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

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Abbreviations

AE	Adverse event
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
AIC	Akaike Information Criteria
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Accelerated phase
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
Benda	Bendamustine
BNF	British National Formulary
BSC	Best supportive care
BSA	Body surface area
C(A)T	Computerised (axial) tomography
CC	Complication/comorbidity (HRG code)
CENTRAL	The Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Clb	Chlorambucil
CLL	Chronic lymphocytic leukaemia
CNS	Central nervous system

CRD Centre for Reviews and Dissemination

CSR Clinical Study Report

DARE The Database of Abstracts of Reviews of Effects

DET Data extraction table

ECOG Eastern Cooperative Oncology Group

EHA European Haematology Association

ELN European LeukemiaNet

EMA European Medicines Agency

EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

EPAR European Public Assessment Report

EQ-5D European Quality of Life- 5 Dimensions questionnaire

ERG Evidence Review Group

ESMO European Society for Medical Oncology

EWB Emotional well-being

FACT-Leu Functional Assessment of Cancer Therapy- Leukemia

FC Fludarabine + chlorambucil

FDA US Food and Drug Administration

FWB Functional well-being

GBP Great British Pounds (currency)

GP General Practitioner

HCHS Hospital and community health services

HM Haematological

HMRN Haematological Malignancy Research Network

HR Hazard ratio

HRG Healthcare Resource Group

HRQoL Health-related quality of life

HTA Health Technology Assessment

ICER Incremental cost-effectiveness ratio

ICLLM International Congress on Leukemia Lymphoma Myeloma

ICU Intensive-care unit

IFR Individual funding requests

INHB Incremental net health benefit

INR International Normalised Ratio

ISPOR International Society for Pharmacoeconomics and Outcomes Research

IV Intravenous

k thousand

kg kilogram

KM Kaplan-Meier

LEUS Leukaemia subscale

mg Milligrams

m metre

MTC Mixed treatment comparison

MUD Matched unrelated donor

NA Not applicable

NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events

NEL No evidence of leukaemia

NHB Net health benefit

NHS National Health Service (UK)

NHS EED NHS Economic Evaluation Database

NHSBT NHS Blood and Transplant

NICE National Institute for Health and Care Excellence

NR Not reported

ObClb obinutuzumab+chlorambucil

ONS Office for National Statistics

OS Overall survival

PAOD Peripheral arterial occlusive disease

PAS Patient Access Scheme

PB Peripheral Blood

PCR Polymerase chain reaction

PD Progressive disease

PenTAG Peninsula Technology Assessment Group

PFS Progression-free survival

PPS Post progression survival

PSA Probabilistic sensitivity analysis

PSS Personal Social Services

PSSRU Personal Social Services Research Unit

PWB Physical well-being

QALY Quality-adjusted life year

QTc Corrected QT interval

RBenda rituximab + bendamustine

RClb rituximab+chlorambucil

RCP Return to chronic phase

RCT Randomised controlled trial

SD Standard deviation

SF-36 Short Form (36) Health Survey

SE Standard error

SM Solid malignancies

SMC Scottish Medicines Consortium

SmPC/SPC Summary of Product Characteristics

SWB Social well-being

TA[number] Technology appraisal [number]

TK Tyrosine kinase

TKI Tyrosine kinase inhibitor

TTO Time trade off

UK United Kingdom

ULN Upper limit of normal

USA/US United States of America

VAS Visual analogue scale

WBC White blood cell

WHO World Health Organisation

WTP Willingness to pay

1. Summary

Italicised sections of text have been copied from the submission by Roche, hereafter referred to as 'the submission'. In the report, we refer to obinutuzumab either by full name or as Ob. In some figures and tables inserted directly from Roche's submission, obinutuzumab is represented as G. In the report we refer to rituximab by full name or as R; chlorambucil by full name or as Clb and bendamustine by full name or as benda.

Overall, we consider the submission from Roche to be of high quality. The economic model is generally appropriate, and has only one wiring error, which is of moderate importance.

1.1. Critique of the decision problem in the manufacturer's submission

The patient population described in the Final Scope is: People with previously untreated chronic lymphocytic leukaemia for whom fludarabine combination chemotherapy is unsuitable. Roche's submission concerns this population.

Roche consider all the comparators in the Final Scope:

- Chlorambucil
- Rituximab in combination with chlorambucil
- Bendamustine monotherapy
- Rituximab in combination with bendamustine

Ofatumumab is currently being assessed for exactly the same patient population. The date of the first NICE appraisal committee meeting is 7th October 2014. However, this is not one of the comparators in the Final Scope.

Roche believe that the most common treatment in the UK for patients unsuited to fludarabine is chlorambucil, and therefore that this is the most important comparator. Our clinical expert disagrees, and instead believes that the vast majority of patients unsuited to fludarabine are treated with rituximab+chlorambucil in the UK. Further differences of opinion come from commentators to this appraisal and clinicians at the Scoping Workshop.

Rituximab+chlorambucil was assessed and not recommended in NICE TA174.[1] The NICE Methods Guide (2013)[2] suggests that it is up to the NICE committee to decide whether this is a valid comparator treatment in the current appraisal.

1.2. Summary of clinical effectiveness evidence submitted by the manufacturer

1.2.1. Obinutuzumab+chlorambucil , rituximab+chlorambucil, chlorambucil effectiveness

The submission from Roche includes one study concerning obinutuzumab, CLL11; a phase III, multicentre, open-label, randomised, three-arm study, evaluating the efficacy and safety of obinutuzumab+chlorambucil against rituximab+chlorambucil or chlorambucil alone. In accordance with the licensed indication, the study considers previously untreated CLL patients with co-existing conditions (Source: Roche Submission, Section 6.2.4, pp37). Our clinician advises us that patients seen in clinical practice are similar to those in the CLL11 trial, with median age of 73. We hence agree with Roche that, overall, the demographics of enrolled participants are reflective of the proposed population in the UK (Source: Roche Submission, Section 6.9.4, pp125). These include older patients who typically have multiple co-existing medical conditions that may exclude them from receiving other intensive treatments, such as FCR.

The study was designed to include two stages and 3 primary analysis time points:

- Stage 1 randomised 589 patients 2:2:1 obinutuzumab+chlorambucil : rituximab+chlorambucil: chlorambucil and was split into two primary analysis time points:

  – Stage 1 a: final analysis for obinutuzumab+chlorambucil versus chlorambucil and futility and efficacy interim analysis for obinutuzumab+chlorambucil versus rituximab+chlorambucil.

  – Stage 1 b: final analysis of rituximab+chlorambucil versus chlorambucil.

- Stage 2: final analysis for 192 additional patients for obinutuzumab+chlorambucil versus rituximab+chlorambucil (randomisation 1: 1) continued into the obinutuzumab+chlorambucil and rituximab+chlorambucil treatment arms only.

Follow-up was performed at 28 days after their last dose of treatments and then quarterly for 3 years. Further follow-ups occurred twice yearly. Assessment of the primary outcome, investigator-assessed progression-free survival (PFS), was performed and defined as the time from randomisation to the first occurrence of progression, relapse, or death from any cause as assessed by the investigator. The open label design of the CLL11 trial means that PFS may be open to bias. However, PFS based on independent review committee (IRC) assessments was also analysed to support the primary analysis and this will reduce any bias. Other secondary outcomes included event-free survival, disease-free survival, duration

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, as our clinical expert believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab+chlorambucil versus chlorambucil is over-estimated 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.

Superseded

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+chlorambucil arm (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+chlorambucil arm and 26.7 months in the obinutuzumab+chlorambucil arm; an 11.5 month improvement.

See Erratum

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 obinutuzumab+chlorambucil), best overall response (p<0.0001 versus chlorambucil and p=0.0001 versus obinutuzumab+chlorambucil), disease free survival (p<0.0001 versus chlorambucil and p=0.0475 versus obinutuzumab+chlorambucil), and time to new treatment (p<0.0001 versus chlorambucil and p=0.0018 versus obinutuzumab+chlorambucil) compared to chlorambucil and rituximab+chlorambucil. The significantly prolonged time to new anti-leukaemia therapy with obinutuzumab+chlorambucil compared with rituximab+chlorambucil or chlorambucil means that patients experience a longer period off treatment.

Superseded
See Erratum

The safety profile of obinutuzumab was generally comparable to that of rituximab+chlorambucil and 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, leukopenia, anaemia, pyrexia, and nasopharyngitis was higher (>5% difference) in the obinutuzumab based arm than in the rituximab+chlorambucil or 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+chlorambucil were less likely to discontinue therapy early owing to adverse events. The imbalance between the obinutuzumab+chlorambucil group and the rituximab+chlorambucil group 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.

Superseded
See Erratum

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.

It is notable that there is no data in the submission for HRQoL from CLL11. Roche state for the patient-reported quality of life outcome, the number of patients was too small and no meaningful statistical comparison of the treatment arms could be made. However, we note that HRQL data was provided in the appendix of the primary paper Goede et al [4]and that the paper cites in its text that Quality of life did not deteriorate during or after antibody therapy as compared with treatment with chlorambucil alone" (Source: Goede et al (2014), p6). However, no data values are given to support the HRQL graphs in the appendix of the Goede paper [4] and it is not possible to comment further due to the limited information available.

1.2.2. Bendamustine effectiveness

The CLL11 trial evaluates the efficacy of obinutuzumab+chlorambucil , rituximab+chlorambucil and chlorambucil alone. Roche claim that it is inappropriate to use data directly from the RCT of bendamustine versus chlorambucil, as they argue that some patients in the trial would be eligible for fludarabine-based therapy because they are, on average, younger than patients in the CLL11 trial.

In an attempt to adjust the results from the single RCT of bendamustine versus chlorambucil, Roche performed a mixed treatment comparison to compare the treatments in CLL11 with bendamustine. The PFS hazard ratio was the response variable in the evidence network. A total of 17 RCTs, encompassing 14 pharmacological interventions, were included. The analysis was performed in WinBUGS. In their base case, Roche used a fixed effects model with meta-regression on median patient age. When the mixed treatment comparison was adjusted for age in this way, the hazard ratio between bendamustine and chlorambucil increased from 0.35 to 0.51, and the hazard ratio between obinutuzumab+chlorambucil and bendamustine decreased from 0.55 to 0.40. Roche use the PFS hazard ratio of 0.40 between obinutuzumab+chlorambucil and bendamustine in the base case analysis in their economic model.

We believe that Roche's WinBUGS code is appropriate, and we agree that it would not be appropriate to include the bendamustine vs. chlorambucil PFS hazard ratio into the evidence network without adjustment, because some of the patients in the RCT were eligible for fludarabine therapies.

However, we believe that the mixed treatment comparison is redundant because we have located the PFS for patients aged <65 and separately ≥ 65 in the bendamustine versus chlorambucil RCT. An abstract by Knauf et al. (2009)[5] shows that PFS for patients aged <65 and ≥ 65 is very similar (**Figure 19**).

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, p91. Henceforth, we assume that the PFS hazard ratio between obinutuzumab+chlorambucil and bendamustine for patients relevant to this HTA is 0.55.

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).

Superseded

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.

See Erratum

- 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.

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, 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.

Superseded

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 in October 2014.

See Erratum

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.

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

2. Utility in PFS off treatment

3. Drop out in bendamustine+rituximab arm

4. PFS hazard ratio between obinutuzumab+chlorambucil and bendamustine + rituximab

5. Unit costs for treating adverse events

6. PFS HR for obinutuzumab+chlorambucil versus bendamustine

Roche conducted a systematic review for cost-effectiveness evidence relating to the decision problem. The searches identified one unique study which met the inclusion criteria (Walzer et al., 2013[6]). Although aligned with the marketing authorisation and relevant to the decision problem, this was a preliminary analysis conducted by Roche as part of the HTA submission.

Roche therefore developed a de novo economic model to answer the decision problem. Roche consider all treatments in the NICE Scope in their model, and their base case ICERs are:

- obinutuzumab+chlorambucil vs. rituximab + bendamustine £20,000 per QALY.
- obinutuzumab+chlorambucil vs. rituximab+chlorambucil £21,000 per QALY.
- obinutuzumab+chlorambucil vs. bendamustine £26,000 per QALY.
- obinutuzumab+chlorambucil vs. chlorambucil £24,000 per QALY.

1.3.1. Model checking

In order to check the wiring of Roche's cost-effectiveness model, we built a simplified model that is completely independent of their model. We feel confident that there are no major wiring errors in Roche's model because the results from our independent model are very similar to those of Roche's.

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 treatment with fludarabine. 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+chlorambucil and 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.

Superseded

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.

See Erratum

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 6 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). However, we understand that PFS data should be available from October 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 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.

Superseded

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

See Erratum

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 £7,000
- 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+chlorambucil arm 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.

Superseded

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.

See Erratum

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+chlorambucil from the CLL11 trial.

Roche cites NHS Reference Costs 2012/2013 and HRG codes as the source for the costs. However, we disagree with several of Roche's unit costs. Using our estimates of unit costs, all ICERs increase slightly:

- obinutuzumab+chlorambucil vs. rituximab + bendamustine increases from £20,000 to £21,000 per QALY.

- obinutuzumab+chlorambucil vs. rituximab+chlorambucil increases from £21,000 to £22,000 per QALY.

- obinutuzumab+chlorambucil vs. bendamustine increases from £26,000 to £27,000 per QALY.

- obinutuzumab+chlorambucil vs. chlorambucil increases from £24,000 to £25,000 per QALY.

This constitutes Item 5 of the PenTAG base case (**Table 45**, p156).

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.

Superseded

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.

See Erratum

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

patients are taking cycles 2 to 6 of obinutuzumab of 0.82, corresponding to PFS off treatment. Instead, we believe that the value of 0.67 should be used, corresponding to PFS on IV treatment. In this case, the ICER for:

- obinutuzumab+chlorambucil vs. rituximab + bendamustine increases from £20,000 to £23,000 per QALY.
- obinutuzumab+chlorambucil vs. rituximab+chlorambucil increases from £21,000 to £23,000 per QALY.
- obinutuzumab+chlorambucil vs. bendamustine increases from £26,000 to £28,000 per QALY.
- obinutuzumab+chlorambucil vs. chlorambucil increases from £24,000 to £25,000 per QALY.

This change constitutes Item 1 of the PenTAG base case (**Table 45**, p156).

Second, we note that Roche's utility of 0.82 corresponding to PFS when off treatment is higher than that of members of the UK general public at the appropriate age, which we estimate as 0.76. It is likely that the true value for the utility in PFS after treatment will be clearly lower than that of the general public at the same age given that patients have CLL and comorbidities. However, we know of no reliable data to give a more accurate figure. In the absence of such data, the utility of 0.76 should be seen as an upper bound. Using this value, the ICER for:

- obinutuzumab+chlorambucil vs. rituximab + bendamustine increases from £20,000 to >£23,000 per QALY.
- obinutuzumab+chlorambucil vs. rituximab+chlorambucil increases from £21,000 to >£24,000 per QALY.
- obinutuzumab+chlorambucil vs. bendamustine increases from £26,000 to >£30,000 per QALY.
- obinutuzumab+chlorambucil vs. chlorambucil increases from £24,000 to >£27,000 per QALY.

This change constitutes Item 2 of the PenTAG base case (**Table 45**, p156).

As a sensitivity analysis, we assume a disutility from that of the general UK public of 0.05 after treatment, in PFS, as patients have CLL and comorbidities. In this case, the utility in PFS off treatment is 0.71 and, the ICER for:

- obinutuzumab+chlorambucil vs. rituximab + bendamustine increases from £20,000 to £27,000 per QALY.
- obinutuzumab+chlorambucil vs. rituximab+chlorambucil increases from £21,000 to £27,000 per QALY.
- obinutuzumab+chlorambucil vs. bendamustine increases from £26,000 to £34,000 per QALY.
- obinutuzumab+chlorambucil vs. chlorambucil increases from £24,000 to £30,000 per QALY.

1.3.7. End of Life criteria

The End of Life criteria are not relevant to this appraisal, as life expectancy on comparator treatments are 5–6 years, far in excess of the maximum 2 years.

1.3.8. Roche model results

The obinutuzumab+chlorambucil arm accrues the most QALYs (4.03), with 2.18 in the progression free state and 1.85 in progressed disease (Table 1).

Chlorambucil has the least QALYs of all the arms, accruing 2.92 QALYs overall, with 0.77 QALYs in progression free and 2.15 QALYs in progressed disease (PD). Chlorambucil had the largest QALY gain in progressed disease and obinutuzumab the largest QALY gain in the progression free state.

Costs in PFS are split into drug cost, administration, supportive care and adverse events costs. The obinutuzumab arm has the largest costs in all these categories, totalling £30,577. As chlorambucil has the least time in PFS and the lowest drug acquisition costs, it has the lowest costs of all the arms in PFS £3,061. Costs in PD are primarily driven by time spent in PD and therefore the costs in PD are similar: £4,311in the obinutuzumab+chlorambucil arm to £4,959 in the chlorambucil arm.

When the obinutuzumab+chlorambucil arm is compared to all the other arms independently, Roche's base ICERs are all approximately between £20,000 and £30,000 per QALY gained. When the arms are compared simultaneously, only the obinutuzumab+chlorambucil , bendamustine only and chlorambucil only arms sit on the cost-effectiveness frontier.

Bendamustine has an ICER of £19,983 per QALY gained compared to chlorambucil, and obinutuzumab+chlorambucil has an ICER of £26,463 per QALY gained compared to bendamustine.

Table 1 Roche base case results

	ObClb	RBenda	RClb	Benda	Clb
Life years (undiscounted)[1]					
PFS	2.83	2.25	1.68	1.60	1.00
PD	3.86	4.00	4.15	4.18	4.25
Total	**6.68**	**6.24**	**5.82**	**5.77**	**5.24**
QALYs (discounted)					
PFS	2.18	1.70	1.28	1.23	0.77
PD	1.85	1.95	2.05	2.07	2.15
Total	**4.03**	**3.64**	**3.33**	**3.30**	**2.92**
Costs *(discounted)*					
Technology cost	£23,157	£15,241	£9,545	£4,745	£286
Administration cost	£3,736	£4,835	£3,314	£3,991	£1,320
Supportive care costs (PFS)	£1,140	£911	£693	£663	£420
Adverse events	£2,544	£1,694	£1,694	£1,362	£1,036
Cost in progressed disease	£4,311	£4,531	£4,756	£4,796	£4,959
Total	**£34,888**	**£27,213**	**£20,002**	**£15,557**	**£8,020**
ICERs					
ICER vs. ObClb with Clb	**-**	**£19,898**	**£21,275**	**£26,463**	**£24,256**
Simultaneous ICERs	£26,463	Extended dominated	Extended dominated	£19,983	-
Net health benefit at £20,000/QALY	2.28	2.28	2.33	2.52	2.52
Net health benefit at £30,000/QALY	2.87	2.74	2.66	2.78	2.65

Key: Benda = bendamustine; Clb = chlorambucil; ICER = incremental cost-effectiveness ratio; ObClb = obinutumab+chlorambucil; PD, progressive disease; PFS = progression free survival; QALY = quality-adjusted life year; RBenda = rituximab+bendamustine; RClb = rituximab+chlorambucil
Notes: Figures may not add up due to rounding. Extended dominated refers to arms where a more effective arm has a lower ICER (the cost/QALY is smaller).

Roche conducted one-way sensitivity analyses, including scenario analyses of the PFS distributions. The most important parameters were those that altered costs or QALYs in PFS between the arms (e.g., utility off treatment in PFS, PFS HRs), as this is where the benefits of obinutuzumab+chlorambucil are gained.

Roche also conducted a PSA, and at a willingness to pay threshold of £30,000 per QALY gained, obinutuzumab+chlorambucil had a probability of 63% of being the most cost-effective strategy.

1.4. Robustness of evidence submitted by Roche

1.4.1. Strengths

- Roche's analysis was clearly described in their report.

- The structure of Roche's model is appropriate and consistent with the natural history of CLL.

- We found no major wiring errors, although we did find one error of moderate importance.

- The clinical effectiveness evidence for obinutuzumab+chlorambucil , rituximab+chlorambucil and chlorambucil is of high quality, as it is taken from a large RCT.

- Roche have made good attempts to incorporate the clinical evidence for the remaining two treatments identified in the NICE Scope: bendamustine and bendamustine + rituximab.

1.4.2. Weaknesses & areas of uncertainty

There is substantial uncertainty in Roche's economic model.

- The results from the MaBLe trial of bendamustine+rituximab vs. rituximab+chlorambucil are not yet available. Therefore the clinical effectiveness and hence the cost-effectiveness of bendamustine + rituximab, is highly uncertain.

- The clinical effectiveness evidence from the CLL11 trial of obinutuzumab+chlorambucil , rituximab+chlorambucil and chlorambucil and from the trial of bendamustine vs. chlorambucil may be biased, as these trials were open label. In particular, progression free survival and the incidence of adverse events may be biased.

- The dose of chlorambucil given in CLL11 was far lower than used in routine UK clinical practice. This may bias the relative effectiveness of obinutuzumab+chlorambucil versus chlorambucil.

- OS for patients in the obinutuzumab+chlorambucil trial is very immature. Furthermore, post-progression survival for all treatments was taken from a different trial.

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.

Superseded

- 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

See Erratum

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, we understand that this information will become publicly available in October 2014.

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, as our clinical expert believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab+chlorambucil versus chlorambucil is over-estimated in CLL11. The ICER of obinutuzumab+chlorambucil versus chlorambucil of >£29,000 may therefore be an underestimate.

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, 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 versus bendamustine in favour of obinutuzumab+chlorambucil. The ICER of obinutuzumab+chlorambucil versus bendamustine of >£33,000 may therefore be an underestimate.

Superseded

See Erratum

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	(see p146)	23,000	23,000	28,000	25,000
2	Utility PFS off treatment decreased from 0.82 to 0.76	(see p146)	>23,000	>24,000	>30,000	>27,000
3	Mean dose of bendamustine and rituximab in bendamustine+rituximab arm	(see 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	(see p142)	26,000	n/c	n/c	n/c
5	Unit costs of adverse events	(see p 152)	21,000	22,000	27,000	25,000
6	PFS hazard ratio ObinClb vs. Benda from 0.40 to 0.55	(see p 93)	n/c	n/c	37,000	n/c
1+2			>25,000	>25,000	>31,000	>28,000
1+2+5			>26,000	>26,000	>33,000	>29,000
1+2+3+4			>44,000	>25,000	>31,000	>28,000
1+2+3+4+5+6	**PenTAG base case**		**>45,000[2]**	**>26,000[1]**	**>46,000[3]**	**>29,000[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

Superseded

See Erratum

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

Superseded
See Erratum

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 4and Table 5). As explained in section 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 (see p146)	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

Superseded

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 (see p146)	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

See Erratum

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+chlorambucil provide 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. Obinutuzumab+chlorambucil is poor value. Rituximab+chlorambucil offers slightly worse value.

For patients unsuited to bendamustine, we find a difference of opinion about whether chlorambucil or rituximab+chlorambucil is 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**, p 141). We repeat that rituximab+chlorambucil was assessed and not recommended in NICE TA174.[1]

Superseded

See Erratum

2. Background

2.1. Critique of manufacturer's description of underlying health problem

2.1.1. Natural History

Chronic lymphocytic leukemia (CLL) is an indolent disease with a long time course. Many CLL patients initially present with lymphocytosis only but no other symptoms. Advanced disease stages are characterized by the appearance of lymphadenopathy, hepato- or splenomegaly, and bone marrow failure. B-symptoms (i.e. fever, night sweats, and weight loss), general fatigue and recurrent infections are common in patients with late stage CLL but occasionally can be found earlier in the course of the disease (Source: Roche Protocol BO21004: RO5072759 Version J-F, Section 1.1.1.1, pp38).

2.1.2. Epidemiology

CLL is described in the submission as the most common form of adult leukaemia in Western Europe, accounting for 31%–37% of all leukaemias [10] with approximately 2–6 new cases in every 100,000 individuals per year. [11-13] In the UK, the average incidence rate is 8.9 in males and 5.1 in females per 100,000 population. (Table 6) [14] The incidence and prevalence of CLL is higher in the elderly (Table 6), with an estimated median age at first diagnosis reported at 71-72 years (Table 6),[13-15] and a median age of 75 at the time therapy is initiated [16] (Source: Roche Submission, Section 2.1, p22).

Table 6 Median age at diagnosis and incidence rate of CLL in the UK (per 100 000 population)

Group	15-59 Years	60-74 Years	75+ Years	Total
Incidence				
Male	2.8	31.7	52.9	8.9
Female	1.3	13.9	26.3	5.1
Total	2.0	22.3	36.0	6.9
Median age at diagnosis			**71.0**	

Source: HMRN 2014 CLL: Chronic Lymphocytic Leukaemia Source: Roche Submission, Section 2.1, Table A10, pp22)

However, other estimates exist. Based on ONS data, NICE suggest a rate of 3.9 per 100,000. [17] Smith et al indicated a rate of 5.9 per 100,000 for years 2004–2009 in the UK, coupled with a median age at diagnosis of 71 years. [18] This is in line with the median age at

diagnosis stated in the submission of between 71 and 72 years (Source: Roche Submission, Section 2, p22).

2.1.3. Prognosis

The prognosis for patients with CLL can vary widely and while some patients live for over 10 years with their disease, others may die within one to two years of diagnosis, due to the variability in the disease course [13] (Source: Roche Submission, Section 2.1, pp22).

For CLL patients, the median survival from diagnosis varies between 18 months and over 10 years. [13] In the UK, the median survival is 9.53 years (95% CI [8.20 to 10.18]), for all stages of CLL combined. [19] However, on average only 44% of male patients and 52% of female patients will live for 5 years or more after being diagnosed.[20] More specifically, the elderly patient population (median age ≥70 years) treated with chlorambucil in clinical trials had an overall survival of 4 years to 5 years. [21, 22] (Source: Roche Submission, Section 2.2, pp24).

As CLL is a disease that typically affects the elderly (>70 years of age), a high proportion of patients with CLL suffer from co-existing medical conditions. An analysis from the Mayo Clinic Database (from 1995 to 2006) revealed that nearly 90% of CLL patients had one or more comorbidities and 46% of patients had at least one major comorbidity [23] (Source: Roche Submission, Section 2.1, pp22). Medical conditions, such as cardiac or renal problems, have an impact on the prognosis of CLL and are associated with shorter survival. [4, 23] As a result, it is stated in the submission that these patients have limited treatment options as fludarabine, cyclophosphamide, and rituximab (FCR), the standard of care in fit CLL patients, is not well tolerated and often withheld from patients with comorbidities and age-related changes in organ function [16, 23] (Source: Roche Submission, Section 2.1, pp22). A recent study investigating the impact of comorbidity in patients with CLL found that in patients with two or more comorbidities CLL was the major cause of death, and that durable control of haematological disease is most critical to improve overall outcome in such patients. [4] In addition, a sustained remission for patients with CLL is associated with long-term health-related quality of life (HRQL) benefit [24, 25] (Roche Submission, Section 2.1, pp23).

There are two clinical staging systems currently in use for CLL allowing a rough division of patients into three prognostic groups: good, intermediate and poor prognosis (Source: Roche Protocol BO21004: RO5072759 Version J-F, pp38).

The Binet staging system[14, 26] (**Table 7**), where CLL is divided into three stages A, B and C,[27] is a tool frequently used in Europe to determine prognosis and appropriate therapy, whereas

the Rai system, where CLL is divided into 5 stages (0 to IV), is used more commonly in the United States.[28].

Table 7 Binet staging system

Stage	Organ enlargement*	Haemoglobin (g/dL)	Platelets ($\times 10^9$/L)
A	<3 areas	–	–
B	3.5 areas	≥10	≥100
C	Not considered	<10	≥10
Notes: *One area = lymph nodes >1cm in neck, axillae, groin or spleen, or liver enlargement.			

Binet stage A patients comprise almost two thirds of all patients with CLL and have 0 to 2 areas of node or organ enlargement with normal levels of haemoglobin and platelets. Patients with stage A disease generally survive for at least 10 years. Binet stage B patients (25-30%) have 3 to 5 areas of node or organ enlargement and an intermediate prognosis with a median survival of 5-7 years (Source: Roche Protocol B021004: R05072759 Version J-F, Section 1.1.1.1, p.38). Binet stage C patients (10-15%) have anaemia and/or thrombocytopenia, with or without lymphadenopathy or organomegaly, and a median survival of 2 years (Source: Roche Protocol BO21004: RO5072759 Version J-F, pp38).

2.1.4. Burden and quality of life

The impact of CLL on quality of life is not acknowledged in Roche's submission, although briefly mentioned in the background section of Roche's protocol as follows:

- B-symptoms (constitutional symptoms) (i.e. fever, night sweats, and weight loss)
- General fatigue and recurrent infections

(Source: Roche Protocol BO21004: RO5072759 Version J-F, Section 1.1.1.1, pp38).

It is notable that older patients with CLL are highly susceptible to infections, some of which can have serious consequences and are of particular relevance to the people concerned in this study. However, no information about the impact of infection on patient quality of life is given in the submission. Indeed, no data is provided in the submission relating to health-related quality of life (HRQL) assessments as assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQC30 and QLQ-CLL-16 module scoring manuals. (Roche Submission, Section 6.3.5, pp51).

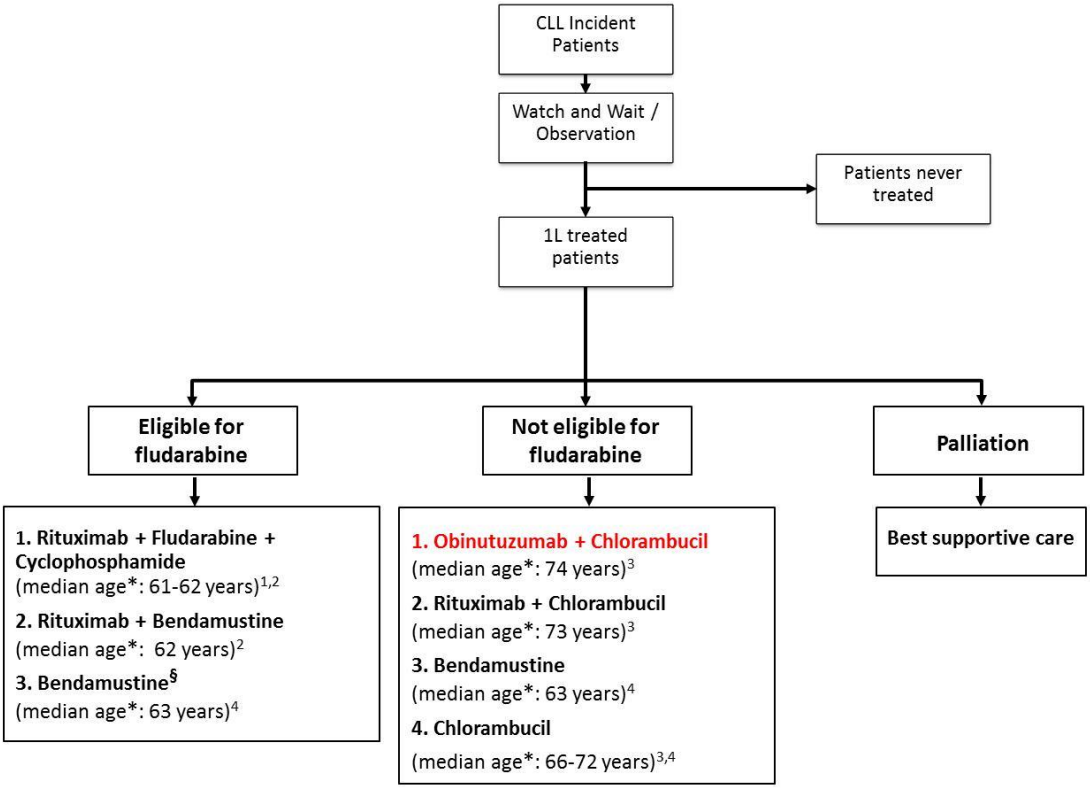
2.1.5. Rationale for obinutuzumab

In Section 2.5 (page 28) of the manufacturer's submission, the rationale for obinutuzumab in combination with chlorambucil is given to effectively treat the typical CLL patient. It is

stressed in the submission that treatment options are required that are effective yet tolerable for 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).

2.2. Critique of manufacturer's overview of current service provision

Figure 1 Roche's example of the place obinutuzumab could occupy in the clinical pathway in chronic lymphocytic leukaemia (Source: Roche Submission, Section 2.5, Figure A4, p.25)



Notes: Based on Roche internal forecasting assumptions, market research and clinical trials data; CLL8 and CLL10 trials1,2 , CLL11 trial3, and Knauf trial4 *Age in each parenthesis reflects the median age in the phase III study of the therapy. §Although the bendamustine licence is in patients for whom fludarabine combination chemotherapy is not appropriate the phase III trial population included patients who would have been considered eligible for fludarabine-based therapy.

Key: Abbreviations: CLL: Chronic Lymphocytic Leukaemia; 1L: First Line

Based on internal forecasting assumptions, market research and clinical trials data, Roche suggest that obinutuzumab+chlorambucil be placed first-line for previously untreated adult CLL patients who are not suitable for full-dose fludarabine-based therapy. Other first line treatment options include rituximab+chlorambucil, bendamustine and chlorambucil.

According to real world data from clinical practice in the UK, chlorambucil (+/- rituximab) occupies 36% of treatment share in first line treatment of CLL patients.

As there is no survival benefit associated with early intervention, [29-31] asymptomatic patients with early stage CLL (Binet stage A and B) are usually not treated but are followed on a "watch and wait" principle. Treatment is usually initiated when the patient becomes symptomatic or progresses to late stage CLL (Binet stage C). During disease evolution, 50% of CLL patients ultimately require therapy (Source: Roche Protocol BO21004: RO5072759 Version J-F, Section 1.1.1.2, pp38).

