival when comparing obinutuzumab plus chlorambucil and rituximab,
- half the base case value for the overall survival value for the transition probabilities, and
- a progression free survival transition probability using the Gompertz tail and the Gompertz distribution.

5.27 Probabilistic sensitivity analyses were performed for utility values, parameter estimates for the parametric progression free survival and PPS function, number of adverse events, costs of adverse events, monthly supportive care costs for the progression free survival and progressed health states, administration costs, and hazard ratio of the indirect treatment comparisons. The probabilistic base-case ICER for obinutuzumab plus chlorambucil was £25,779 per QALY gained. The probabilistic sensitivity analyses showed that obinutuzumab plus chlorambucil had a 63.4% chance of being the most cost effective treatment option at a threshold of £30,000 per QALY gained and

bendamustine had the next highest probability at 28.5%. A probabilistic sensitivity analysis on an alternative base-case (using a Weibull function in its entirety rather than using data from a Kaplan Meier curve and parametric extrapolation) resulted in a probabilistic ICER of £26,206 per QALY gained and a 62.8% change of obinutuzumab being the most cost-effective treatment option.

5.28 The company identified the key drivers of the model as the long term projection of progression free survival, the post-progression death rate, the results of the network meta-analysis and the utility values used.

ERG comments

5.29 The ERG highlighted that the dose of chlorambucil in CLL11 is substantially lower than that used in routine clinical practice. The ERG stated that if chlorambucil is more effective at higher doses and obinutuzumab plus chlorambucil is insensitive to the dose of chlorambucil, the estimated effectiveness of obinutuzumab plus chlorambucil compared with chlorambucil alone was over-estimated in CLL11. However, the ERG acknowledged that obinutuzumab plus chlorambucil may be more effective at higher doses as well.

5.30 The ERG stated that the ICER between obinutuzumab plus chlorambucil and bendamustine is uncertain because the progression free survival hazard ratio between these treatments (0.40) has been estimated using an indirect comparison. The ERG stated that it is possible to estimate a progression free survival value for obinutuzumab plus chlorambucil compared with bendamustine in patients aged 65 years or older based on the Knauf et al publication relating to the trial that compared bendamustine with chlorambucil and the CLL11 results. Using this method, the ERG estimated a figure very similar to the company's estimate of 0.55 from the fixed effects analysis of the mixed treatment comparison without adjustment for age. The ERG have addressed this in their base case (see sections 5.32 and 5.33).

5.31 The ERG stated that the ICER between obinutuzumab plus chlorambucil and bendamustine plus rituximab is also highly uncertain because the progression free survival hazard ratio between rituximab plus bendamustine and rituximab plus chlorambucil was not available. The ERG acknowledged that the estimated hazard ratio between bendamustine plus rituximab and rituximab plus chlorambucil (which impacts on the hazard ratio for obinutuzumab plus chlorambucil and bendamustine plus rituximab) from the network meta-analysis depends substantially on the data used to calibrate the correlation between the hazard ratio and the percentage of complete responders. The percentage of complete responders is estimated by the company based on the sample size of the ongoing MaBLe trial. The ERG believed that it would be more appropriate to base the estimate of complete responders on the interim percentage of complete responders from MaBLe instead. The ERG believed that the best estimate for the hazard ratio between rituximab plus bendamustine and obinutuzumab plus chlorambucil is 0.76, compared to the company's estimate of 0.68. The ERG have addressed this in their base case (see sections 5.32 and 5.33).

ERG exploratory analyses

5.32 The ERG explored several changes to the company's assumptions in their base case and exploratory analyses. These are presented in table 12.

Table 12. Scenarios explored by the ERG

Scenario number	Assumption	Company's value	ERG's value	ERG's rationale for change
1	Utility value whilst on obinutuzumab	0.82	0.67	0.82 corresponds to progression free survival off treatment whereas 0.67 corresponds to progression free survival on IV treatment (section 5.22).
2	Utility value for progression free survival off treatment	0.82	0.76	Company's value is higher than utility value of general public of comparable age (section 5.22). ERG suggest average utility value of general public at average age of treatment.
3	Mean dose of bendamustine and rituximab in bendamustine plus rituximab arm	Bendamustine 100% Rituximab 100%	Bendamustine 90% Rituximab 98.8%	Values should match those for bendamustine monotherapy in the model and for rituximab plus chlorambucil arm in CLL11 (section 5.24).
4	Progression free hazard ratio of obinutuzumab plus chlorambucil compared with bendamustine plus rituximab	0.68	0.76	Company's hazard ratio is highly uncertain and based on complete responders from a sample size calculation from MaBLe. ERG used interim percentage of complete responders patients from MaBLe (section 5.31).
5	Progression free hazard ratio for obinutuzumab plus chlorambucil vs. bendamustine	0.40	0.55	Company estimate from network meta-analysis. ERG's estimate from Knauf et al (2009) for bendamustine vs. chlorambucil and CLL11 for obinutuzumab plus chlorambucil vs. chlorambucil (sections 4.30 and 5.30).