In the recent past, first-line treatment of CLL has developed from single-agent therapy with alkylating drugs (e.g. chlorambucil [Clb]) to modern combination therapy incorporating purine analogues (i.e. fludarabine, pentostatin, cladribine) and monoclonal antibodies (i.e. rituximab, alemtuzumab) [32-38] (Source: Roche Protocol BO21004: RO5072759 Version J-F, pp39). Currently, immunochemotherapy with fludarabine, cyclophosphamide and rituximab (FCR) is the standard of care in previously untreated patients with CLL requiring treatment (Source: Roche Protocol BO21004: RO5072759 Version J-F, Section 1.1.1.2, pp39). A large RCT has shown favourable outcome of FCR treatment for untreated patients with CLL (complete response rate of 52% and a median progression free survival of 43 months [39]), although favourable outcome of FCR treatment has not been assessed in patients with major co-morbidities, organ dysfunctions or low performance status [39] (Source: Roche Protocol BO21004: RO5072759 Version J-F, Section 1.2, pp39).

The majority of CLL patients are of advanced age. More than two thirds are 65 years old or more and almost 50% are older than 75 years.[40] Such elderly patients are frequently compromised by concurrent pathological conditions and/or physiological decline of organ function. Major co-morbidities are present in 46% of unselected patients with newly diagnosed CLL and advanced age.[23] Since elderly and medically unfit patients have been under-represented in clinical trials, it is unclear how these patients should be managed at best. (Source: Roche Protocol BO21004: RO5072759 Version J-F, Section 1.2, pp38).

Immunochemotherapy with FCR is often withheld from medically unfit patients because co-morbid conditions and age-related changes of the organ function may facilitate the occurrence and increase the severity of sustained cytopenia, T-cell depletion and opportunistic infections. CLL patients considered to be ineligible for fludarabine-based immunochemotherapy due to co-morbidity and/or other age-relate problems are frequently treated with chlorambucil (Source: Roche Protocol BO21004: RO5072759 Version J-F, Section 1.2, pp39). Although chlorambucil is generally well tolerated, complete responses

are rare and remission durations are usually shorter than 1.5 years.[36, 38, 41, 42] In medically unfit patients, trial data that convincingly demonstrate superiority of modern treatment approaches to chlorambucil are currently lacking (Source: Roche Protocol BO21004: RO5072759 Version J-F, Section 1.2, pp39).

With regard to the number of patients considered to be eligible for obinutuzumab, Roche's submission states that of 2,008 first line treated patients, less than or equal to 1,165 patients per year are obinutuzumab-eligible (Source: Roche Submission Section 2.2, Figure A3, pp23). These patients are defined in the submission as "fludarabine-ineligible 1L CLL patients" and Roche state that there is a significant need for effective new treatment options for patients with comorbidities who are typically unsuitable for fludarabine-based therapy, in order to improve their overall survival and health-related quality of life (HRQL) (Source: Roche Submission, Executive Summary, p.6).

NICE guidelines recommend bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.[43] Similarly, the Scottish Medicines Consortium (SMC) recommends bendamustine hydrochloride for first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.[44] The British Committee for Standards in Haematology Guidelines for CLL (BCSH) recommends that options for patients unfit for FCR include chlorambucil or bendamustine. [45] The National Comprehensive Cancer Network (NCCN) recommends obinutuzumab and chlorambucil for patients 70 years of age or younger with comorbidities.[46] The European Society for Medical Oncology (ESMO) note that in patients with relevant co-morbidity, chlorambucil seems to be the standard therapy[47] (Source: Roche Submission, Section 2.3, Table A11, pp24).

The example of the place Roche suggest obinutuzumab could occupy in the clinical pathway in chronic lymphocytic leukaemia is in accordance with these existing guidelines and recommendations (Source: Roche Submission, Section 2.4, Figure A3, pp25) and is in accordance with the population included in the obinutuzumab clinical trial CLL11.

In Roche's assessment of current clinical practice, the treatment pathway for patients with CLL is complex and depends on many factors such as age, performance status, and comorbidities. With almost 70% of patients >65 years of age at the time of diagnosis[48] elderly patients with comorbidities represent typical CLL patients. However, this population of CLL patients is significantly under-represented in clinical trials and subsequently is not optimally treated in clinical practice.[49] According to real world data from clinical practice in the UK, chlorambucil (±rituximab) occupies 36% of treatment share in first-line treatment of

all CLL patients. In contrast, this compares with only 14% for bendamustine (±rituximab). [50] Therefore, although there is no defined standard of care for patients with CLL who are ineligible for full-dose fludarabine-based treatment, Roche believe that it is clear that chlorambucil is the main therapeutic approach for these patients in UK practice. They go on to state that, in this context, no first line treatment for CLL has yet proved to be superior to chlorambucil in terms of overall survival (OS), in a typical, older patient population with coexisting conditions[22, 51] (Source: Roche Submission, Section 2.5, p26).

There is currently a lack of definitive criteria for determining which patients are 'unfit' for treatment with fludarabine combination therapy and, as a result, the group of patients currently treated with chlorambucil in the UK is heterogeneous with regard to performance status, age and co-morbidities. The decision about first-line treatment hence lies with physician and patient judgment.

The submission acknowledges the requirement of intravenous (i.v.) administration for obinutuzumab and rituximab, utilising more clinical time and costs than chlorambucil, which is an oral preparation. However, Roche state that no additional infrastructure is required (Source: Roche Submission, Section 2.10. pp28).

2.2.1. Current treatments for CLL

The main comparator identified by Roche is chlorambucil as CLL patients considered ineligible for fludarabine-based immunochemotherapy because of co-morbidity and/or other age-related problems, are most frequently treated with chlorambucil and sometimes with chlorambucil combined with rituximab (rituximab+chlorambucil), according to Roche. [50, 52, 53] Our clinical expert disagrees, and instead believes that the vast majority of patients unsuited to fludarabine are treated with rituximab+chlorambucil in the UK. Further differences of opinion come from commentators to this appraisal and clinicians at the Scoping Workshop. Rituximab in combination with chlorambucil has recently been added as a treatment for unfit CLL patients in the NCCN guidelines. [46] However, this treatment was assessed by, and not recommended by NICE in TA174. [1]

Bendamustine monotherapy has been recommended as a treatment option in patients with CLL for whom fludarabine combination chemotherapy is not appropriate due to lack of alternative treatment options. However, the patient population from the pivotal bendamustine trial is different from the typical patients with CLL seen in clinical practice. The randomised Phase III trial of Benda vs. Clb in previously untreated CLL patients included a much younger population than the typical CLL patient (median age 63 years in the Benda treatment arm) and excluded patients aged 75 years or older [54] Another limitation is the lack

of comorbidity burden assessment in the patient population enrolled. [55] The majority of patients within this trial were therefore of a younger, biologically fitter nature, who in routine practice would often be suitable for fludarabine-based treatment. In their submission, Roche recommend bendamustine to be reserved as clinical comparator in patients eligible for fludarabine-based therapy. However, this is outside the scope of their appraisal.

Bendamustine+rituximab is another comparator identified in the NICE Scope for this HTA

3. Definition of decision problem

3.1. Population

The population considered by the submission is described as follows:

“adult patients with previously untreated CLL for whom full-dose fludarabine based therapy is unsuitable”

This is an adequate description of the population under consideration, and concurs with that defined in the NICE scope [56]. Overall, we agree that the population considered is appropriate.

3.2. Intervention

The intervention is obinutuzumab (Gazyva) administered on a 28 day cycle basis for six cycles. On Days 1, 8, and 15 of cycle 1, and day 1 of cycles 2-6, 1,000mg is administered by intravenous infusion, with the first dose administered as a split infusion over day 1 (100 mg) and Day 2 (900 mg).

There is no definitive treatment pathway for the treatment of CLL. Regional and national guidelines offer information on the various treatment options available but are not prescriptive. The manufacturer has defined the proposed treatment pathway (UK) based on real world data (market research) and clinical trials. Obinutuzumab is being considered for patients who are not suitable for fludarabine-based combination therapy.

3.3. Comparators

The comparators in the Final Scope are as follows:

- Obinutuzumab+chlorambucil
- Chlorambucil
- Rituximab+chlorambucil
- Bendamustine
- Bendamustine+rituximab

The comparators in the submission are as in the Final Scope.

3.4. Outcomes

The outcomes in the Final Scope are as follows:

- Overall survival

- Progression-free survival
- Response rates
- Minimal residual disease negativity
- Adverse effects of treatment
- Health-related quality-of-life (HRQL)

Data was provided in Roche's submission for most of these outcome measures. Roche give most consideration to the primary outcome measure (PFS), and also report data for event-free survival, overall survival, end of treatment response, MRD status at end of treatment, best overall response, disease-free survival and time to new anti-leukaemia treatment. They state that for both disease free survival and HRQL, the number of patients was too small and no meaningful statistical comparison of the treatment arms could be made. We note that while Roche include some data for disease-free survival in their submission (Source: Roche Submission, Section 6.5.3, Table B20, pp71), there is an absence of any data for HRQL. This is notable considering HRQL was provided in the appendix of the primary CLL11 paper.[4]

There was one primary endpoint in the main RCT of obinutuzumab: progression free survival. 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. Although the primary efficacy endpoint is investigator-assessed PFS, PFS based on independent review committee (IRC) assessments was also analysed to support the primary analysis (Source: Roche Submission, Section 6.3.5, pp49).

Secondary endpoints in the RCT included event-free survival, disease-free survival, duration of response, time to re-treatment / new anti-leukaemic therapy, overall survival, end of treatment response, best overall response, best overall response within one year of study treatment, molecular remission, safety and patient reported outcomes/HRQL.

The outcomes are in line with those outlined in the final NICE scope[56] and are valid outcomes in oncology trials.[57] Progression-free survival is generally considered to be indicative of overall survival and as such is an appropriate indicator of clinical benefit. The validation of progression free survival by an independent review committee blinded to treatment assignment adds further credibility to the study results and mitigates, to some extent, the lack of blinding in the study.

Roche state in their submission that there is a significant need for effective new treatment options for CLL patients with comorbidities who are typically unsuitable for fludarabine-based therapy, in order to improve their overall survival and HRQL (Source: Roche Submission,

Executive Summary, pp.6). However, Roche go on to say in their submission that no meaningful conclusions regarding HRQL can be drawn from the CLL11 study as patient-reported quality of life was an outcome for which the number of patients was too small and no meaningful statistical comparison of the treatment arms could be made (Source: Roche Submission, Section 6.5.3, pp71).

4. Clinical effectiveness

4.1. Critique of the methods of review(s)

We validated the search strategy, and critically appraised the RCTs described in the manufacturer submission

4.1.1. Searches

The manufacturer provided detailed information on the search strategy. The database search strategies (as included in the manufacturer submission) are reproduced in Appendix 1 (p170). In summary, searches were carried out in the following databases:

MEDLINE (Embase.com);

EMBASE (Embase.com);

PubMed (www.ncbi.nlm.nih.gov);

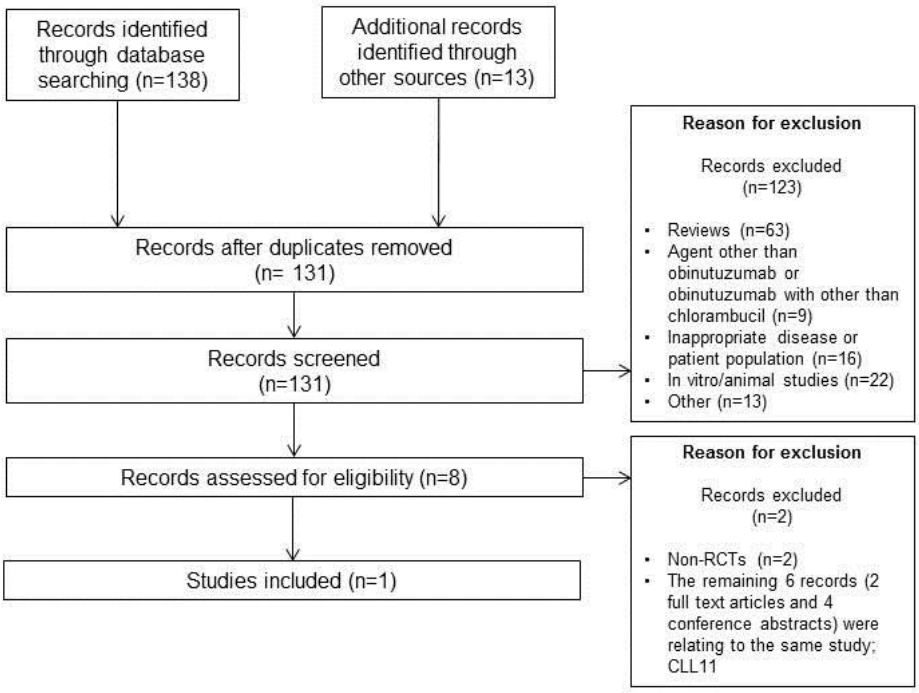
The Cochrane Library.

The websites of the American Society of Clinical Oncology (ASCO), the American Society of Haematology (ASH) and the European Haematology Association (EHA) were also searched for conference proceedings.

The searches were carried out in April 2014. The database searches combine free-text and MeSH terms for “chronic lymphocytic leukaemia” and “Obinutuzumab”. A variety of synonyms are used to ensure an appropriate balance of sensitivity and specificity. A suitable clinical trials filter is applied to the MEDLINE and EMBASE searches. All searches are date limited from 1992 to April 2014. The choice of databases is appropriate for the topic and the translation of search terms and syntax for each database is accurate.

The PRISMA flow diagram records that 138 clinical effectiveness studies were retrieved by the database searches (Source: Roche Submission, Section 6.2.2, pp36). There is a slight discrepancy between the PRISMA flow diagram and the database search strategies detailed in the appendix (Source: Roche Submission, Section 10.2.4, pp235-236), which record 139 clinical effectiveness studies. An additional 13 records were identified by searching websites for conference abstracts.

Figure 2 A flow diagram of the numbers of studies included and excluded at each stage



4.1.2. Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate

Eligibility criteria are described in **Table 8**.

Table 8 Eligibility criteria used in search strategy

Inclusion criteria	<u>Population</u> • Adult patients (≥18 years) <u>Interventions</u> • <u>Outcomes</u> Efficacy: Safety/Tolerability: <u>Study Design</u> • Prospective randomised controlled trials (RCTs)
Exclusion criteria	<u>Study Design</u> • Observational studies • Single case studies <u>Language restrictions</u> Non-English publications were excluded. However, English abstracts of foreign language publications were included

4.1.3. Critique of data extraction

The submission explains the processes used in study selection and data extraction which is in line with the standard review process. The screening of the literature was performed by one reviewer and inclusion and exclusion criteria were verified by a second reviewer. Any disputes were resolved by a third party. The following data extraction strategy was used:

Patient characteristics at baseline

Roche state that the treatment groups were generally comparable with respect to demographic characteristics (Table 9, p52) (Source: Roche submission, Section 6.3.4, Table B18, p47).

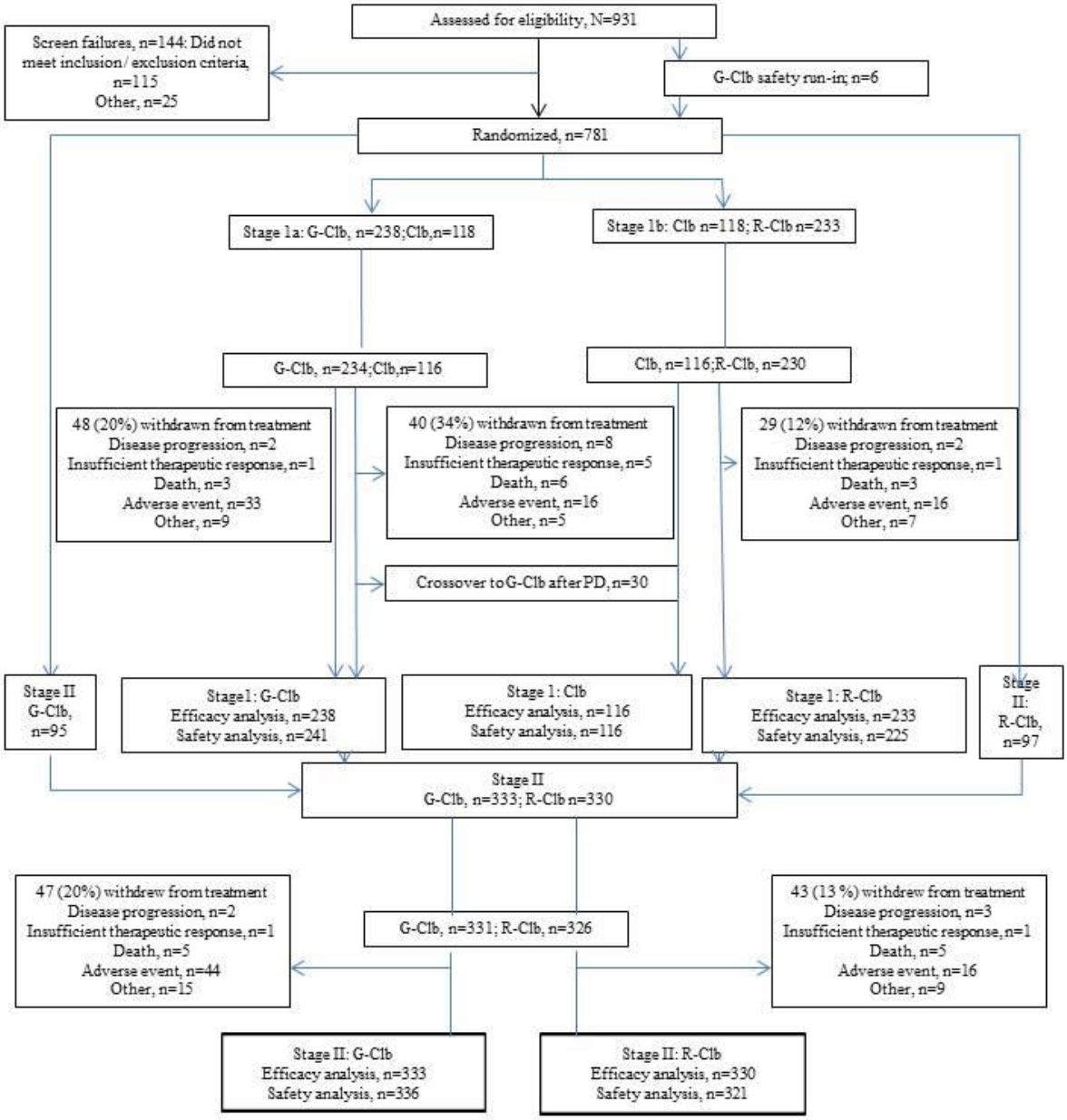
The median age in all treatment arms at stage 1a and stage 1b was >70 years, with ~80% of people in both arms aged more than 65 years (82% in the obinutuzumab+chlorambucil arm, 78% in the chlorambucil arm and 79% in the rituximab+chlorambucil arm). Roche state in their submission that the age of this recruited population is older than the ages of participants recruited in previous landmark CLL studies[36, 58-60] and typical of the general CLL population [61-63].The majority of people were categorised as either White (96% in the obinutuzumab+chlorambucil arm compared with 92% in the chlorambucil arm, and 95% in the rituximab+chlorambucil arm) or Asian (2% in the obinutuzumab+chlorambucil arm compared with 5% in the chlorambucil arm, and 3% in the rituximab+chlorambucil arm).

The patients had a CIRS score >7 at baseline. Most patients (82%) had more than three co-existing conditions, and nearly one third (27%) had at least one co-existing condition that was not well controlled at baseline according to CIRS grading.

Similarly, in the stage 2 treatment arms, the median age was >71 years, with ~80% of people in both arms aged more than 65 years (81% in the obinutuzumab+chlorambucil arm and 78% in the rituximab+chlorambucil arm). The majority of people were categorised as either White (95% in both arms) or Asian (2% in both arms).

There were two stages of recruitment to the CLL11 trial as detailed in the diagram below (**Figure 3**).

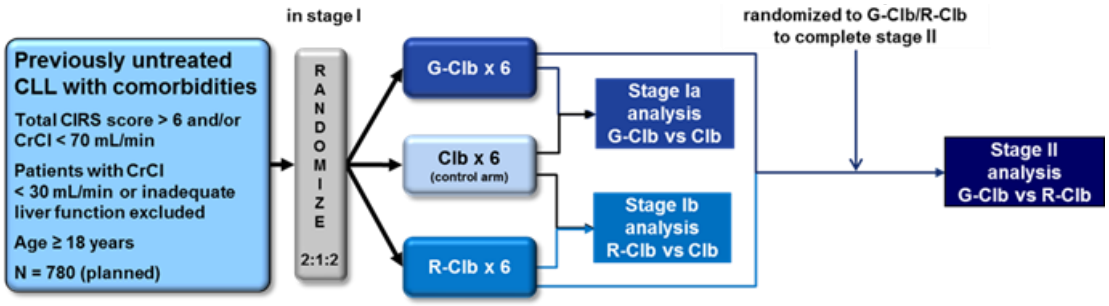
Figure 3 CLL11 study design and stages of recruitment



Key: G-Clb, obinutuzumab+chlorambucil ; R-Clb, rituximab+chlorambucil; Clb, chlorambucil; PD, progressive disease (Source: Adapted from Goede et al 2014, Appendix, Fig S1,p 14).

The study enrolled 781 patients; 589 patients were randomized in Stage 1 on a 2:1:2 (G-Clb :Clb:R-Clb) basis between the three treatment arms and an additional 192 patients in Stage 2 on 1:1 (GClb:RClb) basis between the two treatment arms (**Figure 4**).

Figure 4 Patient enrollment in CLL11 RCT. CIRS: Cumulative Illness Rating Scale; Clb: Chlorambucil; CrCl: Creatinine Clearance; G: Obinutuzumab; R: Rituximab



(Source: Roche Submission, Executive Summary, Figure 1, p 8)

Table 9Characteristics of participants in CLL11 across randomised groups (stage 1a, stage 1b, and stage 2)

	ObClb (n=238) stage 1a	Clb (n=118) stage 1a / 1b	RClb (n=233) stage 1b	ObClb (n=333) stage 2	RClb (n=330) stage 2
Age (yrs, median [Min–Max])	74.0 (39 - 88)	72.0 (43 - 87)	73.0 (40 - 90)	74.0 (39 - 89)	73.0 (40 90)
Male	140 (59%)	75 (64%)	149 (64%)	203 (61%)	204 (62%)
Race					
White	229 (96%)	108 (92%)	222 (95%)	317 (95%)	313 (95%)
Black	-	1 (<1%)	-	-	-
Asian	4 (2%)	6 (5%)	6 (3%)	6 (2%)	7 (2%)
American Indian or Alaska Native	-	1 (<1%)	-	-	-
Other	5 (2%)	2 (2%)	4 (2%)	10 (3%)	9 (3%)
Unknown	-	-	1 (<1%)	-	1 (<1%)
Ethnicity					
Hispanic	6 (12%)	3 (11%)	3 (8%)	15 (11%)	10 (8%)
Non-hispanic	46 (88%)	24 (89%)	37 (93%)	122 (89%)	117 (92%)
Binet stage at baseline					
A	55 (23%)	24 (20%)	49 (21%)	74 (22%)	74 (22%)
B	98 (41%)	50 (42%)	100 (43%)	142 (43%)	135 (41%)
C	85 (36%)	44 (37%)	84 (36%)	117 (35%)	121 (37%)
Total CIRS score at baseline					
Mean±SD	7.8 (±3.11)	7.9 (±3.30)	7.5 (±3.04)	8.0(±3.30)	7.7 (±2.99)
Calculated creatinine clearance [ml/min]					
Mean±SD	70.96 (±90.423)	68.96 (±26.874)	66.76 (25.590)	70.86 (±77.603)	66.73 (±25.727)
Comorbidities					
Vascular disorders	182 (76%)	91 (77%)	-	241 (72%)	243 (74%)

	ObClb (n=238) stage 1a	Clb (n=118) stage 1a / 1b	RClb (n=233) stage 1b	ObClb (n=333) stage 2	RClb (n=330) stage 2
Cardiac disorders	115 (48%)	57 (48%)	-	159 (48%)	149 (45%)
Gastrointestinal disorders	101 (42%)	54 (46%)	-	131 (39%)	121 (37%)
Metabolism and nutrition disorders	100 (42%)	49 (42%)	-	146 (44%)	122 (37%)
Renal and urinary disorders	92 (39%)	40 (34%)	-	119 (36%)	131 (40%)
Musculoskeletal and connective tissue disorders	79 (33%)	30 (25%)	-	112 (34%)	109 (33%)

Key: Benda = bendamustine; Clb = chlorambucil; ObClb = obinutuzmab+chlorambucil; RClb = rituximab+chlorambucil (Source: Roche Submission, Section 6.3.4, Table B18, pp47)

4.1.4. Quality assessment

Only one RCT (Goede et al 2014) was included. Details of the manufacturer's critical appraisal of Study CLL11, alongside our critique, can be seen below in **Table 10**. The critical appraisal was performed using the CRD assessment criteria for risk of bias in RCTs.

Table 10 Critical appraisal of Study CLL11

Critical appraisal criterion	Roche assessment	ERG comment
Study design	Open label RCT. However, an independent response review panel, blinded to treatment assignment, confirmed CLL diagnosis and Rai stage and determined response and date of disease progression for each patient (Source: Roche Submission, Section 10.4.1, Appendix 5, pp259-269)	This is an open-label study and therefore lacks blinding for both participants and investigators. This introduces the risk of bias for the primary outcome, progression-free survival. (PFS) However, outcomes were reviewed by an independent response review panel.(Source: Roche Submission, Section 10.4.1, Appendix 5, pp259-269) CL11 is a phase III, multicentre, open-label, randomised, three-arm study evaluating the efficacy and safety of obinutuzumab plus chlorambucil against rituximab plus chlorambucil or chlorambucil alone in previously untreated CLL patients with co-existing conditions (Source: Roche Submission, Section 6.2.4, pp37)
Were selection criteria adequately reported?	Yes – (Source: Roche Submission, Section 6.3.2, fig B6, pp41)	Yes, the study eligibility criteria are specified and match those outlined in the Final Scope. To be eligible patients were required to be adults with previously untreated CLL for whom fludarabine based immunochemotherapy is unsuitable because of co-morbidity and/or other age-related problems (Source: Roche Submission, Section 2.7, pp26)
Were participants included in the	Yes – Study CL11 compares obinutuzumab+chlorambucil with obinutuzumab + rituximab and with chlorambucil in	Roche state that The age of the recruited population is typical of the general CLL population (Source: Roche Submission, Section 6.3.4, pp45)

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. However, if, as our clinical expert

Superseded
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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)	believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab+chlorambucil vs. chlorambucil is over-estimated in CLL11.
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)

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See Erratum

Critical appraisal criterion	Roche assessment	ERG comment
		by investigator review. There is a chance that these results may be biased by additional unscheduled assessments and knowledge of treatment allocation (Roche Submission, Section 6.4.1, Table B19, pp62) However, the investigators' assessments of patients' responses were checked by an independent review committee (IRC); members of the IRC were blinded to treatment (Source: Roche Submission, Section 10.4.1, Appendix 5, pp259-269) which should reduce the risk for bias Similar results for PFS were found between investigators and reviewers.(Source: Roche Submission, Section 6.5.3, pp64-69)
Was follow-up adequate and was loss to follow-up reported or explained?	Yes – Follow-up and loss to follow-up was reported. (Source: Roche Submission, Section 6.3.8, Figs B7 – B9,pp58-60)	Follow up was performed at 28 days after their last dose of treatment. The next follow-up was 3 months after the end of treatment and then every 3 months until 3 years from last treatment. Further follow-ups occurred every 6 months and this will continue until 5 years from the date of randomization of the last patient entering the study. It is stated in the protocol that follow-ups will then occur annually for 8 years after the last patient enters the study (Source: Roche Protocol). The ERG group consider this adequate follow-up. Follow-up data for the primary outcome (progression free survival) were taken at 28 months and 45 months after the first patient was randomised (Source: Roche Submission, Section 6.5.3, Figs B11-B14, pp66-68). The ERG consider this adequate. It should be noted that median survival is two to seven years in the population of interest. Therefore, a longer follow up has been advocated for CLL, for example, a study reported in Oncology Times showed changes in overall survival rates after 6 years. Explanation is given for withdrawals. (Figs B7-B9, pp58-60). 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. (Source: Roche Submission, Section 6.10.1, pp123)
Were the statistical analyses used appropriate?	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 (Source: Roche Submission, Section 6.3.6, pp53) Adjustments for multiplicity were done using a three-arm closed-test procedure. The first test was for any difference	The approach to the statistical analysis of Study CLL11 is considered appropriate

Critical appraisal criterion	Roche assessment	ERG comment
	between the three treatment groups at an □□= 5 %. No adjustment for multiplicity was made for secondary endpoints; all were treated using a two-sided 5% alpha level. Time-to-event endpoints (e.g. EFS, DFS, DOR, time to re-treatment/new anti-leukaemic therapy and OS) were analysed in a manner similar to the primary analysis (Source: Roche Submission, Section 6.3.6, pp53-55).	
Were appropriate measures of variability reported?	Yes (Source: Roche Submission, Section 6.3.6 pp53-55).	95% CIs and/or P values are available for primary outcome (PFS) (Source, Roche Submission, Section 6.3.6, pp53) and secondary outcomes (Source, Roche Submission, Section 6.3.6, pp55).
Was an intention-to – treat analysis undertaken?	Yes – the ITT population was the primary analysis population for the primary endpoint, and consisted of all patients who were randomised. (Source: Roche Submission, Section 6.3.6, pp53.)	Yes, the analysis adopts 'intention to treat' principles. Safety analyses were conducted on people who received at least one dose of study medication (Source: Roche Submission, Section 6.4.1, Table B19, p62).
Were there any confounding factors that may attenuate the interpretation of the results of the study?	None reported.	Patients were randomised on study entry and the patient demographics and characteristics were generally well balanced in all arms and stages of the study. (Source: Roche Submission, Section 6.4.1, Table B19, p62) Reasons are given for patients who withdrew from the study (Source: Roche Submission, Section 6.3.8, Figs B7-B9, pp58-60). However, lack of blinding may have introduced some bias.
Did the study report data for relevant prognostic factors?	Yes – (Source: Roche Submission, Section 6.3.7 pp48-57)	Pre-planned subgroup analysis for independent review of PFS was performed for the following: age group, race, Binet stage at baseline, total CIRS score at baseline, calculated creatine clearance, beta-2-microglobulin, IVGH mutational status, hierarchical model at baseline, time from diagnosis to randomisation, FCyRlla, FCyRllla, circulating count at baseline (Source: Roche Submission, Section 6.3.7, pp57) The submission states that prognostic factors were assessed in an exploratory analysis using logistic regression (Source: Roche, Submission, Section 6.3.6, pp55)

We note that some discrepancy between Goede et al's paper and the submission exists in relation to the description of the number of countries and number of centres involved in the trial. Goede et al describe the trial as "conducted in 26 countries; 189 centres enrolled

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]

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.

Superseded

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.

See Erratum

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+chlorambucil versus 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)

Study CLL11, Statistical Analysis: Secondary endpoints

No adjustment for multiplicity was made for secondary endpoints: all were tested using a two-sided 5% alpha level. Time-to-event endpoints were analysed in a manner similar to the primary analysis. Best overall response rates and end of treatment response rates in the treatment groups were compared using a chi-square test with continuity correction. In addition, 95% confidence limits for the difference using the Anderson-Hauck approach were calculated. Response rates and 95% confidence limits according to Pearson-Clopper are provided for each treatment group. The proportion of responders and the corresponding 95% CI for each of the response categories by treatment group is presented. The effect of prognostic factors is assessed in an exploratory analysis using logistic regression (Source: Roche Submission, Section 6.3.6, p55).

4.1.7. Study CLL11, Statistical Analysis: Sample size and power calculation

The primary endpoint of investigator assessed PFS was used to determine the sample size for the study. For stage 1a, to detect an HR of 0.44 for PFS between obinutuzumab+chlorambucil and chlorambucil, approximately 105 events were required to achieve 80% power at a two-sided significance level of 0.5%. For stage 1b, to detect an HR of 0.6 for PFS between rituximab+chlorambucil and chlorambucil (20 months vs 12 months) approximately 145 events were required to achieve 80% power at a two-sided significance level of 0.5%. For stage 1 globally, to detect a PFS difference between obinutuzumab+chlorambucil versus rituximab+chlorambucil versus chlorambucil approximately 175 events were required to achieve 80% power at a two-sided significance level of 0.5%. Finally, for stage 2, to detect an HR of 0.74 for PFS between obinutuzumab+chlorambucil and rituximab+chlorambucil, approximately 406 events were required to achieve 80% power at a two-sided significance level of 0.5%. (Source: Roche Submission, Section 6.3.6, p55)

The approach to the statistical analysis of CLL11 was generally sound and the sample size for PFS appears correct. With regard to missing data, for patients without disease progression or death, PFS will be censored at the date of the last response assessment, or if no response assessments were performed after the baseline visit, at the time of randomisation plus one day. If the specified event for EFS (i.e., disease progression/relapse, death, start of a new anti-leukaemic treatment) does not occur, patients were censored at the date of last response assessment. In case no response assessment is available patients were conservatively censored at the date of randomisation plus one day. Patients with no documented progression after CR/CRi were censored at the last date at which they are known to have been in CR/CRi in the analysis of DFS. Patients with no documented

progression after CR/CRi or PR were censored at the last date at which they are known to have had the CR/CRi or PR in the analysis of DOR. Patients who were reported as not having started re-treatment or new anti-leukaemic therapy were censored at the last visit date they were assessed with regard to start of new treatment or the date of death in the analysis of time to re-treatment-new leukaemic therapy. For patients who were still alive, OS was censored at the date when they were last known to be alive. Patients without post-baseline tumour assessment up to 6 months after last administration of last component of study drug (for whatever reason) were considered non-responders in the analysis of best overall response rates within 1 year from start of treatment.

Patients with no end of treatment response assessment (for whatever reason) were considered non-responders in the analysis of end of treatment response rates. Patients with no response assessment (for whatever reason) were considered non-responders in the analysis of end of best overall response rates.

4.2. Summary statement

The submission contains all the relevant studies and, with the exception of HRQL, the relevant data within those studies. The submitted evidence also adequately reflects the decision problem defined in the submission.

4.3. Summary of results

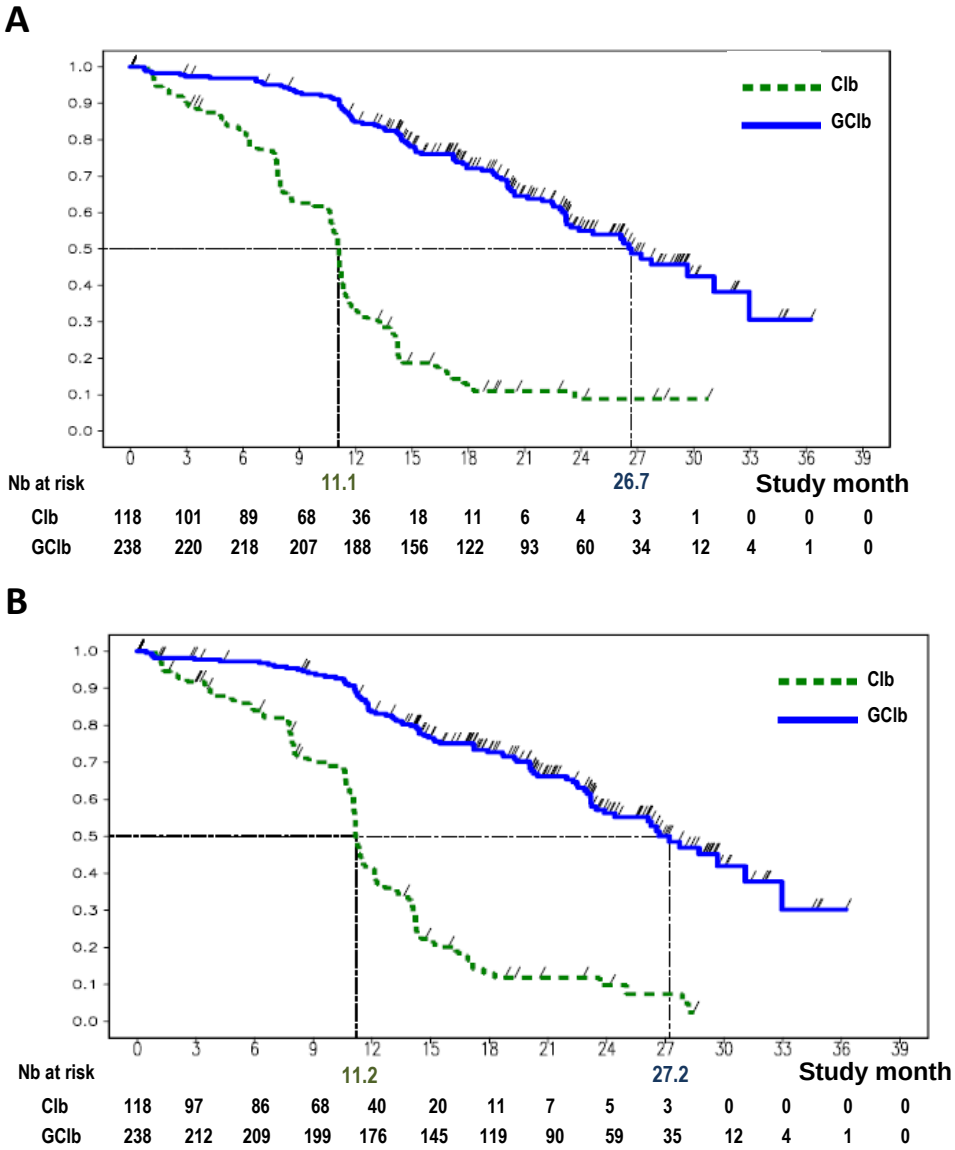
4.3.1. Primary endpoint results

There was one primary endpoint, investigator-assessed progression free survival (PFS).

Progression free survival

Figure 5 shows PFS. At the time of final stage 1a analysis, the addition of obinutuzumab (G) to chlorambucil (Clb) resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of investigator-assessed PFS (stratified HR 0.18 [95% CI: 0.13-0.24]). The Kaplan-Meier estimated median PFS was 11.1 months in the chlorambucil arm and 26.7 months in the obinutuzumab+chlorambucil arm ($p<0.001$). Similar results were found based on the IRC data with an estimated median PFS of 11.2 months in the chlorambucil arm and 27.2 months in the obinutuzumab+chlorambucil arm ($p<0.001$).

Figure 5 Kaplan-Meier plot of PFS for obinutuzumab+chlorambucil vs. chlorambucil (as assessed by the investigator [A] and IRC assessment [B], May 2013 data cut-off) - Stage 1a (ITT) (Source: Roche Submission, Section 6.5.3, Figure B10, p65)

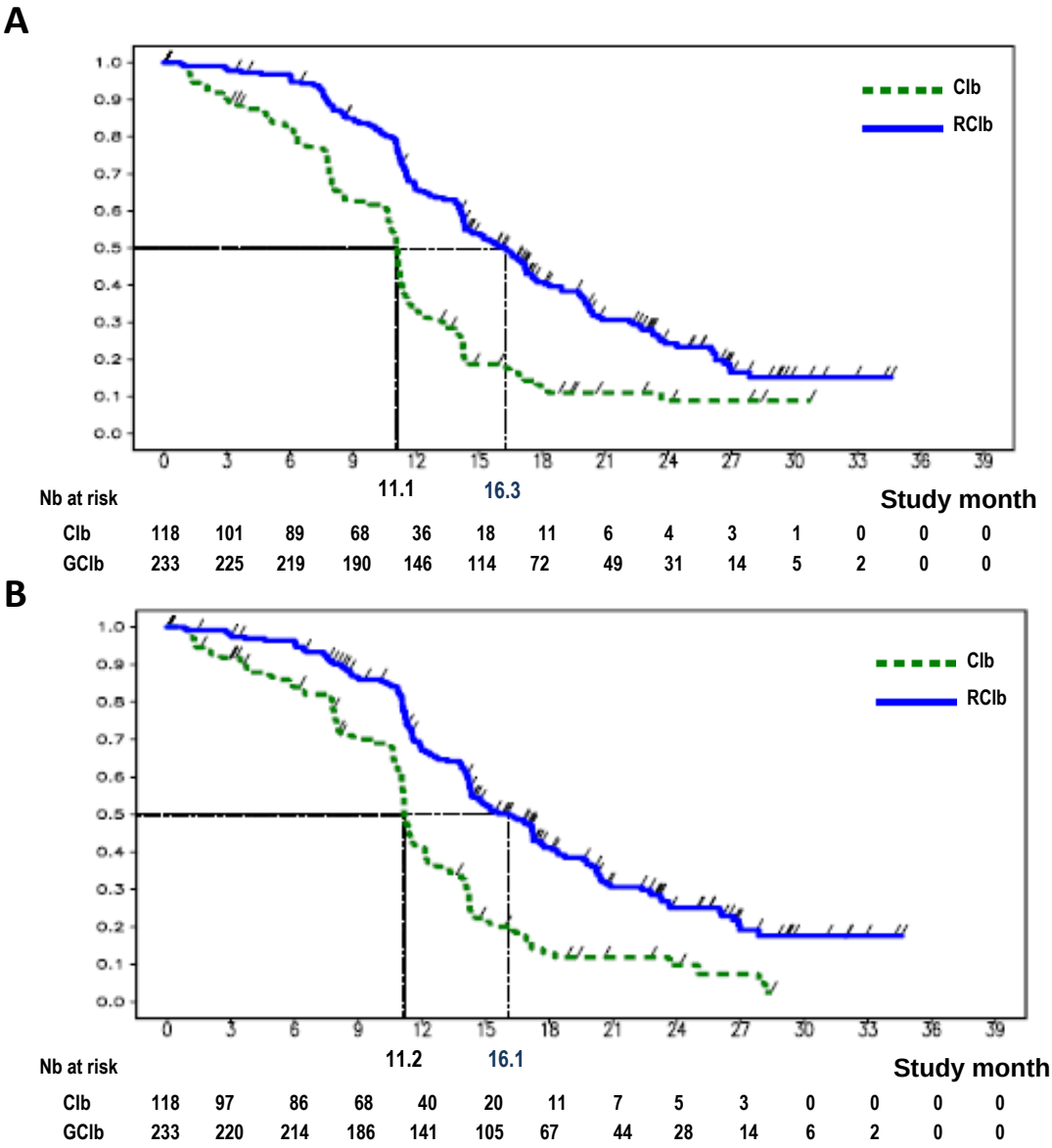


Key: Clb: chlorambucil; RClb: rituximab+chlorambucil; IRC: Independent Review Committee; PFS: Progression Free Survival

In stage 1b, the addition of rituximab to chlorambucil (RClb) also resulted in clinically meaningful and statistically significant improvement in the primary endpoint of investigator-assessed PFS (stratified HR 0.44, 95% CI(0.34-0.57)). The Kaplan-Meier estimated median PFS was 11.1 months in chlorambucil arm and 16.3 months in rituximab+chlorambucil arm (p<0.001). Similar results were found based on the IRC data with an estimated median PFS

of 11.2 months in the chlorambucil arm and 16.1 months in the rituximab+chlorambucil arm (p<0.001) (**Figure 6**).

Figure 6 Kaplan-Meier plot of PFS for rituximab+chlorambucil vs. chlorambucil (as assessed by the investigator [A} and IRC assessment [B], May 2013 data cut-off)- Stage 1b (ITT) (Source: Roche Submission, Section 6.5.3, Figure B11,pp66)



Key: Clb: chlorambucil; RClb: rituximab+chlorambucil; IRC: Independent Review Committee; PFS: Progression Free Survival

Recent commercial in confidence data from the latest cut-off (03 March 2014), show

[redacted]

[redacted]

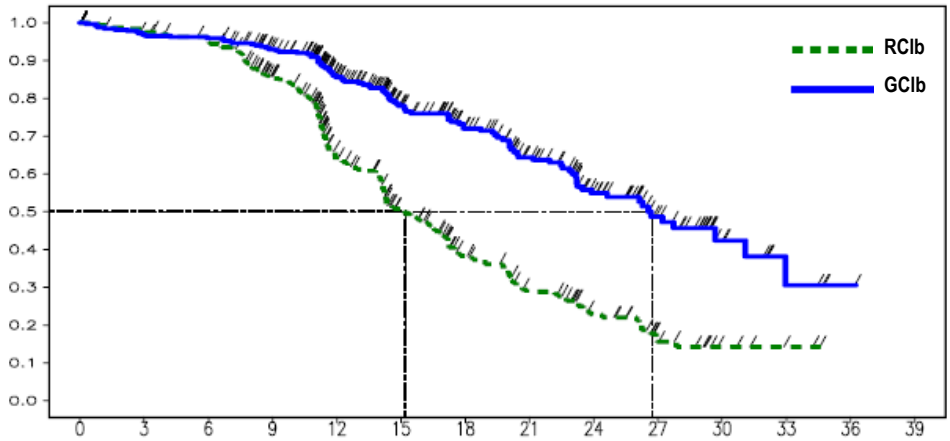
[redacted]

[redacted]

In the May 2013 data cut-off, in stage 2, addition of obinutuzumab to chlorambucil (GClb) 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+chlorambucil arm and 26.7 months in obinutuzumab+chlorambucil arm (p<0.001). Similar results were found based on the IRC data with an estimated median PFS of 14.9 months in the rituximab+chlorambucil arm and 26.7 months in the obinutuzumab+chlorambucil arm (p<0.001) (**Figure 6**).

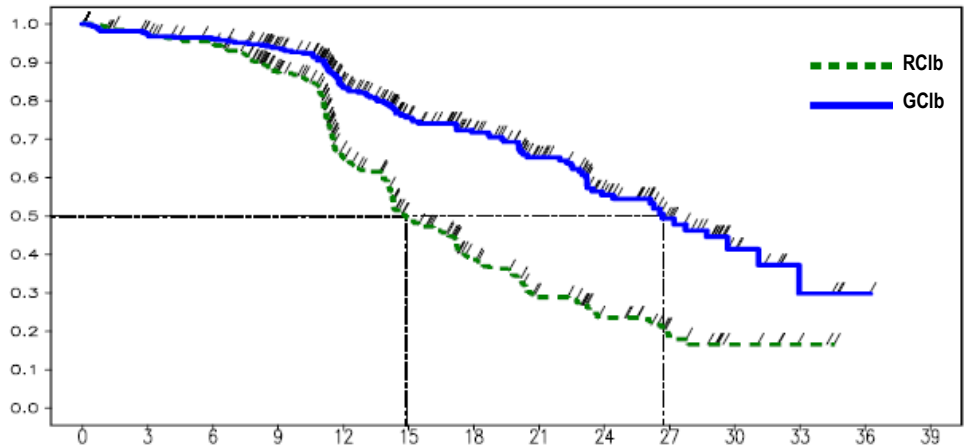
Figure 10 Kaplan-Meier plot of PFS for obinutuzumab+chlorambucil vs. rituximab+chlorambucil(as assessed by the investigator [A] and IRC assessment [B].May 2013 data cut-off) – Stage 2 (ITT) (Source: Roche Submission, Section 6.5.3, Figure B14, pp68)

A



Nb at risk														
RClb	330	317	309	259	163	114	72	49	31	14	5	2	0	0
GClb	333	307	302	278	213	156	122	93	60	34	12	4	1	0

B



Nb at risk														
RClb	330	310	302	251	157	105	67	44	28	14	6	2	0	0
GClb	333	298	290	268	200	145	119	90	59	35	12	4	1	0

Key: RClb : rituximab+chlorambucil; GClb: obinutuzumab+chlorambucil ; IRC: Independent Review Committee; PFS: Progression Free Survival

Recent commercial in confidence data from the latest cut-off (03 March 2014), show

[redacted]

[redacted]]).The Kaplan-Meier estimated median PFS was [redacted] months in

rituximab+chlorambucil arm and [redacted] months in obinutuzumab+chlorambucil arm (Error! Reference source not found.). The median observation time was [redacted] months for obinutuzumab+chlorambucil and [redacted] months for rituximab+chlorambucil.

[redacted]

Overall, the results of the subgroup analyses of investigator-assessed PFS were consistent with the results seen in the overall ITT population for all three stages. In all subgroups the point estimates for the PFS hazard ratios were below 1 favouring obinutuzumab+chlorambucil over chlorambucil alone (stage 1a), rituximab+chlorambucil over chlorambucil alone (stage 1b), and obinutuzumab+chlorambucil over rituximab+chlorambucil (stage 2) (**Figure 12, Figure 13, Figure 14**). The same was true for the subgroup analysis based on IRC assessments of PFS (Roche Submission, Section 6.5.3, pp69).

In stage 1a only, for some subgroups the upper limit of the 95% confidence interval was above 1 (race “other”, cytogenetics 17p deletion and other abnormalities, FCγIIa 131RR and FCγIIIa 158VV). However, it is of note that in some of these subgroups the number of patients is low, and the study was not powered to show significance within subgroups, therefore the subgroup results should be interpreted with caution. (Roche Submission, Section 6.5.3, pp69)

Figure 12 Forest plot for PFS by subgroup: obinutuzumab+chlorambucil vs chlorambucil (ITT) – Stage 1a (ITT) (Source: Roche Submission, Section 6.5.3, Figure B16, p.70)

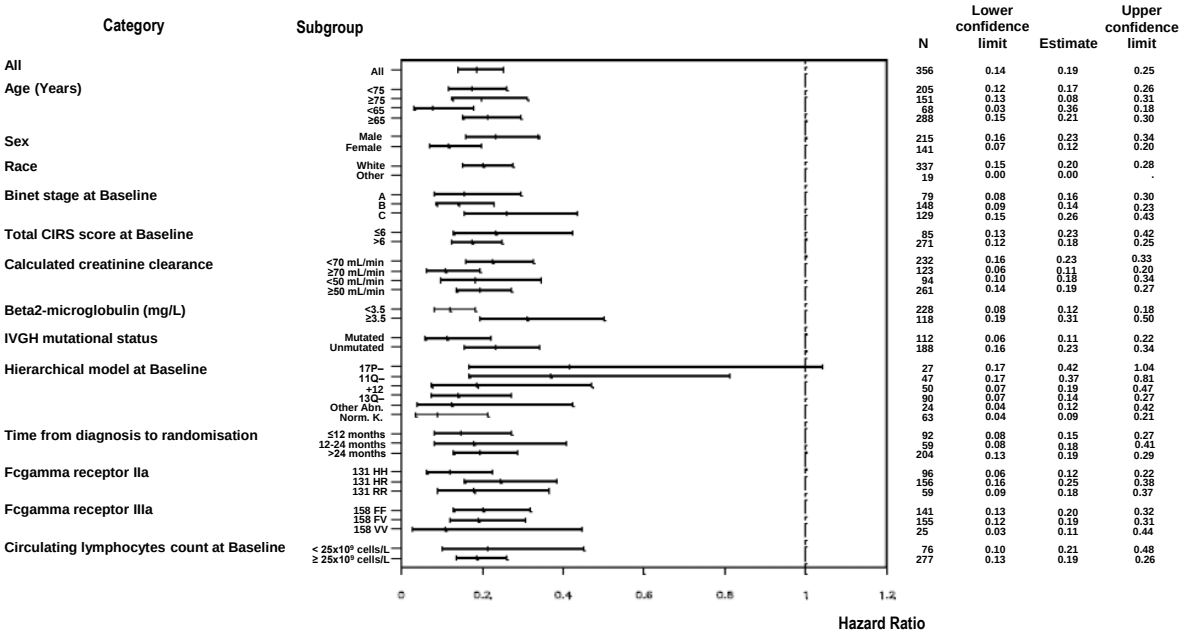


Figure 13 Forest plot for PFS by subgroup: rituximab+chlorambucil vs chlorambucil (ITT) – Stage 1b (ITT) (Source: Roche Submission, Section 6.5.3, Figure B17, p.70)

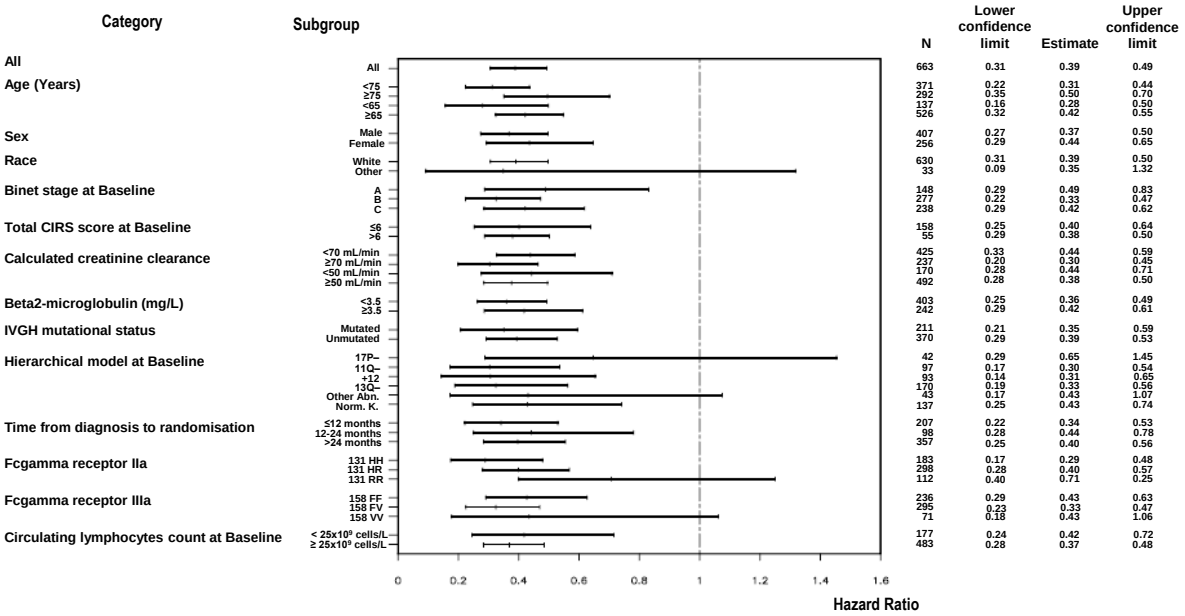
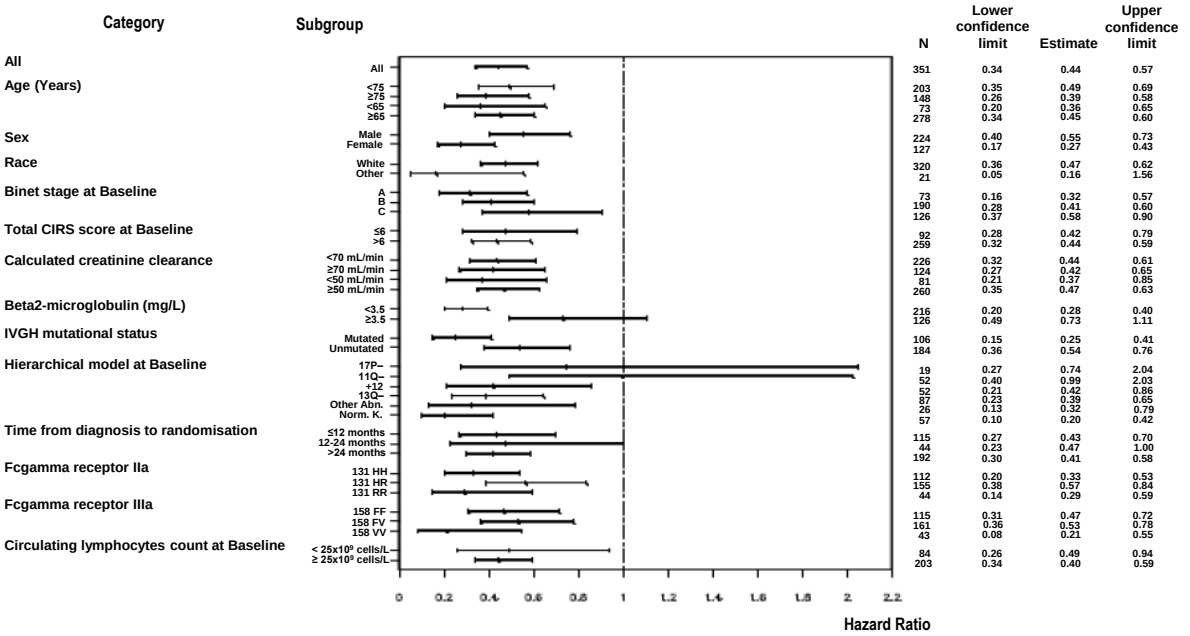


Figure 14 Forest plot for PFS by subgroup: obinutuzumab+chlorambucil vs rituximab+chlorambucil(ITT) – Stage 2 (ITT) (Source: Roche Submission, Section 6.5.3, FigureB18, p.71)



4.3.2. Secondary endpoints

Under a nominal significance level α = 0.05 (two-sided), significant improvements were observed in most of the secondary efficacy endpoints, apart from OS for which the data are immature (Table 11, Table 12). However for stage 1a, OS for obinutuzumab+chlorambucil vs chlorambucil was significant (p=0.0022). Disease-free survival and HRQL were outcomes for which the number of patients was too small and no meaningful statistical comparison of the treatment arms could be made.

Table 11 Secondary efficacy endpoints results for CLL11 (stage 1a, stage 1b, May 2013 data cut-off) and comparisons vs. obinutuzumab+chlorambucil

	Clb n = 118	**GClb n = 238**	**RClb n = 233**
Event–free survival			
Patients with event	96 (81.4 %)	93 (39.1 %)	169 (72.5 %)
Patients without event**	22 (18.6 %)	145 (60.9 %)	64 (27.5 %)
Median time to event (months)	11.1	26.7	15.4
P-value	-	**p<0.0001**	**p<0.0001**
Hazard ratio (stratified[##]) 95%CI	-	0.18 [0.13 – 0.24]	0.44 [0.34 - 0.57]
Hazard ratio (unstratified) 95%CI	-	0.19 [0.14 – 0.25]	0.44 [0.34 - 0.57]
Overall survival			
Patients with event	24 (20.3 %)	22 (9.2 %)	34 (14.6 %)
Patients without event**	94 (79.7 %)	216 (90.8 %)	199 (85.4 %)

	Clb n = 118	GClb n = 238	RClb n = 233
P-value	-	**p=0.0022**	**p=0.1129**
Hazard ratio (stratified[##]) 95%CI	-	0.41 [0.23 - 0.74]	0.66 [0.39 - 1.11]
End of treatment response			
Responders	37 (31.4 %)	184 (77.3 %)	153 (65.7 %)
Difference in response rates 95%CI	-	45.95 [35.6 - 56.3]	34.31 [23.5 - 45.1]
P-value	-	**p<0.0001**	**p<0.0001**
Complete response (CR)	0 (0.0 %)	53 (22.3 %)	17 (7.3 %)
Partial response (PR)	37 (31.4 %)	131 (55.0 %)	136 (58.4 %)
Stable disease(SD)	27 (22.9 %)	12 (5.0 %)	32 (13.7 %)
Progressive disease (PD)	32 (27.1 %)	8 (3.4 %)	28 (12.0 %)
Missing (No Response Assessment)	22 (18.6 %)	34 (14.3 %)	20 (8.6 %)
MRD status at end of treatment (blood and bone marrow combined)			
Patients included in analysis	90 (100.0 %)	168 (100.0 %)	169 (100.0 %)
MRD negative	0 (0.0 %)	45 (26.8 %)	4 (2.4 %)
MRD positive^	90 (100.0 %)	123 (73.2 %)	165 (97.6 %)
Difference in MRD rates, 95%CI	-	26.79 [19.5 - 34.1]	2.37 [-0.5 - 5.2]
Best overall response			
Responders[$]	39 (33.1 %)	186 (78.2 %)	154 (66.1 %)
Non-responders	79 (66.9 %)	52 (21.8 %)	79 (33.9 %)
Difference in response rates, 95%CI	-	45.10 [34.7 - 55.5]	33.04 [22.1 - 43.9]
P-value	-	**p<0.0001**	**p<0.0001**
Disease–free survival			
Patients with event	2 (100.0 %)	12 (16.4 %)	9 (32.1 %)
Patients without event**	0 (0.0 %)	61 (83.6 %)	19 (67.9 %)
Median time to event (months)	1.5 [0.1 - 3.0]	22.9 [18.4;.]	18.4 [15.0 - .]
P-value	-	**p<0.0001**	**p=0.0002**
Hazard ratio (stratified##) 95%CI	-	NR	0.03 [0.00 - 0.39]
P-value	-	p=0.9996	p=0.0068
Time to new anti-leukaemia treatment			
Patients with new treatment	65 (55.1%)	51 (21.4%)	72 (30.9%)
Hazard ratio (stratified) 95%CI	-	0.24 [0.16 - 0.35]	0.34 [0.24 - 0.48]
P-value	-	p<0.0001	NR

Key: Clb: chlorambucil; GClb: obinutuzumab+chlorambucil ; RClb: rituximab+chlorambucil## including censored observations. **Notes:** ** Stratified by Binet stage at baseline, ^ Bone marrow aspirate at EoT response supposed to be taken only for CR/CRi patients. MRD negativity is defined as a result below 0.0001, $ Follow up month 3 visit not reached by the cut- off date; patients are not included in the analysis (Source: Roche Submission, Section 6.5.3, Table B20, pp71)

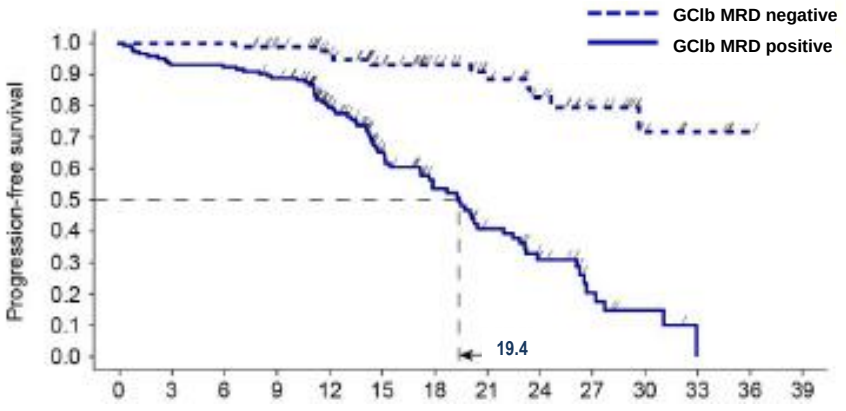
Table 12 Secondary efficacy endpoints results for CLL11 (stage 2, May 2013 data cut-off)

	RClb n = 330	GClb n = 333
Event –free survival		
Patients with event	208 (63.0 %)	118 (35.4 %)
Patients without event**	122 (37.0 %)	215 (64.6 %)
Median time to Event (months)	14.3	26.1
P-value		**p<0.0001**
Hazard ratio (stratified[##]) 95%CI	-	0.42 [0.33 – 0.54]
Hazard ratio (unstratified) 95%CI	-	0.42 [0.33 – 0.54]
Overall survival		
Patients with event	41 (12.4 %)	28 (8.4 %)
Patients without event**	289 (87.6 %)	305 (91.6 %)
P-value	-	**p=0.0849**
Hazard ratio (stratified[##]) 95%CI	-	0.66 [0.41 - 1.06]
End of treatment response		
Responders	214 (65.0 %)	261 (78.4 %)
Difference in response rates 95%CI	-	13.33 [6.4 - 20.3]
P-value	-	**p<0.0001**
Complete response (CR)	23 (7.0 %)	69 (20.7 %)
Partial response (PR)	191 (58.1 %)	192 (57.7 %)
Stable disease(SD)	50 (15.2 %)	17 (5.1 %)
Progressive disease (PD)	35 (10.6 %)	12 (3.6 %)
Missing (no response assessment)	30 (9.1 %)	43 (12.9 %)
MRD status at end of treatment		
Total (blood and bone marrow combined)		
Patients included in analysis	244 (100.0 %)	239 (100.0 %)
MRD negative	6 (2.5 %)	61 (25.5 %)
MRD positive^	238 (97.5 %)	178 (74.5 %)
Difference in MRD rates, 95%CI	-	23.06 [17.0 - 29.1]
Patients with CR		
n	**23**	**69**
with MRD marrow sample, n	14	39
MRD-negative / patients with CR, n (%)	2/23 (9%)	14/69 (20%)
MRD-negative / patients with MRD result, n (%)	2/14 (14%)	14/39 (36%)
with MRD blood sample, n	17	48
MRD-negative / patients with CR, n (%)	4/23 (17%)	26/69 (38%)
MRD-negative / patients with MRD result, n (%)	4/17 (24%)	26/48 (54%)
Patients with PR		
n	**191**	**192**

	RClb n = 330	GClb n = 333
with MRD blood sample, n	146	151
MRD-negative / patients with PR, n (%)	3/191 (2%)	59/192 (31%)
MRD-negative / patients with MRD result, n (%)	3/146 (2%)	59/151 (39%)
Best overall response		
Responders[$]	218 (66.3 %)	265 (79.6 %)
Non-Responders	111 (33.7 %)	68 (20.4 %)
Difference in Response Rates, 95%CI	-	13.32 [6.5; 20.2]
P-value	-	**P=0.0001**
Disease–free survival		
Patients with event	9 (26.5 %)	12 (12.8 %)
Patients without event**	25 (73.5 %)	82 (87.2 %)
Median time to event (months)	18.4 [15.0 - .]	22.9 [18.4 - .]
P-value	-	**P=0.0475**
Hazard ratio (stratified[##]) 95%CI	-	0.42 [0.17 – 1.02]
P-value	-	**P=0.541**
Time to new anti-leukaemia treatment		
Patients with new treatment	86 (26.1%)	55 (16.5%)
Hazard ratio (stratified) 95%CI	-	0.59 [0.42 - 0.82]
P-value	-	**P=0.0018**

Key: GClb: obinutuzumab+chlorambucil ; RClb: rituximab+chlorambucil [##] including censored observations, ** **Notes**: Stratified by Binet stage at baseline, ^ Bone marrow aspirate at EoT response supposed to be taken only for CR/CRi patients. MRD negativity is defined as a result below 0.0001, [$] Follow up month 3 visit not reached by the cut-off date; patients are not included in the analysis (Source: Roche Submission, Section 6.5.3, Table B21, pp72-73)

Figure 15 PFS by minimum residual disease (MRD) status in patients treated with obinutuzumab+chlorambucil (Stage 2) (Source: Roche Submission, Section 6.5.3, Figure B19, pp74)



Nb at risk														
GClb MRD negative	87	87	87	80	68	57	45	37	28	19	8	4	1	0
GClb MRD positive	144	134	133	127	89	54	38	26	16	7	3	0	0	0

Key: GClb : obinutuzumab+chlorambucil ; MRD: Minimal Residual Disease:

In stage 2, among all patients for whom a result for minimal residual disease was available for those who had progressive disease or who died, the rate of minimal residual disease negativity in bone marrow and peripheral blood was significantly higher after obinutuzumab+chlorambucil treatment than after rituximab+chlorambucil treatment (bone marrow, 19.5% vs 2.6%; blood, 37.7% vs. 3.3%, respectively). Negative testing for minimal residual disease in blood after obinutuzumab+chlorambucil treatment was associated with a favourable disease course during follow-up (

Figure 15).