5.33 The results of the ERG's base case and exploratory scenario analyses for obinutuzumab plus chlorambucil compared with the comparators are

presented in table 13. The ERG's base case used all of the ERG's assumptions in scenarios 1 to 5.

Table 13. ERG's base case ICER (cost per QALY gained) and exploratory analyses of obinutuzumab plus chlorambucil compared with 4 comparators

Scenario*	Comparators			
	Rituximab plus bendamustine	**Rituximab plus chlorambucil**	**Bendamustine**	**Chlorambucil**
Company's base case	£20,076	£21,275	£26,463	£24,256
Scenario 1	£23,000	£23,000	£28,000	£25,000
Scenario 2	> £23,000	> £24,000	> £30,000	> £27,000
Scenario 3	£25,000	n/c	n/c	n/c
Scenario 4	£26,000	n/c	n/c	n/c
Scenario 5	n/c	n/c	£37,000	n/c
Scenarios 1 + 2	> £25,000	> £25,000	> £31,000	> £28,000
Scenarios 1 + 2 + 3 + 4	> £43,000	> £25,000	> £31,000	> £28,000
ERG's base case (scenarios 1 to 5)	> £43,000	> £25,000	> £44,000	> £28,000

Abbreviations: QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio; N/C ICER has not changed from the company's base case

*See table 12 for description of each scenario

5.34 The ERG performed a sensitivity analysis on the utility value whilst patients are off treatment in progression free survival. The company used a utility value associated with progression free survival off treatment, whereas the ERG stated that a value corresponding to progression free survival on IV treatment would have been more appropriate. The results of the ERG's sensitivity analysis are presented in table 14.

Table 14. Results of the ERG's sensitivity analysis: ICERs (costs per QALY gained) for obinutuzumab plus chlorambucil compared with 4 comparators

	Comparators			
	Rituximab plus bendamustine	**Rituximab plus chlorambucil**	**Bendamustine**	**Chlorambucil**
Company's base case	£20,000	£21,000	£26,000	£24,000
ERG's base case	> £43,000	> £25,000	> £44,000	> £28,000
Utility value of 0.71 for progression free survival off treatment applied in ERG's base case	£48,000	£28,000	£49,000	£31,000
Utility value of 0.71 for progression free survival off treatment applied in company's base case	£27,000	£27,000	£34,000	£30,000

5.35 The ERG stated that there were no other sensitivity analysis for which there is a credible value and for which the ICER changes substantially.

5.36 The ERG stated that, using their base case and a willingness to pay threshold of £20,000 to £30,000 per QALY gained, obinutuzumab plus chlorambucil is poor value for money in patients for whom bendamustine is suitable. In patients for whom bendamustine is not suitable, obinutuzumab plus chlorambucil is poor value at a willingness to pay threshold of £20,000 per QALY gained. At a willingness to pay threshold of £30,000 per QALY gained, obinutuzumab plus chlorambucil and chlorambucil provide the best value for money and are very similar.

Innovation

5.37 Justifications for considering obinutuzumab to be innovative:

- The company claims obinutuzumab results in a step-change in the treatment of chronic lymphocytic leukaemia.
- The company claims obinutuzumab is a first-in-class anti-CD20 antibody that combines with chlorambucil (currently the main therapeutic approach for chronic lymphocytic leukaemia patients in the UK who are ineligible for full dose fludarabine) to target the CD20 antigen with chemotherapy.
- The company claims obinutuzumab provides improved progression free survival, improved overall response rate, longer time to next treatment and a landmark improvement in overall survival.
- The company claims obinutuzumab significantly improves outcomes in older chronic lymphocytic leukaemia patients with coexisting conditions and a significant improvement in overall survival compared to chlorambucil.

5.38 Justifications for not considering obinutuzumab to be innovative:

- The company states that all health-related benefits are likely to be captured in the QALY calculation.

6 Equalities issues

6.1 No equalities issues were identified by the company, the ERG, or the consultees.

7 Authors

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Appendix A: Supporting evidence

Existing NICE guidance for first-line treatment of chronic lymphocytic leukaemia

NICE Technology Appraisal Guidance 174 (July 2009)

Rituximab for the first-line treatment of chronic lymphocytic leukaemia

1.1 Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia in people for whom fludarabine in combination with cyclophosphamide is considered appropriate.

1.2 Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of chronic lymphocytic leukaemia.

NICE Technology Appraisal Guidance 216 (February 2011)

Bendamustine for the first-line treatment of chronic lymphocytic leukaemia

1.1 Bendamustine is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

EPAR for obinutuzumab

The EPAR is available online:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002799/WC500171596.pdf