Recent commercial in confidence data from the latest cut-off (03 March 2014) show [redacted] when compared to the May 2013 analysis. Roche state that the Stage 1a and 1b comparison can be considered [redacted]

Table 13 Overall survival results for CLL11 (stage 1a.stage 1b and stage 2, March 2014 data cut-off) (Source: Roche Submission, Section 6.5.3, Table B22, pp74

Overall survival		
Stage 1a	**Clb** **n = 118**	**GClb** **n = 238**
Patients with event (death)	[redacted]	[redacted]
P-value	[redacted]	[redacted]
Hazard Ratio 95%CI	[redacted]	[redacted]
Stage 1b	[redacted]	[redacted]
Patients with event (death)	[redacted]	[redacted]
P-value	[redacted]	[redacted]
Hazard Ratio 95%CI	[redacted]	[redacted]
Stage 2	**RClb** **n = 330**	**GClb** **n = 333**
Patients with event (death)	[redacted]	[redacted]
P-value	[redacted]	[redacted]
Hazard Ratio 95%CI	[redacted]	[redacted]

Key: Clb: chlorambucil ; GClb: obinutuzumab + chlorambucil; RClb: rituximab+chlorambucil

4.3.3. Safety

Study CLL11 was the basis for the safety analysis. The data presented in this section are an overview of the cumulative safety data reported at the time of the primary data-cut (9 May 2013) for CLL11[4] Adverse events occurred more frequently in the obinutuzumab+chlorambucil and rituximab+chlorambucil groups than in the chlorambucil alone group and were most frequent with obinutuzumab+chlorambucil treatment (see Table 14, Table 15, Table 16. The incidence of grade 3 or 4 neutropenia was highest with the combination of obinutuzumab and chlorambucil and was lowest with chlorambucil alone. Rates of grade 3 to 5 infection ranged from 11 to 14% and did not differ significantly between the treatment groups. Most reported infections were of bacterial origin.

Table 14 Adverse events of any grade (safety population)

	Stage 1a		**Stage 1b**	**Stage 2**	
	GClb n = 241	**Clb n = 116**	**RClb n = 225**	**GClb n = 336**	**RClb n = 321**
At least 1 AE, n (%)	227 (94)	96 (83)	205 (91)	286 (89)	315 (94)
Any grade AE†, n(%)					
Infusion-related reactions	166 (69)	-	88 (39)	221 (66)	121 (38)
Neutropenia	98 (41)	21 (18)	71 (32)	128 (38)	103 (32)
Nausea	32 (13)	29 (25)	32 (14)	40 (12)	42 (13)
Anaemia	30 (12)	12 (10)	28 (12)	37 (11)	35 (11)
Thrombocytopenia	37 (15)	9 (8)	17 (8)	48 (14)	21 (7)
Diarrhoea	25 (10)	13 (11)	19 (8)	34 (10)	24 (7)
Fatigue	17 (7)	12 (10)	20 (9)	27 (8)	30 (9)
Pyrexia	25 (10)	8 (7)	13 (6)	29 (9)	24 (7)
Constipation	17 (7)	12 (10)	14 (6)	28 (8)	16 (5)
Asthenia	18 (7)	8 (7)	19 (8)	23 (7)	25 (8)
Cough	23 (10)	8 (7)	15 (7)	25 (7)	19 (6)
Headache	18 (7)	8 (7)	16 (7)	21 (6)	18 (6)
Vomiting	13 (5)	14 (12)	16 (7)	19 (6)	22 (7)
Nasopharyngitis	17 (7)	8 (7)	7 (3)	19 (6)	10 (3)
Bronchitis	11 (5)	8 (7)	10 (4)	12 (4)	16 (5)
Decreased appetite	8 (3)	9 (8)	6 (3)	10 (3)	9 (3)
Pneumonia	12 (5)	4 (3)	12 (5)	17 (5)	20 (6)
Dyspnoea	5 (2)	8 (7)	9 (4)	9 (3)	13 (4)
Abdominal pain	11 (5)	6 (5)	7 (3)	14 (4)	10 (3)
Rash	8 (3)	3 (3)	13 (6)	8 (2)	19 (6)
Insomnia	9 (4)	5 (4)	8 (4)	12 (4)	9 (3)
Arthralgia	11 (5)	3 (3)	8 (4)	16 (5)	8 (2)
Oedema peripheral	7 (3)	4 (3)	12 (5)	11 (3)	17 (5)

	Stage 1a		Stage 1b	Stage 2	
	GClb n = 241	**Clb n = 116**	**RClb n = 225**	**GClb n = 336**	**RClb n = 321**
Dizziness	10 (4)	5 (4)	6 (3)	12 (4)	8 (2)
Pruritus	9 (4)	5 (4)	6 (3)	11 (3)	11 (3)
Upper respiratory tract	5 (2)	5 (4)	10 (4)	8 (2)	15 (5)
Back pain	12 (5)	2 (2)	6 (3)	16 (5)	9 (3)
Urinary tract infection	15 (6)	3 (3)	2 (<1)	18 (5)	5 (2)
Abdominal pain upper	8 (3)	5 (4)	4 (2)	9 (3)	6 (2)
Leukopenia	17 (7)	0	6 (3)	21 (6)	6 (2)
Respiratory tract infection	8 (3)	4 (3)	6 (3)	9 (3)	7 (2)
Chest pain	7 (3)	2 (2)	8 (4)	8 (2)	9 (3)
Febrile neutropenia	6 (2)	5 (4)	4 (2)	10 (3)	4 (1)
Dyspepsia	6 (2)	4 (3)	5 (2)	7 (2)	8 (2)
Oral herpes	9 (4)	1 (<1)	3 (1)	11 (3)	5 (2)
Muscle spasms	3 (1)	2 (2)	7 (3)	3 (<1)	7 (2)
Tumour lysis syndrome	10 (4)	1 (<1)	0	14 (4)	0
Oropharyngeal pain	3 (1)	4 (3)	2 (<1)	3 (<1)	3 (<1)
Hyperuricaemia	8 (3)	0	2 (<1)	8 (2)	2 (<1)

Notes: *Safety analysis population (included all patients who received at least one dose of study medication). All AE irrespective of grade, and whether considered related or unrelated to treatment by investigators, were collected and used to calculate the incidence of AE. †Incidence rate of ≥3% in any treatment arm .**Key:** AE: Adverse Event; Clb: chlorambucil; GClb: obinutuzumab+chlorambucil ; RClb: rituximab+chlorambucil(Source: Roche Submission, Section 6.9.2, Table B30, pp112)

Table 15 Adverse events of Grade 3 or higher (safety population)

	Stage 1a		Stage 1b	Stage 2	
	GClb n = 241	**Clb n = 116**	**RClb n = 225**	**GClb n = 336**	**RClb n = 321**
Any AE	175 (73%)	58 (50)	125 (56)	235 (70)	177 (55)
Infusion-related reactions	51 (21%)	-	9 (4%)	67 (20%)	12 (4%)
Neutropenia	84 (35%)	18 (16%)	60 (27%)	111 (33%)	91 (28%)
Anaemia	11 (5%)	5 (4%)	10 (4%)	14 (4%)	12 (4%)
Thrombocytopenia	27 (11%)	5 (4%)	8 (4%)	35 (10%)	10 (3%)
Leukopenia	13 (5%)	0	3 (1%)	15 (4%)	3 (1%)
Infections	27 (11%)	16 (14%)	30 (13%)	40 (12%)	44 (14%)
Pneumonia	8 (3%)	4 (3%)	11 (5%)	13 (4%)	17 (5%)
Febrile neutropenia	4 (2%)	5 (4%)	4 (2%)	8 (2%)	4 (1%)

Notes: * The safety population included all patients who received at least one dose of study medication. Shown are adverse events of grade 3, 4, or 5 with an incidence of 3% or higher in any treatment group, irrespective of whether the event was considered related or unrelated to treatment by the investigators.**Key:** AE: Adverse Event; Clb: chlorambucil; GClb: obinutuzumab+chlorambucil ; RClb: rituximab+chlorambucil(Roche Submission, Section 6.9.2, Table B31, pp113)

Table 16 Serious adverse events (safety population)

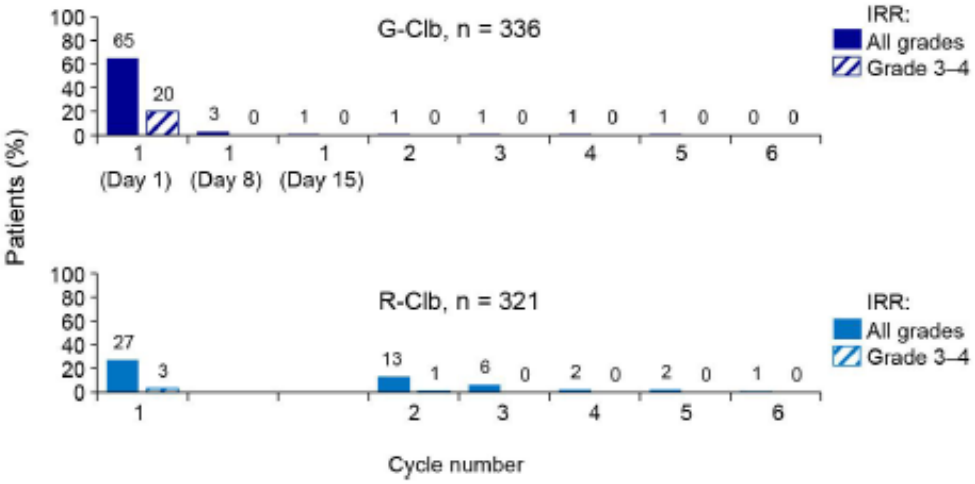
	Stage 1a		Stage 1b	Stage 2	
	GClb n = 241	**Clb n = 116**	**RClb n = 225**	**GClb n = 336**	**RClb n = 321**
Any SAE†, n (%)	99 (41)	44 (38)	76 (34)	131 (39)	102 (32)
Infection	28 (12)	17 (15)	32 (14)	42 (13)	45 (14)
Neoplasm	17 (7)	5 (4)	16 (7)	19 (6)	18 (6)
Infusion-related reaction	27 (11)	n/a	3 (1)	34 (10)	5 (2)
Pneumonia	10 (4)	4 (3)	12 (5)	14 (4)	17 (5)
Febrile neutropenia	2 (<1)	5 (4)	3 (1)	6 (2)	3 (<1)
Respiratory tract infection	2 (<1)	3 (3)	2 (<1)	3 (<1)	2 (<1)
Sepsis	0	3 (3)	0	1 (<1)	1 (<1)
Autoimmune haemolytic anemia	1 (<1)	2 (2)	1 (<1)	1 (<1)	1 (<1)
Neutropenia	3 (1)	0 (0)	0 (0)	4 (1)	2 (<1)
Thrombocytopenia	2 (<1)	0 (0)	1 (<1)	4 (1)	1 (<1)
Tumour lysis syndrome	3 (1)	0 (0)	0 (0)	5 (1)	0 (0)
Anaemia	3 (1)	0 (0)	1 (<1)	3 (<1)	2 (<1)
Cardiac failure	3 (1)	2 (2)	0 (0)	4 (1)	1 (<1)
Myocardial infarction	4 (2)	2 (2)	0 (0)	4 (1)	0 (0)
Septic shock	2 (<1)	2 (2)	0	2 (<1)	0
Squamous cell carcinoma skin	5 (2)	0	2 (<1)	5 (1)	3 (<1)
Erysipelas	1 (<1)	2 (2)	0	2 (<1)	0
Urinary tract infection	3 (1)	1 (<1)	0	3 (<1)	1 (<1)
Cerebrovascular accident	3 (1)	0 (0)	1 (<1)	3 (<1)	1 (<1)
Squamous cell carcinoma	1 (<1)	0	3 (1)	2 (<1)	3 (<1)
Basal cell carcinoma	3 (1)	0	1 (<1)	4 (1)	1 (<1)
Neutropenic sepsis	3 (1)	0	0	3 (<1)	1 (<1)

Notes: *Safety analysis population (included all patients who received at least one dose of study medication). All AE irrespective of grade, and whether considered related or unrelated to treatment by investigators, were collected and used to calculate the incidence of AE. †Incidence rate of ≥1% in any treatment arm.**Key:** AE: Adverse Event; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab; SAE: Serious Adverse Event.(Roche Submission, Section 6.9.2, Table B32, pp113)

Infusion-related reactions

Infusion-related reactions were more frequent with obinutuzumab+chlorambucil treatment than with rituximab+chlorambucil treatment. In the obinutuzumab+chlorambucil group, 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 (**Figure 16**). No deaths were associated with infusion-related reactions. Neither the lymphocyte counts nor the tumour burden at baseline was a strong predictor of obinutuzumab-related infusion reactions (Table 17). Prophylactic measures had only a moderate effect on the frequency of infusion-related reactions (Table 18).

Figure 16 All grade and grade 3-4* infusion-related reactions by day of infusion



Notes: *There were no grade 5 IRR. †Safety analysis population (included all patients who received at least one dose of study medication), stage 2 analysis (G-Clb vs. R-Clb). Key: Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab (Source: Roche Submission, Section 6.9.2, fig B24, p114)

Table 17 Infusion related reactions during obinutuzumab+chlorambucil treatment by baseline characteristics (Source: Roche Submission, Section 6.9.2, Table B33, p115)

Baseline characteristic	Grade 3–4* IRRs No n=269	Grade 3–4* IRRs Yes n=67
Sex		
Male	163 (61)	25 (37)
Female	106 (39)	42 (63)
Age, years, median (range)	74 (39–89)	73 (53–85)
Total CIRS score, median		
≤6, n (%)	59 (22)	17 (25)
>6, n (%)	210 (78)	50 (75)
Calculated CrCl, median		
<70 ml/min	169 (63)	50 (75)
≥70 ml/min	100 (37)	17 (25)
Binet stage, n (%)		
A	58 (22)	17 (25)
B	125 (46)	18 (27)
C	86 (32)	32 (48)
Circulating lymphocyte count, n (%)		
<25×109 cells/L	69 (26)	16 (24)
SPD radiologic assessed lesions, mm^2, median (range)	2338 (108–478990)	2527 (144–36774)

Key: *There were no grade 5 infusion-related reactions. †Stage 2 analysis. CIRS, Cumulative Illness Rating Scale; CrCl, Creatinine Clearance; GClb: obinutuzumab+chlorambucil ; SPD, Sum of the Products of the Diameters

Table 18 Impact of study protocol amendments on infusion-related reactions during obinutuzumab+chlorambucil treatment (Source: Roche Submission, Section 6.9.2, Table B34, pp115)

Baseline characteristic	Enrolled n	All grades n (%)	Grade 3-4 n (%)
Date of enrollment			
Before Nov 2, 2010	53	47 (88)	9 (17)
Nov 2, 2010 – Apr 12, 2011*	74	53 (72)	19 (26)
Apr 13, 2011 – Jun 25, 2011†	33	23 (70)	10 (30)
Jun 26, 2011 – Oct 17, 2011‡	36	22 (61)	5 (14)
After Oct 17, 2011§	140	74 (53)	24 (17)

Notes: *Study protocol amendment: Patients with lymphocytes >25 $\times 10^9$/L received corticosteroid premedication. †Study protocol amendment: Corticosteroid premedication recommended for all patients. ‡Study protocol amendment: Antihypertensive drugs must be paused. § Study protocol amendment: Slow infusion rate and mandatory splitting of the first dose of obinutuzumab

The tumour lysis syndrome (TLS) was reported in 15 patients in the study and resolved in all cases. Frequencies of newly diagnosed neoplasms were similar among the treatment groups (**Table 19)**.

Table 19 Newly diagnosed malignant, benign or unspecified neoplasms starting 6 months after first study drug intake by treatment comparison*(Source: Roche Submission, Section 6.9.2, Table B35, p116)

	Stage 1a		Stage 1b	Stage 2	
	GClb n = 241	Clb n = 116	RClb n = 225	GClb n = 336	RClb n = 321
At least 1 AE, n (%)	12 (5)	5 (4)	12 (5)	13 (4)	13 (4)
Squamous cell carcinoma of skin	5 (2)	0	2 (<1)	5 (1)	2 (<1)
Prostate cancer	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Squamous cell carcinoma	2 (<1)	0	3 (1)	3 (<1)	3 (<1)
Lung adenocarcinoma	1 (<1)	1 (<1)	0	1 (<1)	0
Basal cell carcinoma	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)
Myelodysplastic syndrome	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)
Renal cell carcinoma	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)
Adenocarcinoma gastric	1 (<1)	0	0	1 (<1)	0
Gastrointestinal stromal tumour	0	1 (<1)	0	0	0
Keratoacanthoma	1 (<1)	0	0	1 (<1)	0
Pancreatic carcinoma	0	1 (<1)	0	0	0
Rectal adenocarcinoma	1 (<1)	0	0	1 (<1)	0
Richter's syndrome	0	1 (<1)	0	0	0
Benign neoplasm of skin	0	0	1 (<1)	0	1 (<1)
Breast cancer	0	0	1 (<1)	0	1 (<1)
Colon adenoma	0	0	1 (<1)	0	1 (<1)

	Stage 1a		Stage 1b	Stage 2	
	GClb n = 241	Clb n = 116	RClb n = 225	GClb n = 336	RClb n = 321
Intracranial tumour hemorrhage	0	0	1 (<1)	0	1 (<1)
Metastatic malignant melanoma	0	0	1 (<1)	0	1 (<1)
Skin papilloma	0	0	1 (<1)	0	1 (<1)
Squamous cell carcinoma of lung	0	0	1 (<1)	0	1 (<1)
Transitional cell carcinoma	0	0	1 (<1)	0	1 (<1)

Notes : *Safety analysis population (included all patients who received at least one dose of study medication). All AE irrespective of grade, and whether considered related or unrelated to treatment by investigators, were collected and used to calculate the incidence of AE. **Key**: AE: Adverse Event; Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Discontinuations

As compared with both patients receiving obinutuzumab+chlorambucil and those receiving chlorambucil alone, patients receiving rituximab+chlorambucil were less likely to discontinue therapy early owing to adverse events. This imbalance between the obinutuzumab+chlorambucil group and the rituximab+chlorambucil group was primarily due to infusion-related reactions in the obinutuzumab+chlorambucil group (**Table 20**).

Table 20 Impact of infusion-related reactions and tumour lysis syndrome on clinical course (Source: Roche Submission, Section 6.9.2, Table B36, p117)

	GClb n = 336	RClb n = 321
Infusion-related reactions		
All Grade	221 (66)	121 (38)
Grade 3–4	67 (20)	12 (4)
Leading to		
Hospitalization	26 (8)	5 (2)
Treatment modification*	121 (36)	67 (21)
Treatment discontinuation	25 (7)	3 (<1)
Tumour lysis syndrome		
All Grade	14 (4)	0
Grade 3–4	6 (2)	0
Leading to		
Hospitalization	4 (1)	0
Treatment modification*	2 (<1)	0
Treatment discontinuation	1 (<1)	0

Key: *Interrupted or delayed. Clb: Chlorambucil; G: Obinutuzumab; R: Rituximab

Deaths

The most common grade 5 adverse events were newly diagnosed neoplasms and cardiac events in the obinutuzumab+chlorambucil and rituximab+chlorambucil groups and infections in the chlorambucil group (**Table 21**). The incidence of haemorrhagic events was similar between arms (obinutuzumab+chlorambucil 4 deaths/336, rituximab+chlorambucil3 deaths/321, chlorambucil 2 deaths/116). However, all 4 fatal haemorrhagic events in obinutuzumab+chlorambucil patients occurred in Cycle 1, compared to none in rituximab+chlorambucil patients and 1 in chlorambucil patients.

Table 21 List of deaths (grade 5 adverse events) (Source: Roche Submission, Section 6.9.2, Table B37, p118)

Adverse event*	Treatment received GClb, n=336 RClb, n=321 Clb, n=118	Related to treatment†
Haemorrhagic stroke	G-Clb	Yes
Plasma cell myeloma	G-Clb	Yes
Adenocarcinoma of colon	G-Clb	No
Cerebrovascular accident	G-Clb	No
Chronic obstructive pulmonary disease	G-Clb	No
Colon cancer	G-Clb	No
Death (not further specified)	G-Clb	No
General physical health deterioration	G-Clb	No
Myocardial infarction	G-Clb	No
Myocardial infarction	G-Clb	No
Pulmonary alveolar hemorrhage	G-Clb	No
Pulmonary sepsis	G-Clb	No
Subdural haematoma	G-Clb	No
Septic shock	G-Clb	No
Squamous cell carcinoma of lung	G-Clb	No
Cardiac arrest	R-Clb	Yes
Death (not further specified)	R-Clb	NK
Adenocarcinoma	R-Clb	No
Arrhythmia	R-Clb	No
Cardiac arrest	R-Clb	No
Cardiac arrest	R-Clb	No
Cardiac failure	R-Clb	No
Cerebral haematoma	R-Clb	No
Death (not further specified)	R-Clb	No
Death (not further specified)	R-Clb	No
General physical health deterioration	R-Clb	No

Adverse event*	Treatment received GClb, n=336 RClb, n=321 Clb, n=118	Related to treatment†
Interstitial lung disease	R-Clb	No
Intracranial tumour haemorrhage	R-Clb	No
Lung neoplasm malignant	R-Clb	No
Metastatic squamous cell carcinoma	R-Clb	No
Myelodysplastic syndrome	R-Clb	No
Post procedural haemorrhage	R-Clb	No
Pneumonia	R-Clb	No
Pneumonia	R-Clb	No
Respiratory failure	R-Clb	No
Squamous cell carcinoma	R-Clb	No
Haemorrhage intracranial	Clb	Yes
Respiratory failure	Clb	Yes
Respiratory tract infection	Clb	Yes
Cerebral haemorrhage	Clb	No
Pancreatitis	Clb	No
Pneumonia	Clb	No
Pneumonia	Clb	No
Sepsis	Clb	No
Septic shock	Clb	No
Septic shock	Clb	No
Thrombosis mesenteric vessel	Clb	No

Notes: *Safety analysis population (included all patients who received at least one dose of study medication). †As assessed by investigator.**Key**: Clb: Chlorambucil; G: Obinutuzumab; NK: not known; R: Rituximab

Summary of safety

The safety profile of obinutuzumab in combination with chlorambucil has been evaluated in the CLL11 trial based on data from 336 patients with CLL receiving obinutuzumab (8 infusions) at the proposed dose of 1000 mg and 0.5 mg/kg body weight for chlorambucil, with a clinical cut-off date of 9 May 2013.

Some of the key findings across these studies were:

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

- 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+chlorambucil arm. 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.

Superseded

- 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, leukopenia, anaemia, pyrexia, and nasopharyngitis was higher (> 5% difference) in the obinutuzumab based arm than in the rituximab+chlorambucil or 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).

See Erratum

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+chlorambucil arm 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+chlorambucil arm 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%) had their dosage regime

of rituximab modified or delayed and 5 patients (2%) were hospitalised. (Source: Roche Submission, Section 6.9.2, pp120).

In stage 1, SAE neutropenia occurred more frequently in obinutuzumab+chlorambucil -treated patients than in chlorambucil-treated patients. The incidence of SAE neutropenia was 1% in obinutuzumab+chlorambucil -treated patients compared to 0% in rituximab+chlorambucil-treated patients and 0% in chlorambucil treated patients. In stage 2, SAE neutropenia occurred more frequently in obinutuzumab+chlorambucil -treated patients than in chlorambucil-treated patients with an incidence of 1% for obinutuzumab+chlorambucil and <1% for rituximab+chlorambucil. In stage 1 incidence of SAE thrombocytopenia was <1% in obinutuzumab+chlorambucil -treated patients and <1% in rituximab+chlorambucil-treated patients, in stage 1. In stage 2, the incidence was 1% for obinutuzumab+chlorambucil and <1% for rituximab+chlorambucil. There were no fatalities because of neutropenia or thrombocytopenia in the study (Source: Roche Submission, Section 6.9.2, pp120).

The incidence of infection (SAE) was balanced between the treatment arms with 13% of patients in the obinutuzumab+chlorambucil arm (stage 2), 14% of patients in the rituximab+chlorambucil arm (stage 2) and 15% in the chlorambucil arm (stage 1). However, after taking into account the difference in patients' years at risk the incidence of serious infections and grade ≥ 3 infections was higher in the chlorambucil arm than in the obinutuzumab+chlorambucil arm and balanced in the rituximab+chlorambucil arm. However, for 5 patients in the chlorambucil arm (stage 1), 2 patients in the obinutuzumab+chlorambucil arm (stage 2) and 2 patients in the rituximab+chlorambucil arm (stage 2), the infection was fatal (Source: Roche Submission, Section 6.9.2, pp120).

In summary, these data indicate that obinutuzumab+chlorambucil is well tolerated with manageable additional toxicity. 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. Despite a more potent pharmacodynamic cytotoxic effect of obinutuzumab on CD20-positive B-cells compared with rituximab however, obinutuzumab does not appear to add new or unexpected toxicities (Source: Roche Submission, Section 6.9.2, pp121).

We agree that the AE profile reported is consistent with that expected in this patient population.

4.3.4. Patient-reported outcomes

The effect of CLL on HRQL over time is typically marked by impaired physical, role, cognitive and social functioning.[25, 64] More sleep disturbances are experienced over time, as is increased fatigue, nausea and vomiting, appetite loss and constipation[25, 64] It is also notable that patients with CLL are highly susceptible to infections, some of which can have serious consequences and are of particular relevance to the older population with existing comorbidities included in this study. In the submission, Roche state that patient-reported quality of life was an outcome for which the number of patients was too small and no meaningful statistical comparison of the treatment arms could be made. There is some quality of life data presented in graph format in the appendix of Goede et al 2014 [4], but no exact values are given.

4.4. Mixed treatment comparison

The CLL11 trial evaluates the efficacy of obinutuzumab+chlorambucil , rituximab+chlorambucil and chlorambucil alone. Roche performed a mixed treatment comparison to compare these treatments with bendamustine. The comparison with bendamustine+rituximab is discussed in Section 4.5, p96. The PFS hazard ratio was the response variable in the evidence network. Roche performed a systematic review to identify randomised controlled trials, see Roche's Submission, Section 6.7.1, pp76.

The manufacturer provided detailed information on the search strategy. In summary, searches were carried out in the following databases:MEDLINE (Embase.com); EMBASE (Embase.com); PubMed (www.ncbi.nlm.nih.gov); The Cochrane Library.

The websites of the American Society of Clinical Oncology (ASCO), the American Society of Haematology (ASH) and the European Haematology Association (EHA) were also searched for conference proceedings.

The searches were run in 2013 and updated in April 2014 in order to have conducted a search within 6 months of submission. The database searches combine free-text and MeSH terms for "chronic lymphocytic leukaemia" with the names of a variety of interventions suitable for indirect and mixed treatment comparison with Obinutuzumab. A variety of synonyms are used to ensure an appropriate balance of sensitivity and specificity. A suitable clinical trials filter is applied for the MEDLINE and EMBASE searches. All results are date limited from 1992 to April 2014. The choice of databases is appropriate for the topic and the translation of search terms and syntax for each database is accurate.

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.

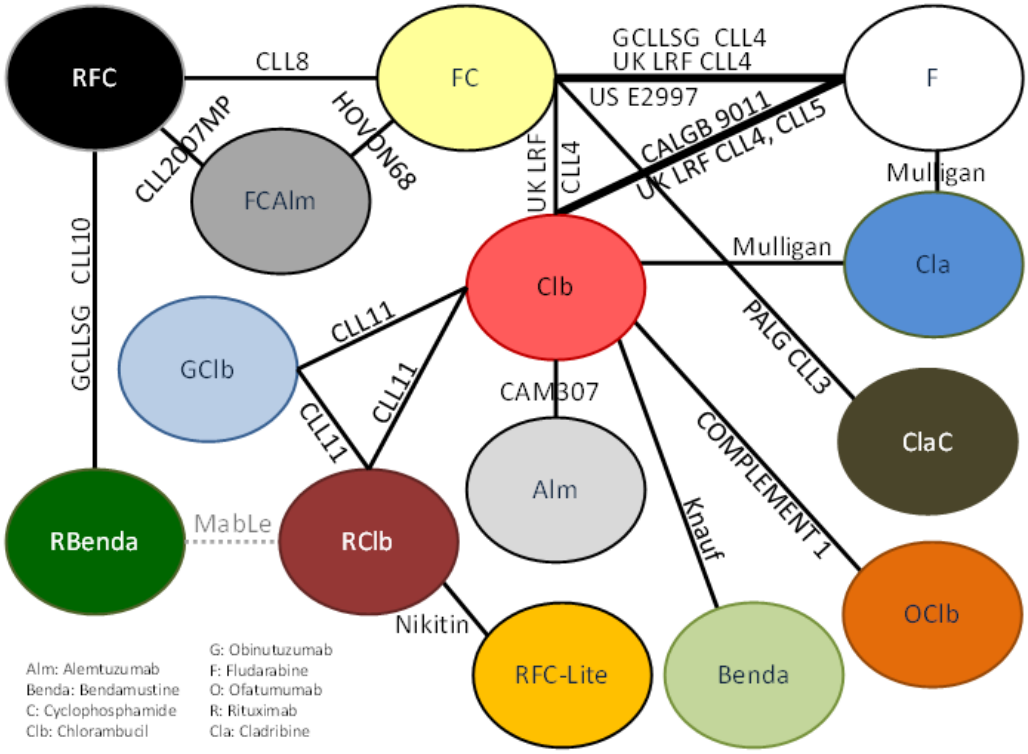
41 studies covering 42 RCTs were identified (Roche Submission, Section 6.7.2, pp80-86). Only 8 studies reported the PFS hazard ratio. The hazard ratio was estimated in another 8 RCTs using published information. This gave a total of 17 studies (including CLL11), encompassing 14 pharmacological interventions. A summary of the RCTs used in the mixed treatment comparison is given in Appendix 2 (p173).

Superseded

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+chlorambucil and 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.

See Erratum

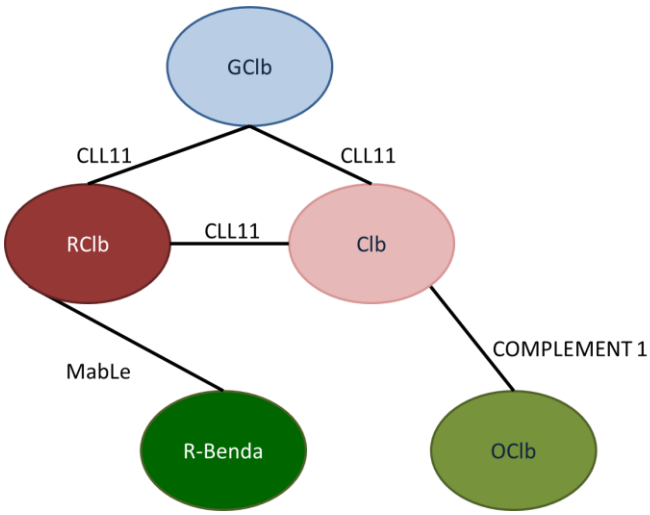
Figure 17 Evidence for large network for mixed treatment comparison. Taken from Roche submission, Figure B22, p99



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

Based on the 17 RCTs, Roche built two different networks. The large network includes all 17 RCTs, regardless of the patients' suitability for fludarabine based therapy (**Figure 17**). The small network includes only studies that excluded patients suitable for fludarabine based treatment (**Figure 18**).

Figure 18 Evidence for small network for mixed treatment comparison. Taken from Roche submission Figure B23, pp100



Key: Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; O: Ofatumumab; R: Rituximab

The small network currently includes only two studies: CLL11 and COMPLEMENT1. Roche intend to add the MaBLe study when the data becomes available.

Importantly, Roche excluded the Knauf RCT of bendamustine vs. chlorambucil in the small evidence network, as it did not explicitly exclude patients suited to fludarabine-based therapy. They also argue that patients in the Knauf trial would be eligible for fludarabine-based therapy because they are, on average, younger that patients in the CLL11 and COMPLEMENT1 trials (median ages 63, 73 and 69.5 respectively).

Table 22 summarises the key input data used for the mixed treatment comparison. The median patient age was included in some analyses. As stated in the footnote to the table, when median PFS is reported, the hazard ratio is estimated as the ratio of the median PFS in the two treatment arms. The method of Parmar et al (1998) is used to estimate the standard error of ln(HR). We note that the hazard ratios from the CLL11 RCT correspond to the May 2013 data cut-off (as opposed to the March 2014 cut-off, which was used in the economic model). We also note that the hazard ratio of 0.353 between bendamustine and chlorambucil is the updated value reported in Knauf et al (2012).[55]

Table 22 Summary of results in the trials used to conduct the mixed treatment comparison

Study name	Comparison*	lnHR	se(lnHR)	HR*	95%CI (Lower	-Upper)	Median age	Age range
CLL11	GClb vs Clb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73.0	39-90
	Rtx+Clb (RClb) vs Clb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	GClb vs RClb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
GCLLSG CLL8	Rtx+Flu+Cyc (RFC) vs Flu+Cyc (FC)	0.580	0.103	0.560	0.46	0.69	61.0	30-81
CLL5	Flu (F) vs Clb	-0.051	0.154	0.951	0.70	1.29	70.5	65-78
Knauf 2012	Benda vs Clb	-1.040	0.138	0.353	0.27	0.46	64.5	35-78
CAM307	Alm vs. Clb	-0.545	0.149	0.580	0.43	0.77	59.5	35-86
UK LRF CLL4	Flu (F) vs Clb	-0.151	0.097	0.860	0.71	1.04	65.0	35-86
	Flu+Cyc (FC) vs Clb	-0.799	0.096	0.450	0.37	0.54		
	Flu+Cyc (FC) vs Flu (F)	-0.799	0.133	0.450	0.35	0.59		
Complement 1	Ofa+Clb (OClb) vs Clb	-0.562	0.123	0.570	0.45	0.73	69.5	35-92
CALGB 9011	Flu (F) vs. Clb	-0.386	0.114	0.680	0.55	0.86	63.0	33-89
CLL2007FMP	Rtx+Flu+Cyc (RFC) vs Flu+Cyc+Alm (FCAlm)	-0.29	0.287	0.748[‡]	0.426	1.313	56.7	51-64
HOVON68	Flu+Cyc+Alm (FCAlm) vs Flu+Cyc (FC)	-0.174	0.100	0.840[‡]	0.691	1.022	60.0	27-75
GCLLSG CLL10	Rtx-Benda (R-Benda) vs Rtx+Flu+Cyc (RFC)	0.326	0.159	1.385[‡]	1.014	1.892	62.0	33-82
Nikitin 2013	Rtx+Flu+Cyc+Lite (RFC-Lite) vs Rtx+Clb (RClb)	-0.723	0.252	0.485[‡]	0.296	0.795	71.0	60-84
Mulligan 2014[#]	Cladibrine (Cla) vs Clb	-1.022	0.353	0.360[‡]	0.180	0.719	63.0	56-70
	Cladibrine (Cla) vs Flu (F)	-0.916	0.226	0.400[‡]	0.257	0.623		
GCLLSG CLL4	Flu+Cycl (FC) vs Flu	-0.580	0.180	0.560[‡]	0.390	0.790	59.0	42-65
US intergroup E2997	Flu+Cycl (FC) vs Flu	-0.580	0.180	0.560[‡]	0.390	0.790	61.0	33-86
PALG CLL3	Cladibrine (Cla)+Cycl vs Flu+Cycl (FC)	-0.083	0.124	0.920[‡]	0.720	1.170	59.0	27-81
MaBLe	Rtx+Clb (RClb) vs Rtx+Benda (RBenda)	Not yet included in MTC						

Taken from Table B27, pp108 Roche submission. **Notes**: lnHR: natural logarithm of the reported hazard ratio; se(lnHR): standard error of lnHR; Median age was preferred over the mean value because it was reported by all RCTs. The HR, corresponding 95%CI and age range were not used in the NMAs but are displayed here for completeness.; *A value of HR<1 indicates that the first treatment (left-hand side) performs better; #Mulligan reported PFS results for only 2 out of the 3 comparisons; ǂWhen PFS median is reported, the HR is estimated as the ratio of the two treatment arms. When landmark PFS rate (e.g. 3 year PFS) is reported, exponential distribution is assumed and the parameter lamda is calculated using nQuery for each treatment arm. The HR is estimated as the ratio of the two treatment arms. P value is used for calculating the standard error for lnHR. Parmar et.al 1998 (www.ncbi.nlm.nih.gov/pubmed/9921604) is used to calculate the standard error for lnHR. **Key:** Alm: Alemtuzumab; Benda: Bendamustine; Clb: Chlorambucil; C: Cyclophosphamide; F: Fludarabine; G: Obinutuzumab; HR: Hazard Ratio; lnHR: natural logarithm of the reported Hazard Ratio; NA: Not available; NR: Not reached; Ofa: Ofatumumab; R: Rituximab; se(lnHR): standard error of lnHR

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.

Superseded

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.

See Erratum

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

Critical appraisal criterion	PenTAG appraisal
reported?	in the final scope. To be eligible patients were required to; • *be treatment-naïve, legally competent adults ≤75 years of age,* • *have a WHO Performance Status of 0–2* • *have a life expectancy >3 months* • *have confirmed chronic B-cell lymphocytic leukaemia (co-expression of CD5, CD23 and either CD19 or CD20 or both)* • *have symptomatic Binet Stage B or C disease* *In addition patients had to meet at least one of the following need-to-treat criteria;* • *haematopoietic insufficiency with non-haemolysis-induced haemoglobin ,10g/dl,* • *thrombocytopenia <100 ×10^9/L (equivalent to Binet Stage C)* • *B symptoms* • *rapidly progressive disease* • *risk of organ complications from bulky lymphomas* Patients with concomitant diseases were excluded from the study. This is standard practice in trials in oncology.
Were participants included in the study reflective of patients likely to receive the intervention in UK clinical practice?	Patients unsuitable for fludarabine are accepted to be more elderly with co-morbidities and lower performance status. Therefore the 65–70% of patients in this study with a WHO performance status of 0, coupled with a relatively young mean age of 63–64, may not be wholly representative of the target population
Was the study conducted in the UK (or were one or more centres of the multinational study located in the UK)?	Study 02CLLIII was an international study, employing 45 centres across Europe, one of which was in the UK. No further details are reported regarding other 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)?	The dosage regimen used for bendamustine is the same as the dosage regimen proposed in the Summary of Product Characteristics (SmPC) and is in accordance with the license. However, as already noted, the dosage regimen for chlorambucil is subject to variation in clinical practice
What randomisation technique was used?	*Patients were randomised 1:1 to receive either bendamustine or chlorambucil according to a computer-generated randomisation list. They were randomised consecutively in the order of study entry. Randomisation was in blocks of four (investigators were unaware of this) and was prospectively stratified by study centre and Binet stage*
Were patients recruited prospectively?	Yes, patients were recruited prospectively.
Were patients recruited consecutively?	Unclear. The submission states that participants were randomised consecutively in the order of study entry, not that they were recruited consecutively. Therefore it is not known if all people matching the stated inclusion criteria were enrolled into the study

Critical appraisal criterion	PenTAG appraisal
Were the individuals undertaking the outcomes assessment aware of allocation?	Due to the different routes of administration for the intervention and comparator, blinding was not performed. It is unclear whether it would have been feasible to blind the participants and investigators, but it should be noted that awareness of allocation will have introduced the potential for bias in the study. The investigators' assessments were, however, reviewed by an independent committee for response assessment (ICRA).
Was follow-up adequate and was loss to follow-up reported or explained?	The minimum follow up period was 12 months, with interim analyses carried out quarterly. However, as recruitment took place over four years, and the follow-up period ended one year after the last enrolled patient, some subjects were monitored for approximately five years in total.
Were the statistical analyses used appropriate?	The approach to the statistical analysis of Study 02CLLIII study is considered appropriate
Was an intention-to –treat analysis undertaken?	Yes, the analysis adopts 'intention to treat' principles.
Were there any confounding factors that may attenuate the interpretation of the results of the study?	Patients were randomised on study entry and both groups have similar baseline characteristics. Reasons are given for patients who did not complete the study, and the numbers of these are comparable between arms. However, lack of blinding may have introduced some bias.
Did the study report data for relevant prognostic factors?	The relevant prognostic factors are quoted in the manufacturer's submission as follows: *A post-hoc analysis was carried out to compare the efficacy and tolerability of bendamustine and chlorambucil in subgroups of patients defined by age (<65 years vs. ≥65 years) and specific indicators of disease activity (presence of B-symptoms, Binet stage and lactate dehydrogenase levels). These factors are of interest because each can influence prognosis*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Although no numerical values are given, the submission notes: *Patients' overall quality of life was modestly improved in both groups during treatment with no significant differences between the groups. Significant differences in favour of chlorambucil were seen in the following individual parameters:physical functioning, role functioning, emotional functioning, fatigue and appetite loss. The quality of life data collected during the trial reflected the scenario in which patients receiving a more effective therapy (bendamustine) experienced a greater number of adverse events during the treatment period leading to a quality of life detriment in some health dimensions. The quality of life data collected in the trial were not appropriate to capture the long-term benefit of bendamustine after therapy was stopped, because they were only collected during the treatment period and patients who were discontinued from the study were not followed up with respect to quality of life.*
Source: Hoyle M, Crathorne L, Jones-Hughes T, Stein K. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp 2010. University of Exeter (Report)	

4.4.2. Implementation of Mixed Treatment Comparison in WinBUGS

The WinBUGS code used to parameterise the model uses the natural logarithm of the hazard ration as the continuous outcome variable. The model assumes a normal distribution for the ln (hazard ratio) of arm k relative to arm 1 in trial i, yik , with variance vik. The code was taken from Dias et al DSU document 2.[65]

CLL11, UK LRF CLL4 and Mulligan 2014 are three-arm trials that provide three pairwise comparisons. Roche state that when results from multi-arm trials are presented as continuous treatment differences relative to the control arm, a correlation between the treatment effects is induced because all differences are taken relative to the same control arm. Roche state that this correlation requires an adjustment to the likelihood – which has been done in the WinBUGS code. For example, in CLL11, the comparisons obinutuzumab+chlorambucil vs. chlorambucil, rituximab+chlorambucil vs. chlorambucil are correlated. For details of implementation in WinBUGS, see p103 Section 6.7.5 of Roche's submission.

Roche performed the following analyses.

Small network

Two models were applied to the small network (see p104, Section 6.7.5 Roche's report for more details):

- Fixed effects model
- Random effects model

Roche appropriately state that the use of meta-regression is not feasible due to (a) the limited number of studies and (b) the median age in the two trials in the network differ little.

Roche used the fixed effects model for their base case for the small network. The WinBUGS code is given on p283 Appendix 3.2 of Roche's report.

Large network

Three models were applied to the large network:

- Fixed effects model with meta-regression on age – base case.
- Fixed effects model.
- Random effects model with a weakly informative prior distribution to induce heterogeneity.

Roche claim that age is a potential source of heterogeneity between trials, and that age is a potential confounder of treatment effect as measured by PFS hazard ratio since studies with older patients have a higher baseline risk of death than studies with younger patients. Roche claim that since PFS is a composite endpoint of progression and mortality, the large age difference between trials may bias the relative treatment estimates derived from the mixed treatment comparison. Roche claim that for the random effects model, only an analysis without an age adjustment was implemented since a meta-regression model could not identify the posterior distribution of the age coefficient due to the limited number of studies available. We agree with this.

In the fixed effects meta-regression model age was centred around the median age observed in the CLL11 trial (73 years).

4.4.3. Results of mixed treatment comparison

Full output from WinBUGS is given on p288 Section 3.3 of Roche's report.

When the mixed treatment comparison was adjusted for age in the large network, the hazard ratio between bendamustine and chlorambucil increased from 0.353 to 0.51, and the relative treatment effect of obinutuzumab+chlorambucil improved relative to bendamustine, see **Table 24**.

Table 24 Summary of mixed treatment comparison results for obinutuzumab+chlorambucil vs bendamustine

Comparison	Model	Mean PFS HR	Lower 95%CI	Upper 95%CI
ObClb vs Benda	Fixed effects model with age adjustment	**0.399**	0.218	0.672
	Fixed effects model	**0.546**	0.367	0.783
	Random effects model	**0.554**	0.322	0.892

In summary, Roche use the PFS hazard ratio of 0.399 between obinutuzumab and bendamustine in the base case analysis in their economic model. The other two hazard ratios in **Table 24**.are used in sensitivity analyses. We note that the choice of PFS hazard ratio is important, because under Roche's base case, the ICER between obinutuzumab and bendamustine is £26,000 per QALY, whereas using a value of 0.546, the ICER increases substantially, to £36,000 per QALY.

4.4.4. Critique of mixed treatment comparison

We believe that Roche's WinBUGS code is appropriate. Furthermore, we ran the WinBUGS code, and we were able to recreate the results given in p288 Section 3.3 of Roche's report.

Next, we checked the three items of data for each of the RCTs in the evidence network in **Table 22**, p78: ln(PFS hazard ratio), se(ln(hazard ratio)) and median age. In most cases, we either agree with Roche's values, or estimate very similar values. However, we found the following discrepancies:

- In the CLL2007FMP trial (Lepretre 2012),[66] Roche estimate a hazard ratio of 0.748. Using just the 3 year PFS values, we estimate a hazard ratio of 0.59.

- In the HOVON68 CLL trial (Geisler 2011),[67] Roche estimate a hazard ratio of 0.748. Using the ratio of medians, we estimate a hazard ratio of 0.84. We do not know how Roche estimated their value, as only median values are given in the publication.

In Table B26, p104 of their submission, Roche correctly state that the PALG-CLL3 RCT compared treatments rituximab, fludarabine + cyclophosphamide vs. fludarabine + cyclophosphamide, with a hazard ratio of 0.65. However, on p108, they say that this trial considered the treatments: cladibrine + cyclophosphamide vs. fludarabine + cyclophosphamide with a hazard ratio of 0.92. Having investigated this discrepancy, we find that the former is correct. This error is carried over to the data for the WinBUGS code.

However, we find that the error in the third bullet point changes the estimated hazard ratio for bendamustine vs. chlorambucil only incrementally. Further, changing the other two values corresponding to the first two bullet points also changes the results only marginally. Therefore, we pursue this matter no further.

Our clinical advisor agrees with Roche that the major factors influencing suitability for fludarabine-containing treatments are choice of treatment, age and existence of comorbidities. He also agrees that some of the patients in the Knauf RCT of bendamustine vs. chlorambucil were eligible for fludarabine therapies, and therefore are not directly comparable with patients in the CLL11 RCT. We therefore agree with Roche that it would not be appropriate to include the overall intention-to-treat Knauf PFS hazard ratio into the evidence network without adjustment.

We note that Roche adjust for age only. However, we know that patient eligibility for fludarabine is a function not just of age, but also of comorbidities. Therefore, arguably one should include both age and comorbidities in the mixed treatment comparison. However, we

do not see this as a major criticism of Roche's analysis, as age and comorbidities will be highly correlated.

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.

As discussed in Section 4.4.1(p87), the doses of chlorambucil differed between the CLL11 and Knauf (2010) RCTs. The mean total dose of chlorambucil was 329mg in CLL11, substantially lower than the 549mg in the bendamustine RCT. 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, and hence the true hazard ratios would be greater than those in Table 24, p91.

PFS hazard ratio for bendamustine for patients aged ≥65

We believe that the mixed treatment comparison is redundant because we have located the PFS for patients aged ≥ 65 in the bendamustine versus chlorambucil RCT. An abstract by Knauf et al. (2009)[5] (Appendix 4) shows that PFS for patients aged <65 and ≥ 65 is very similar (**Figure 19**). In particular for:

- patients aged <65, median bendamustine = 20.9 months (n=87) and median chlorambucil = 8.7 months (n=68). The estimated hazard ratio is then approximately 8.7/20.9 = 0.42.

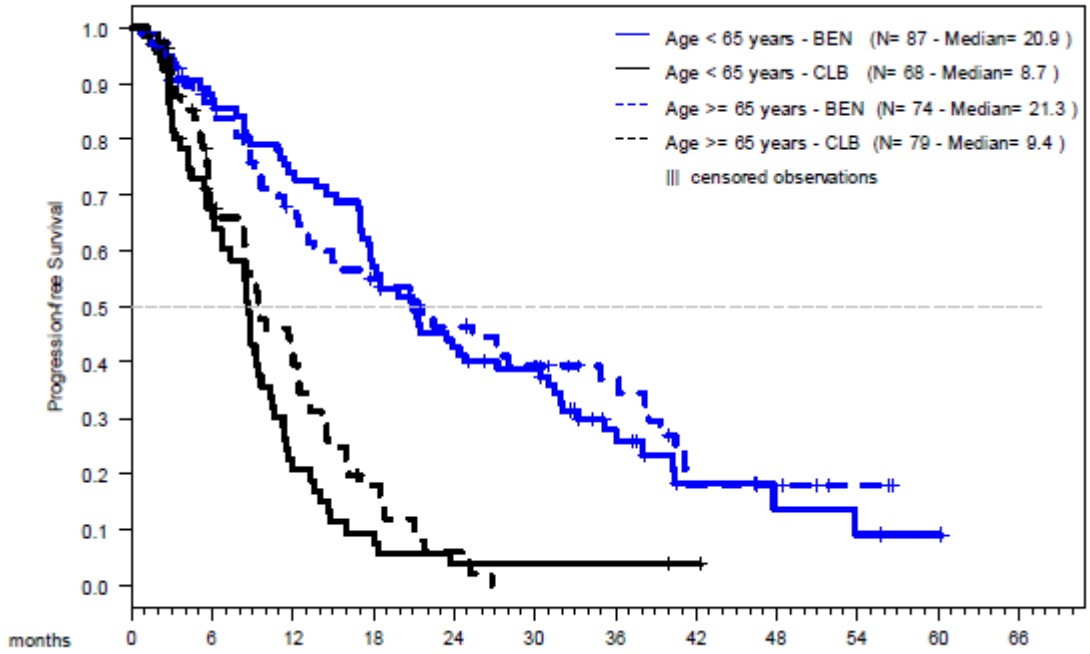
- patients aged ≥65, median bendamustine = 21.3 months (n=74) and median chlorambucil = 9.4 months (n=79). The estimated hazard ratio is then approximately 9.4/21.3 = 0.44.

Given that the estimated hazard ratios 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 the be same as the hazard ratio for all patients in the bendamustine trial, i.e. 0.353. The hazard ratios calculated above, for ages < and ≥65 (0.42 and 0.44) are not quite consistent with the hazard ratio for all patients in the bendamustine trial, 0.353, because (a) the values correspond to different cut-off dates and (b) the 0.42 and 0.44 are approximate values.

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] in **Table 24** (p91). Henceforth, we assume that the PFS hazard ratio between obinutuzumab+chlorambucil and bendamustine for patients relevant to this HTA is 0.55.

We note that Knauf et al. (2009)[5] (Appendix 4) state that *"Regarding ORR, CR, and PFS, respectively, Bendamustine shows its superiority over Chlorambucil across major clinical risk groups. It is of great importance for daily practice that this holds true also in patients ≥65 y of age".*

Figure 19 PFS for bendamustine and chlorambucil in bendamustine RCT for patients aged <65 and ≥65



Notes: Source: Knauf et al (2009)[5]

4.4.5. Comparison of bendamustine plus rituximab and obinutuzumab plus chlorambucil

As mentioned previously, the results of the MaBLe RCT of bendamustine+rituximab vs. rituximab+chlorambucil are not yet published. Roche estimate the PFS HR between bendamustine plus rituximab and rituximab plus chlorambucil as 0.60, and between obinutuzumab+chlorambucil and bendamustine plus rituximab as 0.68 as follows.

Roche noted that the PFS HR between obinutuzumab+chlorambucil and rituximab+chlorambucil at the March 2014 cut off was [redacted], and the percentage of complete responders was 20.7% and 7% respectively, a factor of 2.96. In the MaBLe protocol, the sample size calculation for the primary endpoint of “confirmed complete response rates” after 6 cycles for first-line patients is based on estimated complete response rates of 30% in the bendamustine+rituximab arm and 15% in the rituximab p+ chlorambucil arm, a multiple of 2. Roche then assume perfect correlation between the ratio of complete responders and the PFS HR. They claim that if a multiple of [redacted] leads to a [redacted] reduction in the risk of progression for obinutuzumab vs. rituximab/chlorambucil, then a complete responder % multiple of [redacted] might lead to a [redacted] in the risk of progression for bendamustine+rituximab vs. rituximab+chlorambucil, i.e. a hazard ratio of [redacted] This in turn leads to a hazard ratio between obinutuzumab and bendamustine+rituximab of [redacted] 0.68.

Roche claim that the interim analysis of MaBLe[68] validates the estimated % of complete responders of 30% in the bendamustine plus rituximab arm and 15% in the rituximab+chlorambucil arm. The interim % of responders are 30% and 13% respectively,[68] a ratio of 2.31. Using the same methodology as above, this leads to hazard ratio of 0.54 between bendamustine+rituximab and rituximab+chlorambucil, or a hazard ratio of 0.76 between obinutuzumab and bendamustine + rituximab.

Critique

On p108, Section 6.7.6 of Roche’s report, Roche claim that the mixed treatment comparison did not provide a comparison of bendamustine+rituximab and obinutuzumab+chlorambucil . We disagree, noting that the PFS HR between bendamustine+rituximab and obinutuzumab+chlorambucil estimated by the 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.

Next, we note that the dose of chlorambucil in MaBLe differed to that in CLL11 or in the Knauf RCT of bendamustine vs. chlorambucil. In MaBLe, the dose was 10mg/m2 on days 1-7 for 6 cycles, whereas in CLL11, the dose was 0.5mg/kg body weight given on day 1 and 15 of all treatment cycles 1 to 6. In the Knauf RCT, the dose was 0.8mg/kg on Days 1 and 15, for 6 cycles. It is not known how this affects the relative effectiveness of the treatments being compared.

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 .

Superseded

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".

See Erratum

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 in October 2014.

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.

The submission includes one clinical study: obinutuzumab+chlorambucil against rituximab+chlorambucil or chlorambucil alone in previously untreated CLL patients with coexisting conditions. This was a phase III, multicentre, open-label, randomised, three-arm trial of 781 participants. The submission contains all relevant studies and the relevant data within those studies for the primary outcome measure (progression free survival) and most secondary outcome measures. A notable exception is the omission of any health related quality of life (HRQL) data in the submission, despite HRQL data being published in the supplementary appendix of the Goede et al (2014) paper along with an associated statement that "Quality of life did not deteriorate during or after antibody therapy as compared with treatment with chlorambucil alone" (Source: Goede et al (2014), pp6). No data values are given to support the HRQL graphs in the appendix describing quality of life over time for all treatment comparisons (EORTC QLQ-C30 global health scale) for G-Clb vs. R-Clb (A), G-Clb vs. Clb (B), R-Clb vs. Clb (C)) i [4, 69] and so it is not possible to comment further on this HRQL data due to the limited information available. However, in general we consider that the submitted clinical evidence adequately reflects the decision problem defined in the submission.

The submission from Roche included one clinical study on obinutuzumab: obinutuzumab+chlorambucil compared with rituximab+chlorambucil or chlorambucil in people with previously untreated CLL who have co-existing medical conditions, such as cardiac or renal problems, and/or other age-related problems and for whom full-dose fludarabine based therapy is not appropriate. This was a Phase III, randomised, open-label, multicentre trial of 781 participants. 589 patients were randomised in Stage 1 on a 2:2:1 (obinutuzumab+chlorambucil : rituximab+chlorambucil: chlorambucil) basis between the three treatment arms and an additional 192 patients in Stage 2 on 1:1 (obinutuzumab+chlorambucil : rituximab+chlorambucil) basis between the two treatment arms.

In summary, the identified benefits are as follows:

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 rituximab+chlorambucil arm (HR 0.44, 95% CI [0.34 – 0.57]), p<0.001).

At the end of stage 2, the addition of obinutuzumab to chlorambucil (GClb) 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+chlorambucil arm and 26.7 months in 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]

The overall survival data were not mature at this data cut-off so as to calculate the median OS. However, a statistically and clinically significant (not adjusted for multiplicity) hazard ratio for death in the obinutuzumab+chlorambucil arm was observed when compared with chlorambucil (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). This improvement in survival observed with obinutuzumab+chlorambucil represents the first significant improvement in OS against chlorambucil in a Phase 3 trial in 1L CLL to date. (Source: Roche Submission, Section 6.10.1, p122)

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

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. obinutuzumab+chlorambucil), best overall response (p<0.0001 vs. chlorambucil and p=0.0001 vs. obinutuzumab+chlorambucil), disease free survival (p<0.0001 vs,. chlorambucil and p=0.0475 vs. obinutuzumab+chlorambucil), and time to new treatment (p<0.0001 vs. chlorambucil and p=0.0018 vs. obinutuzumab+chlorambucil) compared to chlorambucil and rituximab+chlorambucil. The significantly prolonged time to new anti-leukaemia therapy with obinutuzumab+chlorambucil compared with rituximab+chlorambucil or chlorambucil means that patients experience a longer period off treatment.(Source: Roche Submission, Section 6.10.1, p131)

Superseded

The safety profile of obinutuzumab was generally comparable to that of rituximab+chlorambucil and 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, anaemia, pyrexia, and nasopharyngitis was higher (> 5% difference) in the obinutuzumab based arm than in the rituximab+chlorambucil or 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)

See Erratum

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

[redacted]

[redacted]

Adverse events occurred more frequently in the obinutuzumab+chlorambucil and rituximab+chlorambucil groups than in the chlorambucil group alone and were most frequent with obinutuzumab+chlorambucil treatment. The incidence of grade 3 or 4 neutropenia was highest with the combination of obinutuzumab and chlorambucil and was lowest with chlorambucil alone. This did not translate into a difference in infection rates however; rates of grade 3 to 5 infection ranged from 11 to 14% and did not differ significantly between the treatment groups. Most reported infections were of bacterial origin.

Infusion-related reactions were more frequent with obinutuzumab+chlorambucil treatment than with rituximab+chlorambucil treatment. In the obinutuzumab+chlorambucil group, 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. No deaths were associated with infusion-related reactions.

The submission contains all relevant studies and the relevant data within those studies for the primary outcome measure (progression-free survival) and most secondary outcome measures. A notable exception is the omission of any health related quality of life (HRQoL) data in the submission. Roche state that for the patient-reported quality of life outcome, the number of patients was too small and that no meaningful statistical comparison of the treatment arms could be made. (Source: Roche Submission, Section 6.5.3, pp71). However, we note that some HRQol data is presented in the supplementary appendix of the primary paper [4]and the paper states in it's main text that HRQL did not deteriorate during or after antibody therapy as compared with treatment with chlorambucil alone. Because no values are given for the HRQL data in the appendix of the Goede paper (Supplementary Appendix to Goede et al.[4]) and no HRQL data is included in the submission, it is not possible for us to comment further due to the limited information available.

5. Cost effectiveness

5.1. Manufacturer's review of cost-effectiveness evidence

5.1.1. Objective

The objective of the manufacturer's cost-effectiveness review was to identify cost-effectiveness studies evaluating obinutuzumab in people with first line CLL. We believe the objective of the cost-effectiveness review was appropriate for identifying existing answers to the decision problem.

5.1.2. Search strategy

The manufacturer provided detailed information on the search strategy. In summary, searches were carried out in the following bibliographic databases:

- EMBASE (ProQuest);
- EMBASE Alert (ProQuest);
- MEDLINE (ProQuest);
- NHS EED (Centre for Reviews and Dissemination);
- EconLIT (searched via the American Economic Association website).

The searches were run in May 2014. They combine free-text terms for "chronic lymphocytic leukemia" (American English spelling only) and free-text and MeSH terms for methods of cost-effectiveness analysis. The results are date limited from 1992 to May 2014.

ERG comment on search strategy

The search strategy uses a variety of synonyms to ensure an appropriate balance of sensitivity and specificity. The lack of the UK English spelling for "leukemia" is a weakness. However, the searches were re-run by our information specialist with the UK English spelling and no additional studies were retrieved, i.e. the number of hits when searching with and without the UK English spelling of "leukemia" is the same.

The term "lymphocytic" is spelt "lymphocitic" in the MEDLINE and EMBASE search strategies. We raised this as a clarification question and the manufacturer responded by sending a revised appendix with a note that the spelling had been corrected. However, the spelling error remains in the revised appendix. We re-ran the searches with the correct spelling and no additional studies were retrieved, i.e. the number of hits when searching with and without the correct spelling of "lymphocytic" is the same. As such, the error does not compromise the quality of the searches.

The translations of the ProQuest (i.e. MEDLINE and EMBASE) search strategies for NHS EED and EconLit are not equivalent to the ProQuest searches but they do contain the same concepts and are appropriate for the topic.

5.1.3. Inclusion and exclusion criteria used in the study selection

Stated inclusion and exclusion criteria for the manufacturer's cost-effectiveness review are shown in **Table 25**.

Table 25. Inclusion and exclusion criteria for systematic review of economic evidence

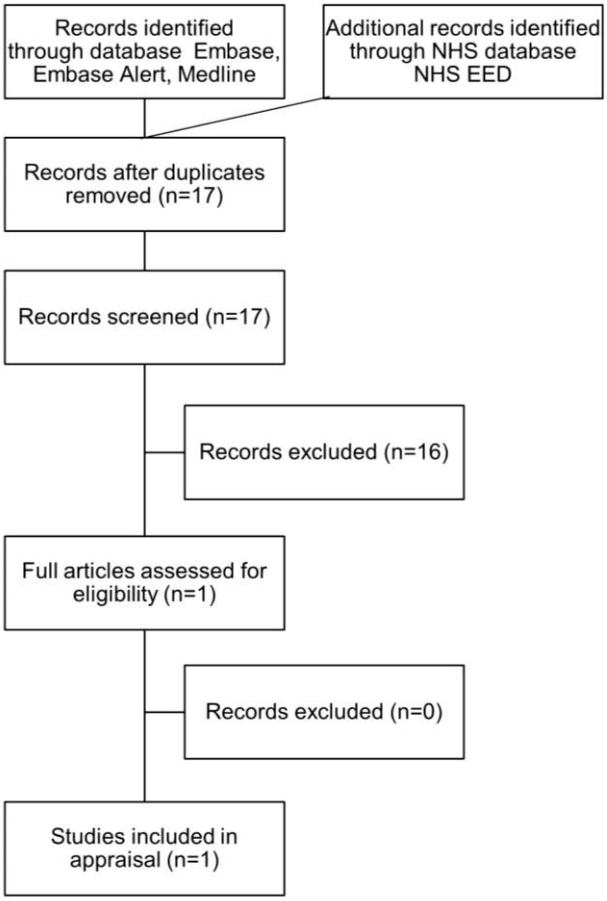
Category	Include	Exclude
Population	People with first line CLL	non-CLL; non-first line
Intervention	Obinutuzumab (GA101)	
Comparators	– Chlorambucil – Rituximab plus chlorambucil – Bendamustine – Rituximab plus bendamustine	
Outcomes	– Cost per quality-adjusted life year gained – Cost per life year gained	
Study type	Economic evaluations: – cost-effectiveness analyses – cost-utility analyses – cost minimisation analyses	RCTs, observational studies, budget impact assessments
Publication type	Not specified	

Key: CLL, chronic lymphocytic leukaemia; RCTs, randomised controlled trials
(Source: Roche Submission, Table B38, pp128)

5.1.4. Results

Figure 20 shows the study flow diagram for the cost-effectiveness review. The searches conducted by the manufacturer identified 17 unique records, one of which met the inclusion criteria (Walzer et al., 2013). The included study, published only as an abstract, evaluated obinutuzumab in combination with chlorambucil versus chlorambucil alone in people with previously untreated chronic lymphocytic leukaemia (CLL).

Figure 20. Study flow diagram for systematic review of economic evidence



Notes: Source: Roche submission, Section 7.1.1, pp129

The quality assessment checklist suggested by NICE was applied even though the study was only published in abstract form (Roche submission, Section 7.1.3). Results from the included analysis, conducted by Roche, are summarised in **Table 26**.

Table 26. Summary list of cost-effectiveness evaluations

Study	Year	Country	Model design	Population[a]	QALYs	Costs (GBP)	ICER (per QALY gained)
Walzer et al.[6]	2013	UK	4-state Markov model	Patients unsuited to fludarabine treatment.	GClb: 3.6 Rituximab+chlorambucil: 3.2 Clb: 2.8	GClb: 21K–25.6K Rituximab+chlorambucil: 13K Clb: 1.4K	GClb vs Rituximab+chlorambucil: 21K–33.6K GClb vs Clb: 25.5K–31.5K

Key: Clb, chlorambucil; GClb: obinutuzumab+chlorambucil; NR, not reported; QALYs, quality-adjusted life years; RClb, rituximab+chlorambucil; UK, United Kingdom

Notes: a, average age in years

5.1.5. Conclusions and ERG critique

The economic literature review identified one study which reported cost per QALY estimates for obinutuzumab+chlorambucil versus chlorambucil alone in the treatment of first line CLL unsuitable for treatment with fludarabine. While we consider the stated inclusion/exclusion criteria appropriate for the review it is likely that cost-effectiveness studies including any of the comparators; i.e. not restricting to obinutuzumab could have provided some insight into appropriate modelling approaches. The results reported in the manufacturer's submission could not all be verified; for example, the QALYs and costs reported are not reported in the abstract. In addition, the ICERs reported in the table in the submission differ to those reported in the abstract: for obinutuzumab+chlorambucil versus chlorambucil alone a cost/QALY was reported as £18,000 to £19,000 and for obinutuzumab+chlorambucil versus rituximab+chlorambucil the cost/QALY was reported as £29,000 to £32,000. Although aligned with the marketing authorisation and relevant to the decision problem, it is important to note that the included cost-effectiveness analysis was a preliminary analysis conducted by the manufacturer as part of the HTA submission process. The model presented in the manufacturer's submission is an updated version of the same model.

5.2. Summary of the manufacturer's submitted evaluation

5.2.1. Model structure

The submission includes a cohort Markov model, comprised of three states: progression free, progression and death. These are demonstrated in **Figure 21**. The progression free health state is divided into two sub-states: on (initial) therapy and off therapy. Individuals in all arms remain on the treatment until they discontinue the therapy (due to adverse events), experience disease progression or die.

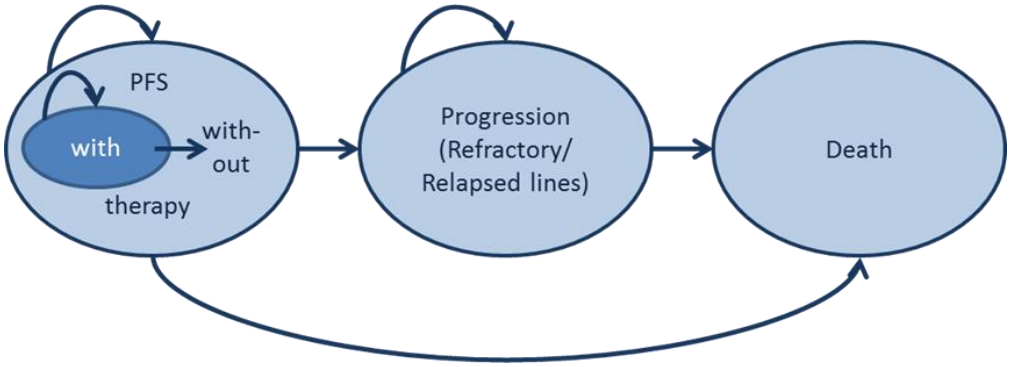
Individuals who have completed or discontinued treatment remain in the progression free health state until they progress or die. People in the progressed state remain in the state until they die and cannot return to the progression free health state. These patients are assumed to receive a course of chlorambucil.

The proportion of the cohort in each state is calculated as follows:

- The total proportion alive is set to the total proportion alive progression free plus the proportion alive in progress disease.
- The proportion in the progression free health state is set to equal the progression free survival curve.
- The proportion in the progression health state at each cycle is the difference between the proportion alive and the proportion that is progression free.

Cycles in the model last one week and a half-cycle correction was applied, except to the drug, administration and pharmacy costs.

Figure 21. Roche's model structure



Key: PFS: Progression free survival
(Source: Roche Submission, Figure B26, Section 7.2.2, pp133.)

5.2.2. Population

Obinutuzumab is indicated for patients with previously untreated CLL, for whom full-dose fludarabine is unsuitable.

Roche estimate that each year 1,034 patients in England and Wales will be eligible to receive obinutuzumab (Roche Submission, Section 8.1, pp 208).

Roche suggest that the CLL11 study is representative of the intended population and hence this forms the basis of the population in the model and for many other parameters in the model.

The average starting age of the population is taken as 71.7 years and weight 73.7kg, with body surface area 1.85m2 used for dose calculation. These values are taken from the CLL11 trial.

The proportion of men in the model is set to 60%, from the CLL11 data and is used to inform background mortality.

No subgroups of the population are considered.

5.2.3. Intervention and comparators

The intervention is obinutuzumab, given in combination with chlorambucil (referred to henceforth as obinutuzumab+chlorambucil or ObClb).

As in the NICE Scope, the comparator treatments are:

- Chlorambucil (Clb)
- Rituximab in combination with chlorambucil (rituximab+chlorambucil, RClb)
- Bendamustine monotherapy (Benda)
- Rituximab in combination with bendamustine (rituximab + bendamustine, RBenda)

All treatments are given until the end of the treatment course, disease progression or death. For all arms, a course of chlorambucil is given as treatment in disease progression.

5.2.4. Perspective, time horizon and discounting

The Roche submission adopts the perspective of the NHS/PSS. Costs of drug acquisition, drug administration, supportive care and adverse events are included. Wider societal costs are not included. Health benefits are only included from the patient population being treated.

The time horizon is lifetime (maximum 20 years). As the patient start age is set to 71.7 years, the time horizon is to age 91.7 years.

Costs and QALYs are discounted at 3.5% per annum, in line with NICE guidance.[2]

5.2.5. Treatment effectiveness and extrapolation

Progression-free survival

Progression free survival (PFS) is one of the most clinically relevant measures of treatment effectiveness and is also a key driver of cost-effectiveness.

Roche use results from CLL11 to inform the PFS of obinutuzumab+chlorambucil; rituximab+chlorambucil; and chlorambucil. [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, p96; 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 Section4.4.3 (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

Superseded
See Erratum

Table 27 (p108).

[redacted]22[redacted]

[redacted]23[redacted]

Table 27. Roche modelling of progression free survival

Treatment	PFS HR vs. ObClb	Base Case PFS	Scenario analysis PFS
ObClb	NA	[redacted]	Change of tail distribution to: Weibull, log-logistic, log-normal or Gompertz. CLL11 KM data fitted to entire curve using: Gamma, Weibull, log-logistic, log-normal, or Gompertz distribution
Clb	[redacted]	[redacted]	
RClb	[redacted]	[redacted]	
Benda	0.40	HR from MTC (FE model with age adjustment) applied to entire ObClb PFS curve	Base case HR applied in above scenarios
RBenda	0.68	HR from indirect comparison using RClb and assumption of full correlation between complete responders and PFS HR, applied to entire ObClb PFS curve	Base case HR applied in above scenarios

Key: Benda: bendamustine; Clb: chlorambucil;, Ob: obinutuzumab; KM: Kaplan Meier; PFS: progression free survival; R: rituximab HR: hazard ratio; MTC: mixed treatment comparison

Progressive disease and overall survival

Overall survival (OS) is another of the most clinically relevant measures of treatment effectiveness and is also a key driver of cost-effectiveness.

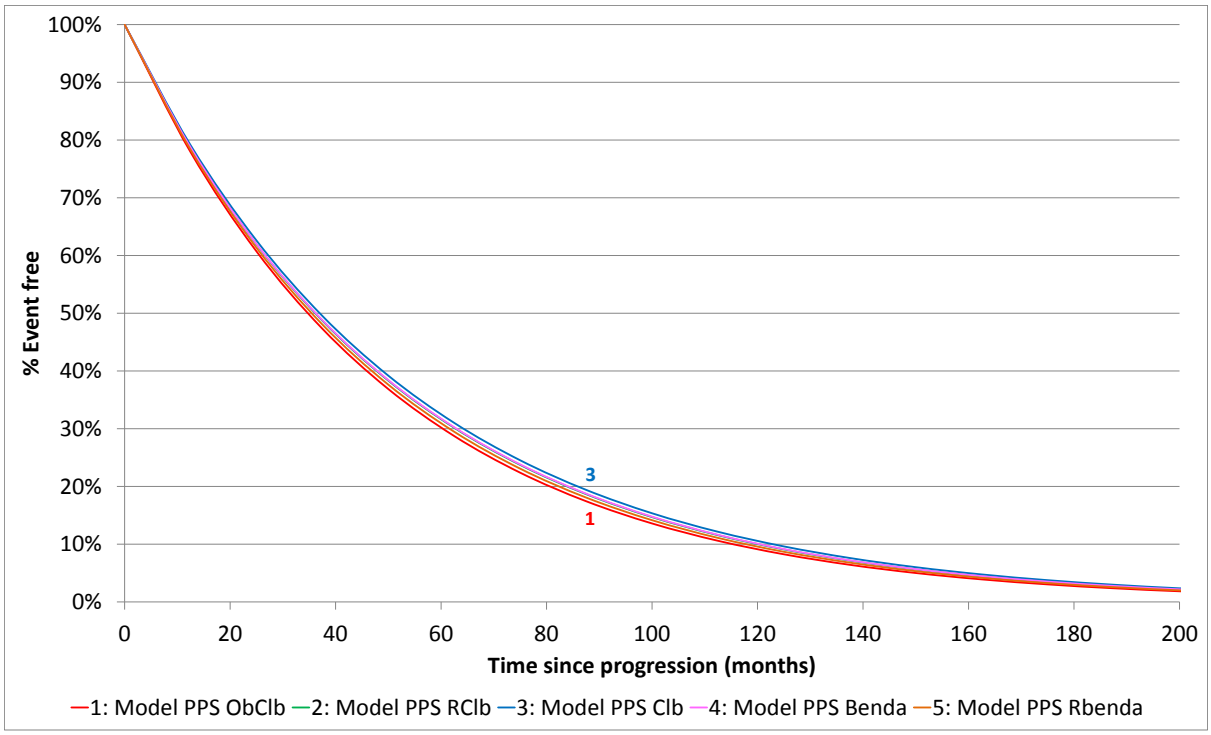
OS data is very immature in CLL11. Roche do not use this information to model PPS. Instead, they fit an exponential distribution to the pooled post-progression death rates from the CLL5 trial.

The CLL5 trial is a Phase III RCT that was conducted in Germany, comparing fludarabine to chlorambucil on previously untreated CLL patients of Binet stages A, B, or C. The age of patients ranged from 65-78 years old, with median ages of 70 years in the chlorambucil arm and 71 years in the fludarabine arm. The median length of follow up was 182 weeks. The primary study reference for this trial is Eichorst et al. 2009.[22] CLL5 was chosen on the basis of a suitably long follow up time, with data available to analyse the post-progression survival.

It was chosen over the CLL8 trial, for which data was also available, as the population in CLL5 was believed to be more similar to that in CLL11; in particular the age of patients in CLL5 was closer to those in CLL11 than CLL8. Furthermore, clinicians advised that there were a great number of deaths from fludarabine intolerability in CLL8, making the data less appropriate.

The exponential distribution was chosen on the basis of the having the lowest AIC value of the parametric survival curves fitted (exponential, Weibull, log-logistic, log-normal, gamma, Gompertz). Roche used a visual inspection to confirm the goodness of fit. The exponential parameter was adjusted for age at progression so that older individuals have worse PPS. As such, arms where individuals progress at an older age, i.e. those with longer time in PFS, have shorter time in progressed disease. Therefore the chlorambucil arm, where individuals progress earliest, has the lowest weekly probability of death from disease progression (0.4294%) and obinutuzumab+chlorambucil , where the PFS is longest, has the highest weekly probability of death from disease progression (0.4534%). The difference in this value between arms is small, as shown in **Figure 24**.

Figure 24. Modelled post progression survival curves used in Roche submission



Key: Benda: bendamustine; Clb: chlorambucil; Ob: obinutuzumab; R: rituximab; PPS: Post progression survival

OS is then modelled according to mortality from progression and from post-progression. OS is validated using the current available Kaplan-Meier OS data from CLL11. The modelled OS curves from Roche's submission are given in [redacted].

[redacted]

5.2.6. Health related quality of life

The cancer-specific EORTC QLQC30 questionnaire was used in the RCT of obinutuzumab versus chlorambucil. Roche did not perform a mapping from this instrument to the EQ-5D because they claimed that no validated mapping function exists.

Health related quality of life literature

Roche conducted a systematic review of the literature searching for studies that assessed utility values for patients with CLL.

The manufacturer provided detailed information on the search strategy. In summary, searches were carried out in the following bibliographic databases:

- EMBASE (ProQuest);
- EMBASE Alert (ProQuest);
- MEDLINE (ProQuest);

- NHS EED (Centre for Reviews and Dissemination);
- EconLIT (searched via the American Economic Association website).

The EMBASE, EMBASE Alert, MEDLINE and NHS EED searches were run in January 2014. The EconLit search was run in July 2014 following a clarification question about why details of the search were not included in the submission. The searches combine free-text terms for “chronic lymphocytic leukemia” (American English spelling only) and free-text and MeSH terms for quality of life. The results are date limited from 1992 to January 2014 except for the EconLit search which is date limited from 1992 to July 2014.

Nine studies were included according to the inclusion and exclusion criteria, see **Table 28**. Roche state that two original references (Hancock 2002[9] and Beusterien 2010[8]) in **Table 28** provide utilities that are arguably suitable for the model since they give values for both the PFS and PD health states. They state that both these studies have limitations. The utilities in Hancock et al. (2002)[9] were derived from expert opinion and therefore may not reflect societal preferences. Roche state that Beusterien et al (2010) uses the standard gamble method as opposed to time trade-off, and Roche state that there is evidence that the standard gamble method yields higher utilities than the time trade-off method. Roche further state the following weaknesses of the two studies:

- Lack of distinction between PFS utility whilst on treatment versus PFS utility whilst off treatment.
- Lack of distinction between PFS utility on an IV treatment versus an oral treatment.
- Lack of distinction between PFS utility for treatments which are not delivered in one sitting. Certain treatments may be administered over two days rather than one per cycle (e.g. bendamustine for all cycles or obinutuzumab for the first cycle only). This increased time spent in the hospital or increased hospital visits may result in a lower QoL than for treatments which are able to have the full cycle dose delivered in one sitting.
- Lack of distinction for PD utility for a patient who has had one previous line versus multiple previous lines of treatment.

Table 28. Assessment of suitability of published literature detailing utility values in 1st-line CLL

Title/Author	Intervention and comparators	Population and sample size	Instrument/method of valuation	Method of elicitation	Mapped to	HRQOL values	Original source if applicable	Appropriateness for use in model
The potential cost-effectiveness of obinutuzumab (GA101) in combination with chlorambucil in chronic lymphocytic leukemia Walzer 2013	G-Clb vs. R-Clb	Previously untreated patients with CLL N=Not clear	Utilities from NICE TA174	N/A	N/A	Utility scores: PFS: 0.8 Prog: 0.6	Hancock 2002	Hancock 2002 utilities were originally derived from expert opinion and may not reflect societal preferences.
Association of health-related quality of life with gender in patients with B-cell chronic lymphocytic leukemia Pashos 2013	First-line, second-line, or subsequent line therapy	Patients with B-cell CLL as they initiate therapy for CLL outside the clinical trial setting. N=1140	EQ-5D, FACT-Leu, Brief Fatigue Inventory	Not clear	N/A	BFI: Female: 4.6 Male: 4.0 p<0.0001 EQ-5D: Female: 0.8 Male: 0.9 p=0.0031 FACT-Leu: Female: 84.4 Male: 85.0 p=0.4815	N/A	No utility values for PFS and/or PD

Title/Author	Intervention and comparators	Population and sample size	Instrument/method of valuation	Method of elicitation	Mapped to	HRQOL values	Original source if applicable	Appropriateness for use in model
Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies: A single center study Oeyen 2013	Not clear	Patients with haematological (HM) or solid malignancies admitted to the medical or surgical ICU of a university hospital N=483 (478 on admission, 392 after 3 months and 331 after 1 year)	EQ-5D, SF-36	Not clear	Not clear	Mortality rates of HM compared to SM: (34 vs. 13 %), 3 months (42 vs. 17 %), and 1 year (66 vs. 36 %) (P\0.001) Poorer QOL at 1 year associated with: Older age: p = 0.007 Severe comorbidity: p = 0.035 HM: p = 0.041	N/A	No utility values for PFS and/or PD

Title/Author	Intervention and comparators	Population and sample size	Instrument/method of valuation	Method of elicitation	Mapped to	HRQOL values	Original source if applicable	Appropriateness for use in model
Bendamustine versus chlorambucil for the first-line treatment of chronic lymphocytic leukemia in England and Wales: A cost-utility analysis Woods 2012	Benda vs. Clb	Previously untreated patients with CLL N=Not clear Patients with inoperable esophaegal cancer (for mapping algorithm) N=199	Utilities from Beusterien 2010	Standard gamble (Beusterien 2010)	European Organization for Research and Treatment of Cancer C30 quality of life data to EQ-5D	Baseline: 0.70 ±0.22 Complete response: 0.91±0.11 Partial response: 0.84±0.14 No change: 0.78±0.14 Progressive disease: 0.68±0.20 No change + 1–2 nausea: 0.73±0.17 No change + 1–2 nausea/vomiting: 0.73±0.16 No change + 1–2 diarrhea: 0.70±0.19 No change + 3–4 anemia: 0.69±0.18 No change + 3–4 pyrexia: 0.67±0.17 No change + 3–4 pneumonia: 0.58±0.19 No change + second-line treatment: 0.71±0.17	Beusterien 2010	Standard gamble rather than TTO methodology used in Beusterien 2010
Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia Hornberger 2012	R-FC vs. FC	Previously untreated patients with CLL N=817	Utilities from Beusterien 2010	Standard gamble (Beusterien 2010)	N/A	PFS: 0.78 PFS Progressed disease: 0.68	Beusterien 2010	Standard gamble rather than TTO methodology used in Beusterien 2010

Title/Author	Intervention and comparators	Population and sample size	Instrument/method of valuation	Method of elicitation	Mapped to	HRQOL values	Original source if applicable	Appropriateness for use in model
Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia Tolley 2013	N/A	UK general public N=110	N/A	Time trade-off, VAS	N/A	Time trade-off: Anchor state: 0.549 ±0.231 (0.506, 0.592) DS 1 PFS responder: 0.671 ±0.236 (0.627, 0.715)* DS 2 PFS responder + AE thrombocytopenia: 0.563 ±0.108 (0.516, 0.610) DS 3 PFS responder + AE neutropenia, no infection:0.508 ±0.163 (0.464, 0.551)* DS 4 PFS responder + AE severe infection: 0.476 ±0.195 (0.432, 0.519)*DS 5 PFS non-responder: 0.394 ±0.219 (0.353, 0.435)* DS 6 PFS non-responder + AE Severe infection: 0.333 ±0.061 (0.294, 0.372)* DS 7 Disease progression: 0.214 ±0.18 (0.180, 0.247)* Own health: n/a *p<0.05 when compared with anchor state	N/A	Utility values for PFS and PD for late stage CLL refractory to 1L and 2L treatments

Title/Author	Intervention and comparators	Population and sample size	Instrument/method of valuation	Method of elicitation	Mapped to	HRQOL values	Original source if applicable	Appropriateness for use in model
Population preference values for treatment outcomes in chronic lymphocytic leukaemia: A cross-sectional utility study Beusterien 2010	N/A	General population N=89	N/A	Standard gamble	N/A	Health State: Mean ± SD (95% CI [lower, upper]) Complete Response: 0.91 ± 0.11 (0.88, 0.93) Partial Response: 0.84 ± 0.14 (0.81, 0.87) Change: 0.78 ± 0.14 (0.75, 0.82) 1-2 Nausea: 0.73 ± 0.17 (0.69, 0.76) 1-2 Nausea/Vomiting: 0.73 ± 0.16 (0.69, 0.76) Second-line Treatment: 0.71 ± 0.17 (0.68, 0.75) 1-2 Diarrhea: 0.70 ± 0.19 (0.66, 0.74) 3-4 Anemia: 0.69 ± 0.18 (0.65, 0.72) Progressive Disease: 0.68 ± 0.20 (0.64, 0.72) 3-4 Pyrexia: 0.67 ± 0.17 (0.63, 0.70) Third-line Treatment: 0.65 ± 0.22 (0.60, 0.69) 3-4 Pneumonia: 0.58 ± 0.19 (0.54, 0.62)	N/A	Standard gamble rather than TTO methodology used

Title/Author	Intervention and comparators	Population and sample size	Instrument/method of valuation	Method of elicitation	Mapped to	HRQOL values	Original source if applicable	Appropriateness for use in model
Economic evaluation of third-line treatment with alemtuzumab for chronic lymphocytic leukaemia Scott 2007	Alemtuzumab vs. RFC	Patients with CLL who were able to tolerate third-line treatment with either alemtuzumab or the comparator cycle of RFC. N=Not clear	Utilities from Grunberg 2002	N/A	N/A	QALY score for patients with 2-year survival with continuous emesis: 0.46 (Grunberg 2002)	Grunberg 2002	3L CLL
Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia Weeks 1991	Intravenous immune globulin vs. no immune globulin	CLL N=Not clear Physicians (to elicit utility values) N=10	N/A	Reference gamble	N/A	CLL without infection: 0.87 (0.50, 0.999) CLL with a trivial infection: 0.86 (0.50, 0.999) CLL with a moderate infection: 0.81 (0.50, 0.999) CLL with a major infection: 0.46 (0.20, 0.90) Intravenous immune globulin infusion: 0.66 (0.20, 0.99)	N/A	Line of treatment not clear, small sample size, non-societal preferences, no PFS/PD values

Notes: For references in this table, see Table B49 Roche's Submission.
(Source: Roche's submission, Section 7.4.6, Table B49)

Health related quality of life in Roche's model

Given the limitations of the utility values in the literature, Roche conducted a utility elicitation study with the UK general public to derive societal preferences for QoL associated with CLL.

Health state descriptions (also known as vignettes) were developed to reflect different states or stages of CLL. The health state titles were chosen to reflect lines of treatment through the disease pathway. The content of these health states were developed using published literature, rounds of in-depth interviews with patients with CLL and treating nurses and clinicians. Nine health states were developed, see **Table 29** and Appendix 3 (p179).

Table 29. Health state titles and definitions

Health State Title	Definition
PFS without therapy	In a state of PFS, not currently receiving any therapy.
PFS on initial therapy IV treatment	In a state of PFS, currently receiving initial therapy administered intravenously.
PFS on initial therapy oral treatment	In a state of PFS, currently receiving initial therapy administered via oral medication.
PFS on initial therapy with increased hospital visits	In a state of PFS, currently receiving initial therapy. Requires attending hospital multiple times for short sessions of treatment.
Progression after first line treatment	CLL progressing following receiving first line treatment. Currently not receiving any therapy.
PFS without second line therapy	In a state of PFS, post second line treatment. Currently not receiving any therapy.
PFS on second line therapy	In a state of PFS, currently receiving second line therapy.
Further progression	CLL progressing following two lines of treatment.
Relapsed lines of treatment	Worsening of CLL following three or more lines of treatment.

Key: CLL: Chronic Lymphocytic Leukaemia; PFS: Progression Free Survival

Face to face interviews with a representative sample of 100 members of the general UK public were conducted and the time trade off methodology was employed to elicit utility scores. The results of the study and their relevance within the model are shown in **Table 30**.

Table 30. Results of Roche's utility elicitation study and relevance within economic model

Health state	Mean Utility	SD	95% CIs (Lower)	(Upper)	Health state & treatment (Tx) arm in model
PFS on initial therapy oral treatment	0.71	0.20	0.67	0.75	PFS w Tx Clb
PFS on initial therapy IV treatment	0.67	0.22	0.63	0.71	PFS w Tx RClb PFS w Tx Benda PFS w Tx RBenda
PFS on initial therapy with increased hospital visits	0.55	0.26	0.50	0.61	PFS w Tx GClb (1st dose)
PFS without therapy	0.82	0.17	0.78	0.85	PFS w/o Tx all arms
Progression after first line treatment	0.66	0.22	0.62	0.71	Progression all arms. A weighted average of the utilities is calculated.
PFS on second line therapy	0.55	0.25	0.50	0.60	
PFS without second line therapy	0.71	0.23	0.66	0.75	
Further progression	0.59	0.23	0.55	0.64	
Relapsed lines of treatment	0.42	0.25	0.37	0.47	

Key: Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; IV: Intravenous; PFS: Progression Free Survival; R: Rituximab; Tx: Treatment

(Source: Roche Submission, Table B51, pp174)

Roche state that the last five health states in **Table 30Table 30** represent the progression health state of the model. In order to obtain one utility value for this state, a weighted average of the utility values of the five health states was calculated. Ideally the weights should be proportional to the time spent by an average patient in this health state. Roche's chosen weights are given in **Table 31**. These represent months and are based on a hypothetical patient population which on average would spend 30 months in this 'Progression (Refractory/Relapsed lines)' health state. They were obtained through a discussion with Dr. Barbara Eichhorst, a CLL specialist working at the Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany.

Table 31. Utility weights for the progressed health state

Health state	Weight for utility for all lines of treatment
Progression after first line treatment	3
PFS on second line therapy	4
PFS without second line therapy	8
Further progression	10
Relapsed lines of treatment	5

Key: PFS: Progression free survival

Table 32 gives Roche's base case utility values.

Table 32. Roche base case utilities

Health state within model	Treatment arm	Mean utility
PFS on initial therapy oral treatment	Chlorambucil	0.71
PFS on initial therapy IV treatment	Rituximab+chlorambucil, Bendamustine, Rituximab + Bendamustine	0.67
PFS on initial therapy with increased hospital visits	Obinutuzumab (1st dose)	0.55
PFS without therapy	All arms	0.82
Progressed disease	All arms	0.60

Key: PFS: Progression free survival; IV: intravenous

Disutilities due to adverse events are not explicitly taken into account. However the PFS utility for treatments that may require more hospitalisations due to adverse events is adjusted by having a separate value attributed to it compared to PFS on treatment (with no hospitalisations) or PFS off- treatment. For example, given that in the obinutuzumab arm 20% of patients had Grade 3 or 4 infusion related reactions during the first infusion, the PFS utility value for the first dose of obinutuzumab is attributed a lower value than for subsequent doses.

5.2.7. Resources and costs

Costs are estimated from the NHS and PSS perspective. Resource use costed in the model included: drug acquisition and administration costs; supportive care costs; and, the cost of treating adverse events.

Resource use systematic review

The manufacturer provided detailed information on the search strategy. In summary, searches were carried out in the following bibliographic databases; EMBASE (ProQuest); EMBASE Alert (ProQuest); MEDLINE (ProQuest); NHS EED (Centre for Reviews and Dissemination); EconLIT (searched via the American Economic Association website).

The EMBASE, EMBASE Alert, MEDLINE and NHS EED searches were run in May 2014. The EconLit search was run in July 2014 following a clarification question about why details of the search were not included in the submission. The searches combine free-text terms for "chronic lymphocytic leukemia" (American English spelling only) and free-text and MeSH terms for quality of life. The results are date limited from 1992 to May 2014 except for the EconLit search which is date limited from 1992 to July 2014.

Titles and abstracts were assessed for relevance according to the pre-defined inclusion criteria; i.e., a CLL population and including information on resource utilisation from a UK NHS perspective. Full papers were obtained and assessed by two reviewers. Of 40 titles and abstracts identified, none were considered relevant for inclusion in the review. (Roche Submission, Figure B44, p179).

Drug acquisition

The cost and dosing schedules of all drugs in Roche's model are given in **Table 33**. All drugs are taken over a maximum of 6, 28-day cycles. Roche state that all drugs requiring dosing in relation to body weight or body surface area are based on the distribution of body weight and height of participants in the CLL11 trial. Body surface area was subsequently calculated via the Mosteller Formula: BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)½. Roche say that in CLL11, the mean patient weight is 73.68kg, mean height is 166.70cm and mean body surface area therefore 1.85m^2.

No vial sharing is assumed for all intravenously administered drugs. Therefore all calculations assume full drug wastage.

In their model, Roche assume a mean of 6.91 out of a maximum of 8 doses of obinutuzumab (**Table 33**). Roche state that this was taken from the CLL11 trial. We find that this value is consistent with the data Table S4 in the Appendix of Goede et al (2014).[4] Next, Roche assume 98.8% of patients received the first administration of rituximab and there was a mean of 4.59 further administrations of rituximab. Again, these values are consistent with the data Table S4 in the Appendix of Goede et al (2014).[4]

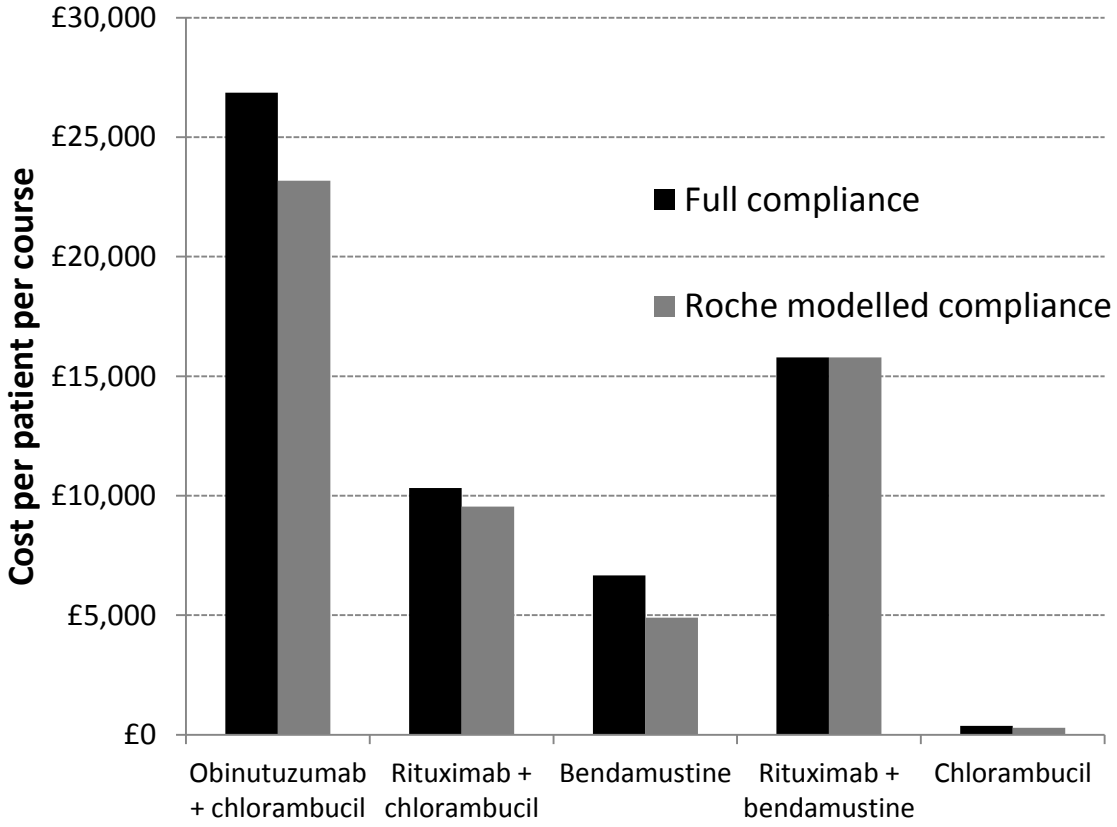
Table 33. Drug costs and dosing schedules

Treatment	Drugs	Cost per unit	Intended Dosing		Roche modelled dosing	
			Dosing	Cost per treatment course	Dosing	Cost per treatment course
ObClb	Obinutuzumab	£3,312 per 1,000 mg vial, recently agreed with DoH	1,000 mg fixed size on Day 1, 8, 15 of 1st treatment cycle, 1,000 mg on Day 1 of Cycles 2-6.	£26,496	Average 6.91[2] out of 8 doses, as in CLL11	£22,889
	Chlorambucil	£40.51 per 25 x 2mg pack[70]	0.5 mg/kg body weight given on Day 1 and 15 of all treatment Cycles 1 to 6.	£369	Average 9.45[2] out of 12 doses, as in CLL11	£291
RClb	Rituximab	£174.63 per 100mg vial[70] £873.15 per 500mg vial[70]	375 mg/m^2 body surface area on Day 1 1st cycle. Next 5 cycles at 500 mg/m^2 on Day 1.	£9,954[1]	98.8% of patients take 1st dose, mean of 4.59 further doses, as in CLL11	£9,223
	Chlorambucil	As above	As above	As above	Average 10.59[2] out of 12 doses, as in CLL11	£326
Benda	Benda	£69.45 per 25mg vial[70] £275.81 per 100mg vial[70]	Separate IV infusions on days 1 and 2 of each cycle, at 100mg/m^2.	£6,667[1§]	Average 4.9 out of 6 cycles at average dose intensity of 90%.	£4,900
RBenda	Rituximab	As above	As above	As above	Average 6 out of 6 doses, i.e. full compliance	£9,954
	Benda	As above	As above, but at 90mg/m^2	£5,834[1¶]	Average 12 out of 12 doses, i.e. full compliance	£5,834
Clb	Clb	As above	As above	As above	Average 9.32[2] out of 12 doses, as in CLL11	£287

Notes: [1] For a patient of mean body surface area 1.85m2, with full vial wastage; § Value estimated by us. Roche estimated as £5,810 on p181, Table B55 and £6,619 (p182, Section 7.4.19 of Roche report); ¶ Value estimated by us. Roche estimated as £5,810 (p181, Section 7.4.19 of Roche report); [2] Calculated by us from Roche's model.

The total drug acquisition costs per patient per course are given **Figure 27**.

Figure 27. Total per patient drug acquisition costs per course of treatment



Drug administration

Costs related to drug administration are given in **Table 34**. Obinutuzumab, rituximab and bendamustine are all given intravenously, and chlorambucil is given orally.

Where a drug is given in conjunction with another drug (i.e. obinutuzumab+chlorambucil , rituximab+chlorambucil, rituximab + bendamustine) pharmacy costs are accounted for each drug separately, whilst administration and consultation costs are captured only once (within the more expensive treatment delivery cost i.e. intravenous infusion).

Table 34. Drug administration costs

	Unit cost	Source
Administration of first dose of IV drug	£514	NHS Reference costs 2012-13[71] DH HRG SB14Z Deliver complex Chemotherapy
Administration of subsequent doses of IV drug	£343	NHS Reference costs 2012/13[71] (SB15Z): Deliver subsequent elements of a chemotherapy cycle

Pharmacy time for dispensing IV drug	£17	15 minutes of pharmacist time, PSSRU (2013)[72]
Administration of oral drug	£136	NHS Reference costs 2012/13[71] (SB11Z): Deliver exclusively oral chemotherapy
Pharmacy time for dispensing oral drug	£6	5 minutes of pharmacist time, PSSRU (2013)[72]
First cycle consultation with haematologist	£134	30 minute consultations. NHS Reference costs[71] 1st consultation 2012/13.
Subsequent cycles consultation with haematologist	£53	30 minute consultations. NHS Reference costs[71] subsequent consultation 2012/13.

In the model, the total drug administration costs are estimated by multiplying the above unit costs by the frequencies of administration for the total number of cycles given in **Table 33** (p122), e.g. a mean of 6.91 out of a maximum of 8 doses of obinutuzumab.

Supportive care costs

Informed by the CLL5 study and clinical opinion (via an advisory board), the manufacturer assumed that all participants would receive one treatment with chlorambucil post-progression. In each instance, the cost of post-progression treatment was divided by the mean time spent in progressed disease in each treatment arm and converted to a weekly supportive care cost in the progressed health state that therefore included post-progression treatment.

Resource use in the progression-free survival and post-progression states was informed by European Society of Medical Oncology (ESMO) guidelines and validated with clinical experts (haematologists) at an advisory board. ESMO guidelines recommend follow-up of asymptomatic patients every 3–12 months and should include a blood cell count every three months as well as regular examinations of lymph node, liver, and spleen. The PFS health state assumes one 60-minute outpatient attendance every three months (£106 per hour). For the post progression state it was assumed that the frequency of visits would increase to one per month.

Adverse events

Adverse events were included for obinutuzumab and comparators and were assumed to occur in the first cycle only.

The following assumptions were made in the submitted model:

- Only adverse events with >2% incidence in any treatment arm of CLL11 or any treatment arm of a comparator-related pivotal trial (Knauf et al. and MaBLe) were assumed to have resource use and quality of life impact due to the increased likelihood of the adverse event occurring via a true effect over random chance.
- 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 Stage 2 rituximab+chlorambucil from the CLL11 trial. This assumption was based on the results reported in the MaBLe abstract which states that safety was similar between the two arms.

Costs of adverse events were included for obinutuzumab and comparators. The manufacturer cites NHS Reference Costs 2012/2013 (NHS Reference Costs 2012/2013).[71]

Frequencies of adverse events included "Grade 3, 4 or 5 adverse events occurring in 2% or more people in any arm of the CLL11 trial,[4] or the Benda and R-Benda arms of the Knauf et al.[54] and MabLe trials[68] respectively" (Roche submission, pp185–186).

Table 35 shows the cost of adverse events used in the model. In the model, the cost of adverse events per patient was calculated by dividing the number of occurrences of the event in an arm by the number of patients in that arm. 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.

Table 35. List of adverse events and summary costs included in the economic model

Adverse event	Grade	GClb % of patients	RClb % of patients	Clb % of patients	Benda % of patients	RBenda* % of patients	Cost per episode (GBP)	Source: NHS Reference Cost 2012/2013 (HRG Code)
Anaemia	3	2.4%	2.1%	2.5%	2.5%	0.0%	2,088	Haemolytic anaemia without CC (SA03F)
Febrile neutropenia	3	0.9%	0.6%	2.5%	0.0%	0.0%	3,894	Febrile neutropenia with malignancy (PA45Z)
Febrile neutropenia	4	1.2%	0.6%	2.5%	0.0%	0.0%	3,894	Febrile neutropenia with malignancy (PA45Z)
Infusion related reaction: bronchospasm	3	3.3%	0.6%	0.0%	0.0%	0.0%	359	Shock and anaphylaxis, without CC (WA16Y)
Infusion related reaction: chills	3	3.6%	0.3%	0.0%	0.0%	0.0%	359	Shock and anaphylaxis, without CC (WA16Y)
Infusion related reaction: dyspnoea	3	4.8%	0.6%	0.0%	0.0%	0.0%	359	Shock and anaphylaxis, without CC (WA16Y)
Infusion related reaction: hypotension	3	4.8%	0.9%	0.0%	0.0%	0.0%	359	Shock and anaphylaxis, without CC (WA16Y)
Leukopenia	3	2.4%	0.9%	0.0%	14.2%	0.0%	942	Blood cell disorders without CC (PA48B)
Lymphopenia	3	0.6%	0.6%	0.0%	6.2%	0.0%	942	Blood cell disorders without CC (PA48B)
Neutropenia	3	23.7%	20.0%	7.6%	22.8%	0.0%	3,894	Febrile neutropenia with malignancy (PA 45Z)
Neutropenia	4	13.8%	9.7%	7.6%		0.0%	3,894	Febrile neutropenia with malignancy (PA 45Z)
Pneumonia	3	1.5%	2.1%	0.8%	0.0%	0.0%	1,353	Lobar, atypical or viral pneumonia without CC (DZ 11C)
Rash maculo-papular	3	0.9%	0.3%	0.0%	2.5%	0.0%	500	Rash or other non-specific skin eruption (PA66Z)
Thrombocytopenia	3	6.6%	1.8%	2.5%	11.7%	0.0%	1,847	Thrombocytopenia without CC (SA12F)
Thrombocytopenia	4	2.4%	0.6%	0.0%		0.0%	1,847	Thrombocytopenia without CC (SA12F)

Key: AE, adverse event; Benda, bendamustine; Clb, chlorambucil; G, obinutuzumab; HRG, healthcare resource groups; NHS, National Health Service; R, rituximab
Notes: * No AE data from MabLe

Estimated total adverse event costs by treatment arm are given in **Table 36**.

Table 36. Total adverse event cost by treatment arm

Treatment arm	Total adverse event cost per patient (£)
Obinutuzumab	2,544
Rituximab+chlorambucil	1,694
Chlorambucil	1,036
Bendamustine	1,362
Bendamustine + rituximab*	1,694

Notes: * No AE data yet for MabLe so assumed to be the same as rituximab+chlorambucil based on MabLE abstract which states that safety was similar between the two arms
(Source: Roche Submission, Table B58, pp189)

5.3. Cost-effectiveness results

This section presents Roche's deterministic base case cost-effectiveness results.

Unless otherwise stated, positive incremental cost-effectiveness ratios (ICERs) mean that the intervention is more costly and more effective than the comparator. Negative ICERs are not shown but instead it is stated whether the intervention "dominates" the comparator (is less costly and more effective) or is "dominated" by the comparator (is more costly and less effective).

The deterministic base case results are presented **Table 38**, **Table 39** and **Table 37**.

5.3.1. Life years and QALYs

According to the Roche base case, obinutuzumab with chlorambucil has the largest life year gain of 6.68 undiscounted life years and chlorambucil the least with 5.24 undiscounted life years gained. In all arms the most life years are accrued in the progressed disease state, ranging from 3.86 (obinutuzumab+chlorambucil) to 4.25 years (chlorambucil). However, when these life years are converted into discounted QALYs these numbers are greatly reduced and, in the case of the obinutuzumab arm, more QALYs accrue in the PFS health state than in PD. In PFS, the obinutuzumab arm accrues the most QALYs of all the arms, with 2.18, compared to 1.70 for the next most effective PFS arm: rituximab with bendamustine. The chlorambucil arm gains the least QALYs in PFS with 0.77 gained. However, due to the nature of how post progression is modelled, chlorambucil has the largest QALY gains in PD (2.15), with the obinutuzumab arm gaining the least number of

QALYs (1.84). Overall, obinutuzumab has the largest QALY gain of 4.03 and chlorambucil the smallest QALY gain, of 2.92.

5.3.2. Costs

Costs in PFS are split into drug acquisition, drug administration, supportive care and adverse events. The obinutuzumab arm has the largest total cost in PFS, at £30,577. This is mostly because the cost of a course of obinutuzumab+chlorambucil is greater than for any other treatment. Obinutuzumab+chlorambucil also has the highest costs for adverse events, as it has the highest incidences of any arm. As chlorambucil has the least time in PFS and the lowest drug acquisition costs, it has the lowest costs of all the arms in PFS £3,061. Costs in PD are based on weekly supportive care and on a second line dose of chlorambucil. The total costs in PD are similar between arms (£4,311 obinutuzumab+chlorambucil to £4,959 chlorambucil) because this is driven by time spent in PD, and given that life years differ little between the arms (3.61-3.10).

5.3.3. ICERs

Three sets of ICERs are compared in the Roche results: all comparator arms versus chlorambucil; obinutuzumab+chlorambucil versus all other arms; and the simultaneous ICERs of treatments on the efficiency frontier. As obinutuzumab+chlorambucil is the treatment of interest to this appraisal, we focus on the latter two sets of ICERs.

When the obinutuzumab+chlorambucil arm is compared to all the arms independently, Roche's base case ICERs are all approx. between £20,000 and £30,000 per QALY. When the treatments are compared simultaneously, only three lie on the cost-effectiveness frontier. Both arms containing rituximab are extended dominated by the obinutuzumab+chlorambucil arm, as they cost more per QALY gained compared to the chlorambucil arm than obinutuzumab+chlorambucil. When compared to the bendamustine only arm, the obinutuzumab+chlorambucil arm has an ICER of £26,463 per QALYs gained.

Table 37. Shading used to denote cost-effectiveness of obinutuzumab

White background	Cost-effective (positive INHB) at WTP £20,000 and £30,000 per QALY
Grey background	ICER between £20,000 and £30,000 per QALY (positive INHB for one WTP, negative INHB for the other)
Black background	Neither cost-effective at WTP £30,000 nor £20,000 per QALY (negative INHB)

Table 38. Summary base case results from Roche

	ObClb	RBenda	RClb	Benda	Clb
Life years (undiscounted)[1]					
PFS	2.83	2.25	1.68	1.60	1.00
PD	3.86	4.00	4.15	4.18	4.25
Total	**6.68**	**6.24**	**5.82**	**5.77**	**5.24**
QALYs (discounted)					
PFS	2.18	1.70	1.28	1.23	0.77
PD	1.85	1.95	2.05	2.07	2.15
Total	**4.03**	**3.64**	**3.33**	**3.30**	**2.92**
Costs *(discounted)*					
Technology cost	£23,157	£15,241	£9,545	£4,745	£286
Administration cost	£3,736	£4,835	£3,314	£3,991	£1,320
Supportive care costs (PFS)	£1,140	£911	£693	£663	£420
Adverse events	£2,544	£1,694	£1,694	£1,362	£1,036
Cost in progressed disease	£4,311	£4,531	£4,756	£4,796	£4,959
Total	**£34,888**	**£27,213**	**£20,002**	**£15,557**	**£8,020**
ICERs					
ICER vs. chlorambucil	**£24,256**	**£26,585**	**£29,369**	**£19,983**	**-**
ICER vs. ObClb	**-**	**£19,898**	**£21,275**	**£26,463**	**£24,256**
Simultaneous ICERs	**£26,463**	**Extended dominated**	**Extended dominated**	**£19,983**	**-**
Net health benefit at £20,000 per QALY[1]	2.28	2.28	2.33	2.52	2.52
Net health benefit at £30,000 per QALY[1]	2.87	2.74	2.66	2.78	2.65

Key: Benda: bendamustine; Clb: chlorambucil; ICER: incremental cost-effectiveness ratio; Ob: obinutuzumab; PD: progressed disease; PFS: progression free survival; R: rituximab **Notes:** [1]. Calculated by us using Roche's model. Figures may not add up due to rounding. Extended dominated refers to arms where a more effective arm has a lower ICER (the cost per QALY is smaller).

Table 39. Incremental results, vs. obinutuzumab+chlorambucil

	RBenda	RClb	Benda	Clb
Life years (undiscounted)[1]				
PFS	-0.58	-1.15	-1.23	-1.83
PD	0.14	0.29	0.31	0.39
Total	-0.44	-0.86	-0.91	-1.44
QALYs (discounted)				
PFS	-0.49	-0.91	-0.96	-1.41
PD	0.10	0.21	0.23	0.30
Total	**-0.39**	**-0.70**	**-0.73**	**-1.11**
Costs *(discounted)*				
Technology cost	-£7,916	-£13,611	-£18,412	-£22,871
Administration cost	£1,099	-£422	£255	-£2,416
Supportive care costs (PFS)	-£229	-£447	-£476	-£720
Adverse events	-£850	-£850	-£1,182	-£1,509
Cost in progressed disease	£220	£445	£484	£648
Total	**-£7,676**	**-£14,886**	**-£19,331**	**-£26,868**
ICERs				
ICER vs. ObClb	**£19,898**	**£21,275**	**£26,463**	**£24,256**

Key: Benda: bendamustine; Clb: chlorambucil; ICER: incremental cost-effectiveness ratio; Ob: obinutuzumab; PD: progressed disease; PFS: progression free survival; R: rituximab
Notes: Figures may not add up due to rounding. Extended dominated refers to arms where a more effective arm has a lower ICER (the cost per QALY is smaller).

5.3.4. Sensitivity analyses

Roche conducted deterministic sensitivity analyses on several parameters, as outlined in Table B72, Section 7.6.7 pp199-201 of the Roche submission, and these are reproduced here in

Table 40 (scenario analyses on PFS and OS) and **Table 41** p125 (sensitivity analyses). They also included a probabilistic sensitivity analysis (p136).

Scenario analyses

Roche conducted scenario analyses on the transition probabilities in PFS and PD. The results are presented in **Table 40** (p132). We have included the results of the log-normal distribution for PFS, which was absent in the original submission report, but was present in the model. The results are similar when either Kaplan-Meier data or fully fitted distributions are used for PFS. When post-progression is modelled without an age-adjustment, the ICERs are slightly reduced compared to the base case.

The three distributions applied to PFS that have the most impact on cost-effectiveness are the Gompertz, log-logistic and log-normal distributions. However, these distributions were shown to either have a poor fit to the data in Roche's submission (Gompertz and log-normal) or were clinically implausible (log-logistic) and therefore unlikely to be true representations of PFS.

Table 40. Scenario analyses by Roche

Variable	Base Case Value (BCV)	Sensitivity Analysis Value	Clb	Benda	RClb	RBenda	ObClb
Roche base case			**-**	**£19,983**	**Extended dominated**	**Extended dominated**	**£26,463 (vs. Benda)**
Transition Probabilities: PFS	KM PFS with Gamma tail (in all arms)	KM PFS with Weibull tail (in all arms)	-	£19,755 (vs. Clb)	Extended Dominated	Extended Dominated	£25,745 (vs. Benda)
		KM PFS with Gompertz tail (in all arms)	-	£20,375 (vs. Clb)	Extended Dominated	Extended Dominated	£30,828 (vs. Benda)
		KM PFS with Log-logistic tail (in all arms)	-	Extended Dominated	Extended Dominated	Extended Dominated	£18,402 (vs. Clb)
		KM PFS with Log-normal tail (in all arms)	-	Extended Dominated	Extended Dominated	Extended Dominated	£16,404 (vs. Clb)
		PFS Gamma distribution (in all arms)	-	£19,751 (vs. Clb)	Extended Dominated	Extended Dominated	£27,567 (vs. Benda)
		PFS Weibull distribution (in all arms)	-	£19,463 (vs. Clb)	Extended Dominated	Extended Dominated	£26,751 (vs Benda)
		PFS Gompertz distribution (in all arms)	-	£20,303 (vs. Clb)	Extended Dominated	Extended Dominated	£31,872 (vs. Benda)
		PFS Log-logistic distribution (in all arms)	-	Extended Dominated	Extended Dominated	Extended Dominated	£18,907 (vs. Clb)
		PFS Log-normal distribution (in all arms)	-	Extended Dominated	Extended Dominated	Extended Dominated	£15,875 (vs. Clb)
Transition Probabilities: OS	Age adjusted post-progression death rate from CLL5 (all arms)	Non-age adjusted post-progression death rate from CLL5 (all arms)	-	£18,464 (vs. Clb)	Extended Dominated	Extended Dominated	£24,460 (vs. Benda)

Key: Benda: bendamustine; Clb: chlorambucil; ICER: incremental cost-effectiveness ratio; Ob: obinutuzumab; OS: overall survival; PFS: progression free survival; R: rituximab
Notes: Extended dominated refers to arms where a more effective arm has a lower ICER (the cost per QALY is smaller). (Source Roche Submission, Section 7.7.7, 199-201)

One-way sensitivity analyses

Roche included one-way sensitivity analyses on transition probabilities in PFS and OS, PFS HR for bendamustine and rituximab with bendamustine arms versus obinutuzumab with

chlorambucil, treatment dose and duration, utility in PFS and PD, and post progression costs (using alternative drug regimens), adverse event costs, time horizon and discounting.

The most important parameters appear to be those influencing PFS, as this is where the benefits of the obinutuzumab arm accrue.

Table 41. One-way sensitivity analyses reported by Roche

Variable	Base Case Value (BCV)	Sensitivity Analysis Value	Clb	Benda	RClb	RBenda	ObClb
Roche base case			-	**£19,983**	**Extended dominated**	**Extended dominated**	**£26,463 (vs. Benda)**
Transition Probabilities: OS	Age adjusted post-progression (PP) death rate from CLL5 (all arms)	BCV x 50% (all arms)	-	£22,854 (vs. Clb)	Extended Dominated	Extended Dominated	£33,133 (vs. Benda)
		BCV x 75% (all arms)	-	£20,979 (vs. Clb)	Extended Dominated	Extended Dominated	£28,645 (vs. Benda)
		BCV x 125% (all arms)	-	£19,383 (vs. Clb)	Extended Dominated	Extended Dominated	£25,221 (vs. Benda)
		BCV x 150% (all arms)	-	£18,985 (vs. Clb)	Extended Dominated	Extended Dominated	£24,406 (vs. Benda)
		BCV x 90% (Clb only)	-	£18,985 (vs. Clb)	Extended Dominated	Extended Dominated	£26,463 (vs. Benda)
PFS HR: GClb vs. Benda	0.40	0.54 (FE model without age adjustment)	-	£13,308 (vs. Clb)	Extended Dominated	Extended Dominated	£35,684 (vs. Benda)
		0.55 (RE model without age adjustment)	-	£13,019 (vs. Clb)	Extended Dominated	Extended Dominated	£36,527 (vs. Benda)
PFS HR: GClb vs. RBenda	0.68	0.82 (BCV x 1.2)	-	£19,983 (vs. Clb)	Extended Dominated	Extended Dominated	£32,145 (vs. Benda)

Variable	Base Case Value (BCV)	Sensitivity Analysis Value	Clb	Benda	RClb	RBenda	ObClb
		0.55 (BCV x 0.8)	-	£19,983 (vs. Clb)	Extended Dominated	Extended Dominated	£26,463 (vs. Benda)
Treatment dose	Actual	Planned	-	£21,733 (vs. Clb)	Extended Dominated	Extended Dominated	£25,590 (vs. Benda)
Treatment duration	Actual	According to label	-	£22,964 (vs. Clb)	Extended Dominated	Extended Dominated	£29,704 (vs. RBenda)
Utility: PFS off treatment	0.82	0.92 (BCV +0.1)	-	£17,417 (vs. Clb)	Extended Dominated	Extended Dominated	£22,148 (vs. Benda)
		0.72 (BCV -0.1)	-	£23,434 (vs. Clb)	Extended Dominated	Extended Dominated	£32,865 (vs. Benda)
Utility: PD	0.60	0.70 (BCV +0.1)	-	£20,720 (vs. Clb)	Extended Dominated	Extended Dominated	£27,990 (vs. Benda)
		0.50 (BCV -0.1)	-	£19,355 (vs. Clb)	Extended Dominated	Extended Dominated	£25,210 (vs. Benda)
PP treatment costs (all arms)	£369 (Clb in all arms)	£5,810 (Benda)	-	£20,014 (vs. Clb)	Extended Dominated	Extended Dominated	£26,527 (vs. Benda)
		£25,226 (ObClb)	-	£20,014 (vs. Clb)	Extended Dominated	Extended Dominated	£26,527 (vs. Benda)

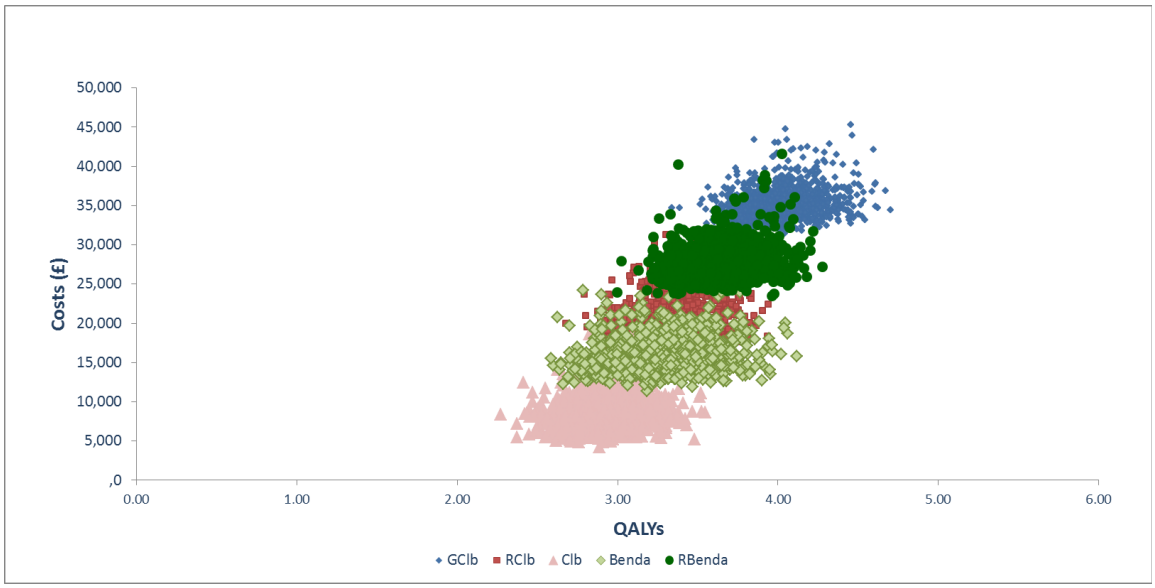
Key: BCV: base case value; Benda: bendamustine; Clb: chlorambucil; FE: fixed effects; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; Ob: obinutuzumab; OS: overall survival; PD: progressed disease; PFS: progression free survival; PP: post-progression R: rituximab; RE: random effects
Notes: Extended dominated refers to arms where a more effective arm has a lower ICER (the cost per QALY is smaller).
(Source: Roche Submission, Table B72, Section 7.7.7, pp199-201)

Probabilistic sensitivity analysis

Probabilistic results are given in **Figure 28** and the cost-effectiveness acceptability curves are given in **Figure 29** copied from the Roche submission.

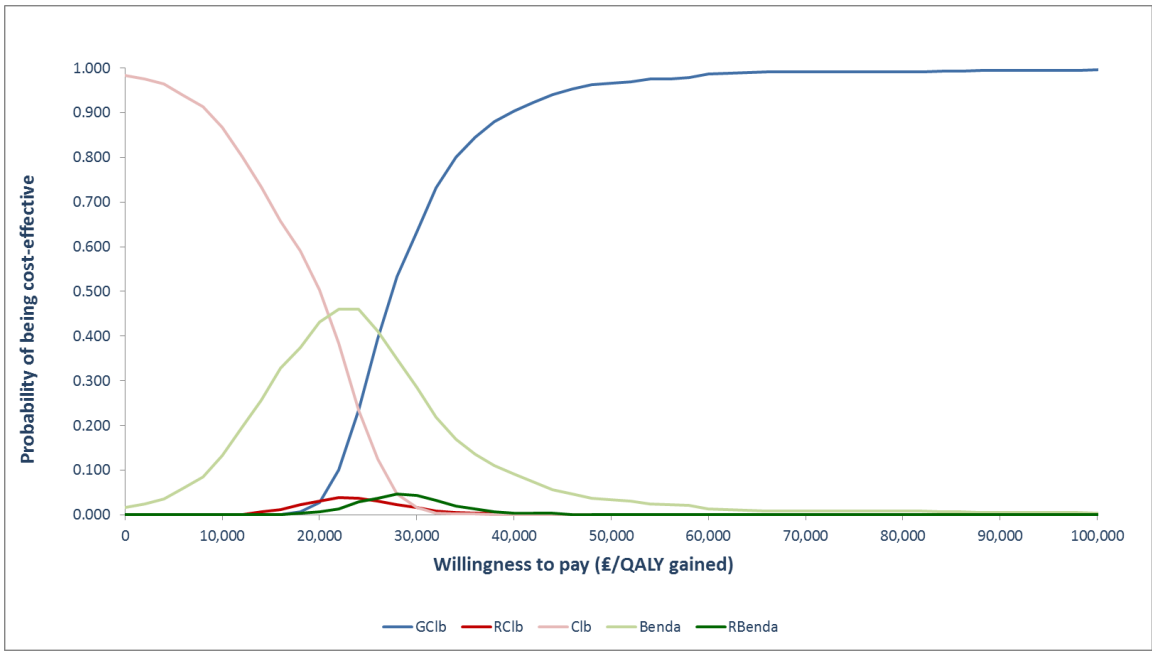
The cost-effectiveness acceptability curves (CEAC) show that at a willingness to pay of £30,000 per QALY, obinutuzumab+chlorambucil has highest probability of being cost-effective with a probability of 63.4%. Bendamustine has the next highest probability of being cost-effective, with a probability of 28.5%. However, when examining the probabilities when the WTP lies between £20,000 and £30,000 per QALY, we see that the strategy with the highest probability of being the most cost-effective varies across the range and the probabilities are all less than 50%.

Figure 28. PSA scatterplot from Roche



Key: Benda: bendamustine; Clb: chlorambucil; G: obinutuzumab; R: rituximab; QALY: quality adjusted life year
(Source: Roche Submission, Section 7.7.8, Figure B45, p202)

Figure 29. Cost-effectiveness acceptability curves, Roche submission



Key: Benda: bendamustine; Clb: chlorambucil; G: obinutuzumab; R: rituximab; QALY: quality adjusted life year
(Source: Roche submission, Section 7.7.8, Figure B46, pp202)

5.3.5. Model validation and face validity check

Roche report that modelling methodology, assumptions and clinical inputs were validated by an advisory board and an independent health economist, though details of these acknowledgements are not given. Roche states that an external consultancy validated the model functionality.

The approaches to PFS and OS modelling were reportedly validated by existing data and a health economist, and CLL clinicians agreed that the extrapolations appeared reasonable.

An external agency conducted an internal and external quality check.

We consider the sources of these validity checks appropriate.

5.4. Critique of manufacturer's submitted evidence

Overall, we consider the economic evaluation from Roche to be of high quality. The economic model is generally appropriate, and has only one wiring error, of moderate importance.

5.4.1. Checking wiring of Roche's model

We checked the wiring of Roche's model in the following three ways:

- We built an independent, simplified version of Roche's model. This model did not use discrete model cycles. Instead, QALYs and costs were estimated by applying unit costs and utilities to the undiscounted life year estimates for each treatment in each arm in Roche's model, and then applying discounting factors to the mean time in each particular health state. The results of the simplified model (e.g. total discounted costs and QALYs, ICERs) were similar to those from Roche's model. For example, obinutuzumab+chlorambucil versus rituximab +chlorambucil has an ICER of £20,463 per QALY gained in our simplified model and £21,275 per QALY gained in Roche's model. This provides strong evidence that there are no serious wiring errors in Roche's model.
- We checked the key formulae in Roche's model.
- We checked that the model outputs were correct when input parameters were set to extreme values.

5.4.2. NICE reference case checklist

Roche mostly completed their model to the standards of the NICE reference case[2] (see **Table 42**); the only specific concern we note is the sourcing of the utility data used in the model. This is discussed in greater detail in Section 5.4.9 (p145). We also believe there may be differences in the clinical community over what comparators clinicians routinely use.

Table 42. NICE reference case checklist for Roche submission

NICE reference case[2] requirement		Critical appraisal	Reviewer comment
Defining the decision problem	The scope developed by the Institute	Y	
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	Y	Roche included all comparators in NICE Scope.
Perspective on costs	NHS and PSS	Y	
Perspective on outcomes	All health effects on individuals	Y	
Type of economic evaluation	Cost-effectiveness analysis	Y	
Synthesis of evidence on outcomes	Based on a systematic review	Y	
Measure of health benefits	QALYs	Y	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	N	HRQL not reported by patients. Heath state vignettes used

Source of preference data for valuation of changes in HRQL	Representative sample of the public	Y	100 members of the general UK public
Discount rate	3.5% p.a. for costs and health effects	Y	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y	
Key: Y – Yes; N – No; U – Unclear; P – Partially; HRQL: health-related quality of life			

5.4.3. Critical appraisal frameworks

When assessing Roche's submission using the Drummond et al. checklist in **Table 43**, we see that the model appears to be well-reported and conducted.

Table 43. Critical appraisal checklist from Drummond and colleagues (1997)

Item	Critical appraisal	Reviewer comment
Is there a well-defined question?	Y	
Is there a clear description of alternatives (i.e., who did what to whom, where and how often)?	Y	
Has the correct patient group / population of interest been clearly stated?	Y	
Is the correct comparator used?	Y	
Is the study type reasonable?	Y	
Is the perspective of the analysis clearly stated?	Y	
Is the perspective employed appropriate?	Y	
Is effectiveness of the intervention established?	P	Phase 3 trial available for comparison of three arms, but indirect methods for comparison with two treatments (see Section 4.4 for details)
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	Y	
Are the costs and consequences consistent with the perspective employed?	Y	
Is differential timing considered?	Y	Discount rates for costs and QALYs 3.5% in line with NICE reference case
Is incremental analysis performed?	Y	
Is sensitivity analysis undertaken and presented clearly?	Y	
Key: Y – Yes; N – No; U – Unclear; P – Partially		

5.4.4. Model structure

The model structure chosen by Roche is a straightforward 3 state structure of progression free, post progression and dead state, which we believe is appropriate, and has been used in numerous cancer HTAs. The structure also includes both on and off treatment states within progression free survival, which we believe appropriate.

This model structure is simpler than the model submitted in the previous CLL STA, TA216, of bendamustine versus chlorambucil, which included additional health states, such as stable disease, complete and partial response states, and second line treatment with fludarabine. 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.

The cycle length of a week seems appropriate considering the treatment administration.

5.4.5. Population

Roche base their economic evaluation mostly on data from the trial CLL11. Population selection in CLL11 was based on Cumulative Illness Rating Score (CIRS) and creatinine clearance.[4] This will certainly identify a less fit group of patients. However, we understand that this is not a generally accepted way of determining ineligibility for fludarabine and is not used widely in UK clinical practice. Nonetheless, we consider the patients in CLL11 to be sufficiently similar to those in clinical practice.

Next, modelled post progression survival is based on data from the trial CLL5, whose population could be treated with fludarabine, which is not appropriate. Furthermore, study CLL5 was conducted in Germany and data may not be directly applicable to a UK population.

Roche have attempted to allow for the younger population of the CLL5 trial by adjusting the mortality rate in PD by regression with age as a covariate. We note that, age is then assumed to account for any impact of comorbidities as well, which according to our clinical expert, seems appropriate. Furthermore, we note that not adjusting for age at progression made little impact on the results.

We note that age at progression and comorbidities were not found to affect mortality significantly in CLL5, but that the Del 17p mutation in individuals was. No adjustment was made for the Del 17p mutation as Roche believe the percentage of patients with the

mutation in CLL11 would be broadly similar. This approach seems appropriate (see Section 5.3.4, p131).

5.4.6. Intervention and comparators

The four comparator treatments are as given in the NICE Scope. We find that the estimated frequency of use of the comparators amongst patients unsuited to fludarabine in the NHS, varies substantially according to the source of information (**Table 44**).

Table 44. Estimated use of comparators in NHS for patients unsuited to fludarabine

Comparator	Dr C Rudin[a] (our clinical expert)	Roche[b]	Other sources
Chlorambucil	5% patients	Chlorambucil is most frequent comparator. Chlorambucil +- Rituximab 36% of all 1st-line CLL treatment	Many patients (clinicians at Scoping workshop)
Rituximab+chlorambucil	>90 % patients		Many patients (commentators to this appraisal)
Bendamustine	0% patients (due to toxicities)	11% of all 1st-line CLL treatment	50% patients (clinicians at Scoping workshop)
Bendamustine + rituximab	<5% patients		Widespread use (one commentator to this appraisal)

[a] consultant haematologist, Royal Devon & Exeter Hospital
[b] Roche report p29. Source cited as IMS. Roche UK CLL Enhanced Tumour Study – Q3 2013. We understand that approx.. 50% of 1st-line CLL patients are not eligible for fludarabine.

We note that rituximab+chlorambucil was assessed and not recommended in NICE TA174.[1] We repeat the following advice from the NICE Methods Guide (2013){National Institute for Health and Care Excellence, 2013 #9: “The committee will normally be guided by established practice in the NHS when identifying the appropriate comparator”. “When the assessment suggests that an established practice may not be considered a good use of NHS resources relative to another available treatment, the Committee will decide whether to include it as an appropriate comparator in the appraisal, after reviewing an incremental cost–utility analysis. The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance”. We therefore leave it up to the NICE Appraisal Committee to decide whether rituximab+chlorambucil is a valid comparator treatment in the current appraisal.

By contrast, bendamustine was recommended by NICE in TA216 for 1st-line CLL patients unsuited to fludarabine.{NICE, 2011 #10}

Bendamustine+rituximab has not been assessed by NICE.

We note that ofatumumab is currently being assessed for exactly the same patient population. The date of the first NICE appraisal committee meeting is 7th October 2014. However, this is not one of the comparators in the Final Scope.

5.4.7. Perspective, time horizon and discounting

Roche state (Roche submission, Section 7.2.6, p135) that a NHS/PSS perspective for costs is adopted in line with the NICE reference case. This is appropriate.

We are satisfied that a time horizon of 20 years is sufficient to account for all costs and benefits relevant to the decision problem.

Discounting is applied at 3.5% per annum as per the NICE reference case.[2] We note that the discount factor is calculated on the basis of integer years from commencing treatment rather than weeks, which we feel would have been more appropriate given the cycle length and technically simple to implement. This however did not significantly impact on cost-effectiveness so we are satisfied that discounting is appropriate.

5.4.8. Treatment effectiveness and extrapolation

Progression-free survival

Roche use Kaplan-Meier estimates from CLL11 trials with Gamma tails to model progression free survival (Section 5.2.5, p106). The proportional hazards assumption between chlorambucil, obinutuzumab+chlorambucil, rituximab+chlorambucil in CLL11 generally looks to hold and is not a requirement in Roche's base case.

However, as hazard ratios are applied in the case of the bendamustine and rituximab with bendamustine arms, there is an inconsistency in that the other arms are modelled independently from obinutuzumab+chlorambucil. We conducted a sensitivity analysis, setting all arms to be modelled such that the appropriate PFS HR was applied to the PFS of the obinutuzumab arm and found very little change in the ICERs from the base case. As such, we consider the modelling in the base case to be acceptable, especially given the current lack of data to inform the bendamustine and rituximab with bendamustine arms.

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). However, we understand that PFS data should be available from October 2014.

As explained in 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).

Superseded

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).

See Erratum

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 (▇▇▇▇), rituximab+chlorambucil(▇▇▇▇) and chlorambucil (▇▇▇▇) 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 (▇▇▇▇). 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 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.

Superseded

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.

See Erratum

[redacted] 30 [redacted]

[redacted]

5.4.9. Health related quality of life

As stated in Section 5.2.6 (p110), the EORTC QLQC30 questionnaire was used in the RCT of obinutuzumab versus chlorambucil. Roche did not perform a mapping from this instrument to the EQ-5D because they claim that no validated mapping function exists. We disagree. The HERC database of mapping functions[73] contains several functions, e.g. Crott & Briggs (2010), Jang et al. (2010).

In our clarification questions to Roche, we asked them why they had not performed a mapping. They replied that they identified no mapping functions. They further said that they were unable to conduct a mapping given the time available to process our questions. They said further that if the NICE Committee consider the mapping function by Kim, Jo, Kim and Ahn (2012)[74] to be preferable to existing utility values, then they would potentially be able to provide this information in response to consultation.

Health related quality of life literature

The search strategy uses a variety of synonyms to ensure an appropriate balance of sensitivity and specificity. The lack of the UK English spelling for “leukemia” is a weakness. However, the searches were re-run by the ERG information specialist with the UK English spelling and no additional studies were retrieved, i.e. the number of hits when searching with and without the UK English spelling of “leukemia” is the same. The term “lymphocytic” is spelt “lymphocitic” in the MEDLINE and EMBASE search strategies. This was raised as a clarification question and the manufacturer responded by sending a revised appendix with corrected spelling.

The translations of the ProQuest (i.e. MEDLINE and EMBASE) search strategies for NHS EED and EconLit are not equivalent to the ProQuest searches but they do contain the same concepts and are appropriate for the topic.

As stated in Section 5.2.6 (p110), 9 studies were included according to the inclusion and exclusion criteria, see **Table 28** (p112). Roche state that two original references (Hancock et al. (2002)[9] and Beusterien (2010)[8]) in **Table 28** provide utilities that are arguably suitable for the model since they give values for both the PFS and PD health states. We agree, noting that the other studies (**Table 28**):

- Tolley (2013)[75] relates to 2nd and 3rd-line treatment of CLL,
- Pashos et al (2013)[76] gives only the utility for males and females separately,
- Oeyen et al (2013)[77] relates to critically ill patients only and does not provide utilities,
- Grunberg (2002)[78] evaluated the health-related quality of life of emesis,

- Weeks (1991)[79] estimated utilities from a small sample (10) of oncologists, line of treatment not given, not split PFS / PD for 1st-line treatment.

Roche then give a list of reasons why Hancock et al. (2002)[9] and Beusterien (2010)[8] offer poor evidence to inform the choice of utilities for the current cost-effectiveness analysis (Section 5.2.6, p110). We agree with all their reasons.

Health related quality of life used in previous NICE TAs

In NICE TA174 of rituximab for 1st-line CLL, the utilities in the manufacturer submission were taken from the HTA report, Hancock et al. (2002),[9] that assessed the cost-effectiveness fludarabine as a first-line treatment for CLL.[1] A utility of 0.80 was attached to PFS and 0.60 to PD. Estimates of utility were not preference based, and were estimated by the authors of the HTA report from condition-specific HRQL data.

In NICE TA216 of bendamustine versus chlorambucil for 1st-line CLL in patients unsuited to fludarabine-based treatments,[43] health-related quality of life data, via the EORTC-QLQC30, was collected in the bendamustine RCT. It was argued that it was only possible to use this for short term follow up. Napp, the manufacturer of bendamustine mapped the EORTC-QLQC30 data to the EQ-5D, using data from patients with oesophageal cancer. In addition to this, utilities were also calculated based on data from Beusterien et al (2010),[8] a study found and dismissed by Roche.

Health related quality of life in Roche's model

We agree with Roche that the literature gives very little relevant information for the choice of utilities for Roche's model. Therefore, we believe that Roche's study on utilities for patients with CLL is valuable. However, we note that the data from this study is considered to be low quality because:

- Health state vignettes are used. It is far preferable to elicit quality of life using a generic questionnaire, such as the EQ-5D.[2]
- Utilities were not elicited from patients, which is the preferred method.[2]

In the absence of better quality of life data, we agree that Roche's study should information the utility values.

We disagree with Roche with respect to two of the utility values:

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

First, we are satisfied that patients have a utility of 0.55 during the first cycle of obinutuzumab treatment (**Table 32**, p120). However, in their model, Roche then assume a utility whilst patients are taking cycles 2 to 6 of obinutuzumab of 0.82, corresponding to PFS off treatment. Instead, we believe that the value of 0.67 should be used, corresponding to PFS on IV treatment. Technically, this is achieved by including the factor u_pfs_treat_iv rather than u_pfs in cells AN13:1313 in worksheet "G-Clb Stage 2". In this case:

- ICER for obinutuzumab+chlorambucil versus rituximab + bendamustine increases from £20,000 to £23,000 per QALY.
- obinutuzumab+chlorambucil versus rituximab+chlorambucil increases from £21,000 to £23,000 per QALY.
- obinutuzumab+chlorambucil versus bendamustine increases from £26,000 to £28,000 per QALY.
- obinutuzumab+chlorambucil versus chlorambucil increases from £24,000 to £25,000 per QALY.

This constitutes Item 1 of the PenTAG base case (**Table 45**, p156).

Second, we note that Roche's utility of 0.82 corresponding to PFS when off treatment is higher than that of members of the UK general public at the appropriate age. We estimate the mean age of patients half way through PFS off treatment in the obinutuzumab arm as 73.3 years, which equals the average of the assumed starting age of 71.68 plus 0.5 years of treatment and the age at progression, 74.51. The UK male general population mean utility at this age is 0.77, and female 0.75, giving an average of 0.76. These values are calculated from the regression equations:[80]

Utility males = 0.9508566 - 0.0002587 x age - 0.0000332 x age2 + 0.0212126

Utility females = 0.9508566 - 0.0002587 x age - 0.0000332 x age2

It is likely that the true value for the utility in PFS after treatment will be clearly lower than that of the general public at the same age given that patients have CLL and have comorbidities. However, we know of no reliable data to give a more accurate figure. In the absence of such data, we can say that the utility of 0.76 should be seen as an upper bound. Using this value (in cell F61, worksheet "Model Inputs"):

- ICER for obinutuzumab+chlorambucil versus rituximab + bendamustine increases from £20,000 to >£23,000 per QALY.
- obinutuzumab+chlorambucil versus rituximab+chlorambucil increases from £21,000 to >£24,000 per QALY.

- obinutuzumab+chlorambucil versus bendamustine increases from £26,000 to >£30,000 per QALY.
- obinutuzumab+chlorambucil versus chlorambucil increases from £24,000 to >£27,000 per QALY.

In all cases, the ICERs increase because patients are in the PFS off treatment health state the longest in the obinutuzumab arm.

This constitutes Item 2 of the PenTAG base case (**Table 45**, p156).

With our two changes combined:

- ICER for obinutuzumab+chlorambucil versus rituximab + bendamustine increases from £20,000 to >£25,000 per QALY.
- obinutuzumab+chlorambucil versus rituximab+chlorambucil increases from £21,000 to >£25,000 per QALY.
- obinutuzumab+chlorambucil versus bendamustine increases from £26,000 to >£31,000 per QALY.
- obinutuzumab+chlorambucil versus chlorambucil increases from £24,000 to >£28,000 per QALY.

Disutilities due to adverse events are not explicitly taken into account. Instead, difference in utilities whilst on drug treatment are purely a function of inconvenience due to hospital visits. Our clinical advisor suggests that, of all the drugs in this HTA, health-related quality-of-life is lowest whilst on bendamustine. This is due to the incidence of fatigue and nausea & vomiting. In the absence of data to quantify this, as a sensitivity analysis, we suggest a further disutility of 0.05 whilst patients are taking bendamustine or bendamustine + rituximab. In this case the ICERs between obinutuzumab+chlorambucil versus bendamustine and obinutuzumab+chlorambucil versus bendamustine+rituximab decrease only incrementally. Therefore, we pursue this matter no further.

5.4.10. Resource use and costs

Resource use systematic review

The search strategy uses a variety of synonyms to ensure an appropriate balance of sensitivity and specificity. The lack of the UK English spelling for “leukemia” is a weakness. However, the searches were re-run by the ERG information specialist with the UK English spelling and no additional studies were retrieved, i.e. the number of hits when searching with and without the UK English spelling of “leukemia” is the same.

The term “lymphocytic” is spelt “lymphocitic” in the MEDLINE and EMBASE search strategies. This was raised as a clarification question and the manufacturer responded by sending a revised appendix with a note that the spelling had been corrected. However, the spelling error remains in the revised appendix. The searches were re-run by the ERG information specialist with the correct spelling and no additional studies were retrieved, i.e. the number of hits when searching with and without the correct spelling of “lymphocytic” is the same.

The translations of the ProQuest (i.e. MEDLINE and EMBASE) search strategies for NHS EED and EconLit are not equivalent to the ProQuest searches but they do contain the same concepts and are appropriate for the topic.

The manufacturer’s systematic review of resource use and costs did not identify any studies relevant to the decision problem.

Drug acquisition

We disagree with one aspect of Roche’s modelling of drug acquisition costs, concerning the estimated mean treatment compliance in the bendamustine+rituximab arm. Roche assume a dose intensity of 100% for both drugs. Ideally, we would take the actual drug dose intensity from the MaBLe trial. But given that this data is not yet available, we consider that the value for bendamustine should be equal to that for bendamustine monotherapy, i.e. 4.9 out of 6 cycles, at 90%, and the value for rituximab should be equal to that for rituximab in the rituximab+chlorambucil arm of CLL11, i.e. 98.8% of patients take 1st dose, and mean of 4.59 further doses.

In this case, the ICER for obinutuzumab+chlorambucil versus bendamustine+rituximab increases from £20,000 to £25,000 per QALY.

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

Technically, this is achieved by changing the parameters in Roche’s model in worksheet “Model Inputs”, cell F116 from 100% to 93% ((0.988 + 4.59)/6), cell F118 from 100% to 82%, and F122 from 100% to 90%.

We are satisfied with all other aspects of Roche’s estimation of drug acquisition costs.

The acquisition cost of obinutuzumab, at £3,312 per 1000 mg vial is provided by Roche, and we understand that this has recently been agreed by the Dept. of Health.

To calculate body surface area, Roche use the Mosteller Formula (p121). Alternatively, the most widely used formula is the Du Bois formula:

Body surface area = 0.007184 W0.425 H0.725

In this case, the estimated body surface area is 1.82m^2, which is sufficiently close to Roche's value of 1.85m2 that we pursue this no further.

We are satisfied that it is appropriate to use the body weights and heights from patients in the CLL11 trial to calculate drug doses. Our clinical expert is satisfied with the assumption of no vial sharing.

Next, Roche assume that bendamustine is taken for a mean of 4.9 out of a total of 6 cycles at 90% dose intensity. We agree, noting that this was also assumed in TA216 (bendamustine versus chlorambucil).[43]

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.

Drug administration

We disagree with some of Roche's unit costs (**Table 34**, p123):

- Roche say they took the unit cost of administration of the first dose of an IV drug from NHS Reference costs 2012-13 DH HRG SB14Z Deliver complex Chemotherapy.[71] This gave them a value of £514. However, we find a value of £319 from this source (https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013, National schedule of reference costs: the main schedule, cell D1860, sheet "Total – HRGs".
- Roche's value for the administration of subsequent doses of an IV drug is £343, but we find £291, cell D1861, same sheet.
- Roche use a value of £136 for administration of an oral drug, whereas we find the value £162.
- Roche use a value of £268 for first visit with a haematologist per hour, whereas we find £209 using WF01B clinical haematologist, Non-Admitted Face to Face Attendance, First.
- Roche use a value of £106 for subsequent visits with a haematologist per hour, whereas we find £143 using WF01C clinical haematologist, Non-Admitted Face to Face Attendance, follow up.

Nonetheless, we pursue this matter no further, because we find that the ICERs change only incrementally when we use our values.

We agree that patients would visit a haematologist once per drug cycle, for approx. 30 minutes, and we agree with the implementation of the administration costs in the model.

Supportive care costs

Based on clinical advice, we are satisfied with assumptions regarding supportive care used in the model.

Assumptions are based on data from the CLL5 study in which participants received a range of treatments on relapse (typically fludarabine, bendamustine, and chlorambucil), and information from a clinical advisory board which confirmed that treatment on progression could vary widely and in addition to first-line remission may also be influenced by an individual's characteristics. The advisory board also noted that given the initial age and comorbidities of CLL11-type participants, second-line treatment may not be appropriate once an individual progresses, emphasised by the large difference between median TTNT and median PFS. All participants were thus assumed to receive a course of chlorambucil post-progression and this was subject to scenario analyses to address potential uncertainty: crossover to obinutuzumab, post-progression treatment for bendamustine, and no post-progression treatment.

Although we were satisfied with the structure of follow-up costs for the PFS and post-progression states, we did note a discrepancy in that Roche use a value of £106 for subsequent visits with a haematologist per hour, whereas we find £143 using WF01C clinical haematologist, Non-Admitted Face to Face Attendance, follow up.[71] However, we do not pursue this, as the ICER changes incrementally using the value of £143.

Adverse events

Incidence rates of adverse events

We believe that the manufacturer's approach to modelling the costs of adverse events is appropriate, namely that adverse event (AE) costs are estimated for Grade 3, 4 or 5 adverse events occurring in >2% of people. Estimates were based on trial data from any arm of the CLL11 trial or the bendamustine and rituximab+bendamustine arms of the Knauf and MabLe trials respectively.[4, 54, 68]

It was not possible to confirm the proportions used in the model for obinutuzumab+chlorambucil, rituximab+chlorambucil, or chlorambucil alone, as the

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**, p126). 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.

Superseded
See Erratum

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), as follows:

- For anaemia, pneumonia, and thrombocytopenia Roche cite NHS Reference Costs 2012/13 HRG SA03F (haemolytic anaemia without CC), DZ11C (lobar, atypical or viral pneumonia without CC), and SA12F (thrombocytopenia without CC) respectively. However, we note that the HRG code stated in the manufacturer'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[81]
    - Roche use a cost for anaemia of £2,088; however, using the above approach we find a value for SA03F of £753 (NHS Reference Costs 2011/2012, Cell

D1345, sheet “Total – HRGs”). Inflating to 2012/2013 price this value becomes £776. It is possible, given the large discrepancy, that the cost cited by the manufacturer may include other factors; however, as this information is not provided, it is not possible to comment on this further.

  - Roche use a value of £1,353 for pneumonia. We find a value for DZ11C of £861 (NHS Reference Costs 2011/2012, Cell D230, sheet “Total – HRGs”) Inflating to 2012/2013 price gives a value of £888
  - Roche use a value of £1,847 for thrombocytopenia (Grade 3 and 4). We find a value for SA12F of £597 (NHS Reference Costs 2011/2012, Cell D1362, sheet “Total – HRGs”). Inflating to 2012/2013 price gives a value of £616.

- Roche use a value of £3,894 for both neutropenia (Grade 3 and 4) and febrile neutropenia (Grade 3 and 4), whereas we find £5,993 using PA45Z (febrile neutropenia with malignancy) (National Schedule of Reference Costs: The Main Schedule 2012/2013, Cell D1571 sheet “Total – HRGs”).
- Roche use a value of £359 for infusion related reactions (bronchospasm, chills, dyspnoea, hypotension), whereas we find £440 using WA16Y (shock and anaphylaxis, without CC) (National Schedule of Reference Costs: The Main Schedule 2012/2013, Cell D1993 sheet “Total HRGs”).
- Roche use a value of £942 for leukopenia and lymphopenia, whereas we find £989 using PA48B (blood cell disorders without CC) (National Schedule of Reference Costs: The Main Schedule 2012/2013, Cell D1575 sheet “Total – HRGs”).
- Roche use a value of £500 for rash maculo-papular, whereas we find £551 using PA66Z (rash or other non-specific skin eruption) (National Schedule of Reference Costs: The Main Schedule, Cell D1608 sheet “Total – HRGs”).

Superseded
See Erratum

Using our unit costs for treating adverse events, all ICERs increase slightly:

- ICER for obinutuzumab+chlorambucil versus rituximab + bendamustine increases from £20,000 to £21,000 per QALY.
- obinutuzumab+chlorambucil versus rituximab+chlorambucil increases from £21,000 to £22,000 per QALY.
- obinutuzumab+chlorambucil versus bendamustine increases from £26,000 to £27,000 per QALY.
- obinutuzumab+chlorambucil versus chlorambucil increases from £24,000 to £25,000 per QALY.

This constitutes Item 5 of the PenTAG base case (**Table 45**, p156).

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.

Superseded

See Erratum

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**, p156). 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 31** and **Figure 32**). The component results of the PenTAG base case are given in **Table 45** (p156) which is to be compared with the results under Roche's base case (Section 5.3.3, p128).

Superseded

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. However, we understand that this information will become publicly available in October 2014.

See Erratum

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, as our clinical expert believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab+chlorambucil versus chlorambucil is over-estimated in CLL11. The ICER of obinutuzumab+chlorambucil versus chlorambucil of >£29,000 may therefore be an underestimate.

The mean total dose of chlorambucil was far lower in CLL11 compared to the bendamustine RCT: 329 versus 549mg (Section 1.2.2, p19). 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 versus bendamustine in favour of obinutuzumab+chlorambucil . The ICER of obinutuzumab+chlorambucil versus bendamustine of >£46,000 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	(see p146)	23,000	23,000	28,000	25,000
2	Utility PFS off treatment decreased from 0.82 to 0.76	(see p146)	>23,000	>24,000	>30,000	>27,000
3	Mean dose of bendamustine and rituximab in bendamustine+rituximab arm	(see 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	(see p142)	26,000	n/c	n/c	n/c
5	Unit costs of adverse events	(see p 152)	21,000	22,000	27,000	25,000
6	PFS hazard ratio ObinClb vs. Benda from 0.40 to 0.55	(see p 93)	n/c	n/c	37,000	n/c
1+2			>25,000	>25,000	>31,000	>28,000
1+2+5			>26,000	>26,000	>33,000	>29,000
1+2+3+4			>44,000	>25,000	>31,000	>28,000
1+2+3+4+5+6	**PenTAG base case**		**>45,000[2]**	**>26,000[1]**	**>46,000[3]**	**>29,000[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).

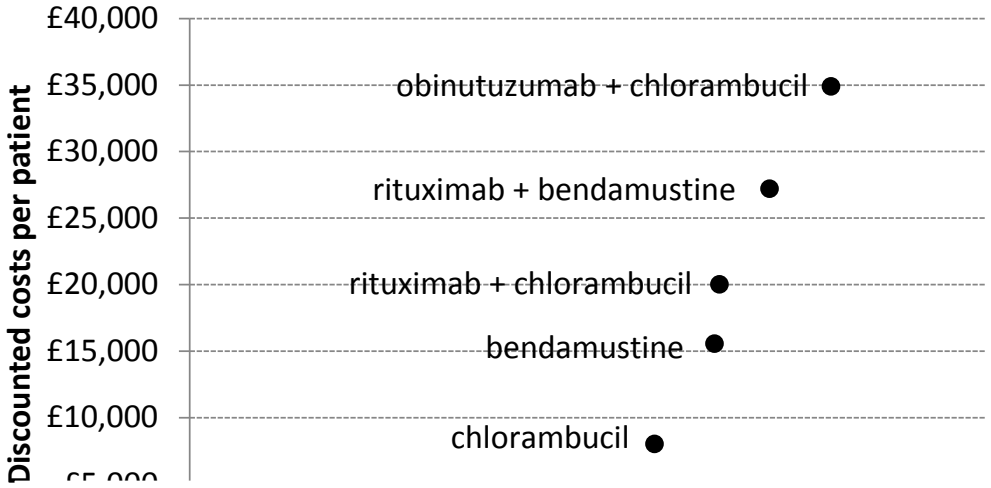
2 Extremely uncertain for reasons in 1 and because PFS hazard ratio between rituximab + bendamustine and rituximab plus chlorambucil is currently unavailable.

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.

Superseded
See Erratum

Figure 31. Roche base case cost-effectiveness plane



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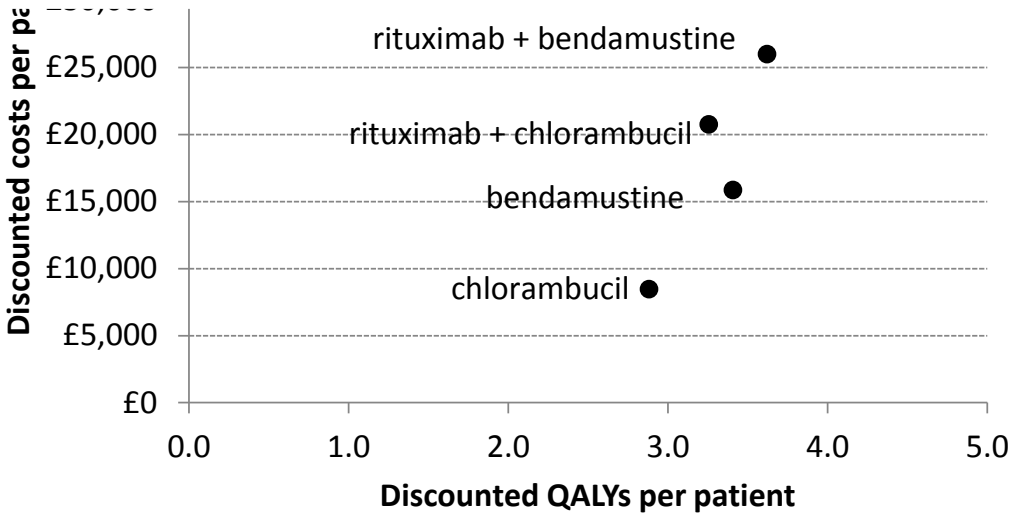

Table 46. Life years, QALYs, costs and net health benefit in PenTAG base case

	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	£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]**

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

Superseded
See Erratum

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	**>45,000[2]**	**>26,000[1]**	**>£46,000[3]**	**>£29.000[1]**
Utility of 0.71 whilst patients are in PFS off treatment (p142)	49,000[2]	29,000[1]	51,000[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

Superseded

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 (p142)	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

See Erratum

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+chlorambucil provide 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. Obinutuzumab+chlorambucil is poor value. Rituximab+chlorambucil offers slightly worse value.

For patients unsuited to bendamustine, there is a difference of opinion about whether chlorambucil or rituximab+chlorambucil is 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 44**, p141). We repeat that rituximab+chlorambucil was assessed and not recommended in NICE TA174.[1]

Superseded

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 29**, p118). 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.

See Erratum

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 differed in their approach to estimating overall survival: Roche estimated the rate of mortality

whilst in PD using data from study CLL5, of fludarabine versus chlorambucil. Conversely, Napp extrapolated overall survival from the RCT of bendamustine versus chlorambucil. As we stated in our critique of Napp's analysis, the resulting estimated overall survival is highly uncertain, as the data was immature. Given this, and that overall survival in CLL11 is also immature, we prefer Roche's method of estimating overall survival.

Next, Napp modelled 2nd-line fludarabine containing therapy, whereas Roche do not. Napp estimated lower adverse event costs, although both manufacturers predict minimal incremental costs. Napp estimated substantial costs due to blood transfusions. However, on our advice, these were later reduced to virtually nil. Napp predicted substantially greater resource use in PD, which was due to visits to a haematologist. Most of the cost in PD in Roche's model is also due to visits to a haematologist.

Table 49. Bendamustine versus chlorambucil: comparison between Roche and Napp

	Benda		Clb		Benda - Clb	
	Roche	**Napp**	**Roche**	**Napp**	**Roche**	**Napp**
Median[1] PFS (undisc)	[redacted]	1.7	[redacted]	0.6	[redacted]	1.1
Median[1] life years (undisc)	[redacted]	8.3	[redacted]	5.8	[redacted]	2.5
Mean QALYs PFS (disc)	1.23	1.52	0.77	0.54	0.45	0.98
Mean QALYs PD (disc)	2.07	3.30	2.15	3.01	-0.08	0.29
Total mean QALYs (disc)	3.30	4.82	2.92	3.55	0.38	1.27
Costs (all disc)						
1st-line drug acquisition	£4,700	£4,700	£300	£150	£4,500	£4,600
1st-line drug admin	£4,000	£2,900	£1,300	£1,700	£2,700	£1,200
2nd-line fludarabine combination therapy drug acquisition and admin	£0	£800	£0	£600	£0	£100
1st-line adverse events	£1,400	£400	£1,000	£200	£300	£100
Blood transfusions	£0	£28,000	£0	£22,000	£0	£6,300
Resource use in PD	£4,800	£10,600	£5,000	£8,200	-£200	£2,400
Other	£700	£1,700	£400	£1,300	£200	£300
Total costs	£15,600	£49,000	£8,000	£33,800	£7,500	£15,200
ICER					**£20,000**	**£12,000**

[1] Median because Napp means are commercial in confidence

7. Implications for research

Research in to the following would be welcome:

- 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. Therefore we would welcome a trial of obinutuzumab+chlorambucil vs. chlorambucil with a dose of chlorambucil in line with UK clinical practice.
- Whilst we have obtained data for patients aged ≥65, the existing RCT of bendamustine versus chlorambucil[54] was not restricted to patients unsuited to fludarabine treatment. Therefore, a randomised trial of bendamustine in the patient population relevant to the current HTA, i.e. patients unsuited to fludarabine treatment, would be welcome.
- The cost-effectiveness analysis should be updated when the MaBLe trail results are published in October 2014.
- Survival in progressive disease in the CLL11 RCT is largely unknown due to the immaturity of the data. We recommend that assumptions related to survival in progressive disease should be revisited when more mature OS data from CLL11 is available.
- EQ-5D-based estimates of utilities in this patient population would be welcome.

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Appendices

Appendix 1: Clinical effectiveness search strategy

Table 50 Search strategy for Embase® and MEDLINE® – Year 1992 - 9 April 2014

No	Search terms	Results
#1	'clinical trial'/exp OR 'clinical trial'	1134974
#2	'randomization'/de	61624
#3	'controlled study'/de	4272398
#4	'comparative study'/de	626382
#5	'single blind procedure'/de	17845
#6	'double blind procedure'/de	116316
#7	'crossover procedure'/de	38603
#8	'placebo'/de	251927
#9	'clinical trial'	1134974
#10	'clinical trials'	213803
#11	'controlled clinical trial'	507141
#12	'controlled clinical trials'	12240
#13	'randomised controlled trial'	13728
#14	'randomized controlled trial'	393832
#15	'controlled trials'	66282
#16	'randomized controlled trials'	34458
#17	'randomisation'	5744
#18	'randomization'	75652
#19	random*	1005618
#20	Rct	16006
#21	'random allocation'	1462
#22	'randomly allocated'	20182
#23	'allocated randomly'	1927
#24	allocated NEAR/2 random	863
#25	assign* NEAR/2 random*	84068
#26	randomi*	676422
#27	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)	207920
#28	placebo*	328523
#29	'prospective study'/de	243474
#30	Nrct	53
#31	'n rct'	3
#32	n?rct	21
#33	'controlled clinical trial'/exp	455221
#34	'prospective study'/exp	243474
#35	'intervention study'	24255
#36	(clinical NEXT/1 trial*):ab,ti	280274
#37	'major clinical study'/exp	2194637
#38	compar*:ab,ti	4470496
#39	group*:ab,ti	3323171
#40	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR	10525641

	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	
#41	'case study'/de	35782
#42	'case report'	1953674
#43	'abstract report'/de	89607
#44	'letter'/de	808968
#45	#41 OR #42 OR #43 OR #44	2719673
#46	#40 NOT #45	10252532
#47	'chronic lymphatic leukemia'/de	24816
#48	'b cell leukemia'/exp	5031
#49	lymphom* NEAR/2 lymphocyt*	7817
#50	(leuk?em* OR leu?em* OR lymph*) NEAR/2 (lymphocyt* OR lymphoblast* OR linfoid* OR 'b cell')	1153485
#51	chronic OR cronic OR 'well differential'	1287233
#52	#50 AND #51	119365
#53	#47 OR #48 OR #49 OR #52	131184
#54	'obinutuzumab'/syn OR afutuzumab OR 'ga 101' OR ga101 OR 'r 7159' OR r7159	403
#55	#46 AND #53 AND #54 AND [1992-2014]/py AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [erratum]/lim OR [note]/lim OR [short survey]/lim)	103

Table 51 Search strategy for Medline-in Process (via PubMed) – Year 1992 - 8 April 2014

No	Search terms	Results
#1	Leukemia, Lymphocytic, Chronic, B-Cell	11272
#2	"chronic lymphocytic leukaemia"[All Fields] OR ("leukemia"[All Fields] AND "lymphocytic"[All Fields] AND "chronic"[All Fields] AND "b-cell"[All Fields]) OR "b-cell chronic lymphocytic leukemia"[All Fields] OR ("chronic"[All Fields] AND "lymphocytic"[All Fields] AND "leukemia"[All Fields]) OR "chronic lymphocytic leukemia"[All Fields]	13609
#3	obinutuzumab OR afutuzumab OR â€˜ga 101â€™ OR 'ga101' OR 'r 7159' OR r7159 OR â€˜ro 5072759â€™ OR 'ro5072759'	71
#4	#1 or #2	13609
#5	#4 AND #3	34

Table 52 Search strategy for Cochrane Library – 8 April 2014

No	Search terms	Results
#1	Leukemia, Lymphocytic, Chronic, B-Cell	283
#2	b cell leukaemia' or 'b cell leukemia'	1410
#3	lymphom* near/2 lymphocyt*	90
#4	(leuk?em* or leu?em* or lymph*) near/2 (lymphocyt* or lymphoblast* or linfoid* or 'b cell')	12835

#5	(chronic or cronic or 'well differential')	67392
#6	#4 and #5	2128
#7	#1 or #2 or #3 or #6	3173
#8	(obinutuzumab or afutuzumab or ‘ga 101’ or ga101 or r 7159 or r7159 or ‘ro 5072759’ or ro5072759):ab,ti,kw	19
#9	#7 and #8	2

Appendix 2: Summary of the trials used to conduct the indirect comparison

Table 53 Summary of the trials used to conduct the indirect comparison I; taken from Table B24, p94 Roche's submission

	GCLLSG CLL8	GCLLSG CLL10	Knauf	UK LRF CLL4	COMPLEMENT 1
Primary study reference	Hallek 2010(37)	Eichhorst 2013 (38)	Knauf 2009(51)	Catovsky 2007(48)	Hillmen 2013(52)
Publication type	Journal article	Conference proceeding	Journal article	Journal article	Conference proceeding
Intervention	Rituximab Fludarabine Cyclophosphamide (N=408)	Bendamustine Rituximab (N=280)	Bendamustine (N=162)	Chlorambucil (N=387)	Ofatumumab + Chlorambucil (n=221)
Comparator (all active controlled)	Fludarabine Cyclophosphamide (N=409)	Rituximab Fludarabine Cyclophosphamide (N=284)	Chlorambucil (N=157)	Fludarabine Cyclophosphamide (N=196) Fludarabine (N=194)	Chlorambucil (N=226)
Location	Non-USA sites	Unclear	Non-USA sites	Non-USA sites	USA and non-USA sites
Design	RCT Phase III	RCT Phase III	RCT Phase III	RCT Phase III	RCT Phase III
Method of randomisation	Adequate	Unclear	Unclear	Adequate	Unclear
Method of blinding	Open label	Unclear	Open-label	Unclear	Open-label
Cross-over permitted	No	Unclear	No	No	No
Primary outcome	PFS	PFS	PFS, RR	OS	PFS:
Secondary outcomes	OS, RR,, DOR, Safety, TTR, TTNT, QoL, Withdrawals	CR, EFS, Safety	OS, Safety, DOR, TTNT, Withdrawals	PFS, RR, Safety, QoL, Withdrawals	OS, ORR
Patient population: previous treatment	Previously untreated	Previously untreated	Previously untreated	Previously untreated	Previously untreated and inappropriate for fludarabine-based therapy
Patient population: age	30 years - 81 years Median: 61	33 years – 82 years Median: 62	≤75 years Median: 63.3	35 years – 86 years Median: 65, 65, 64	35 years – 92 years Median: 69, 70
Patient population:	• Binet stage A, B or C	• Binet stage A, B and	• Binet stage B or C	• Binet stage A, B or C	• Binet stage A, B, and

CLL stage		C	• WHO performance status of 0 to 2 and a life expectancy of at least 3 months		C • Median CIRS score 8 – 9 • Creatinine clearance 69 -72 ml per minute
Patient population: comorbidities	• ECOG performance status of 0–1 and a low comorbidity, defined as a CIRS ≤6 and a creatinine clearance of at least 1.17 mL/s	• Median CIRS: 2	Patients were excluded in case of: • hepatic dysfunction • renal dysfunction • significant medical or mental disorders	Unclear	Yes 70% - 73% of patients had 2 or more coexisting conditions
Study duration	Median follow-up: 306.80 weeks	median observation time: 27.9 months	Median observation time: 234 weeks	Median follow-up: 177.67 weeks	Median follow up: 29 months

AEs: Adverse Events; CIRS: Cumulative Illness Rating Scale; CLL: Chronic Lymphocytic Leukaemia; CR: Complete Response; DOR: Duration of Response; EFS: Event-free Survival; IRC: Independent Review Committee; MRD: Minimal Residual Disease; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-free Survival; QoL: Quality of Life; RCT: Randomised Controlled Trial; RR: Response Rate; TTNT: Time to Next Treatment; TTR: Time to Relapse; USA: United States of America

Table 54 Summary of the trials used to conduct the indirect comparison II; taken from Table B24, p94 Roche's submission

	CLL11	**CLL5**	**CALGB 9011**	**CAM307**	**MaBLe**
Primary study reference	Goede 2014(27)	Eichhorst 2009(15)	Rai 2000(49)	Hillmen 2007(50)	Leblond 2012(156)
Publication type	Journal article	Journal article	Journal article	Journal article	Conference proceeding
Intervention	Obinutuzumab+chlorambucil (N=238 [stage 1] and N=333 [stage 2])	Chlorambucil (N=100)	Fludarabine (N=188)	Alemtuzumab (N=149)	Chlorambucil + Rituximab (N=68)
Comparator (all active controlled)	Chlorambucil (N=118) Rituximab+chlorambucil(N=233 [stage 1] and N=330 [stage 2])	Fludarabine (N=93)	Chlorambucil (N=189) Chlorambucil Fludarabine (N=141)	Chlorambucil (N=148)	Bendamustine+rituximab (N=58)
Location	USA and non-USA sites	Germany	Not reported	USA and non-USA sites	Non-USA sites
Design	RCT Phase III	RCT Phase III	RCT Phase III	RCT Phase III	RCT Phase IV
Method of	Adequate	Unclear	Unclear	Unclear	Unclear

randomisation					
Method of blinding	Open-label but assessor-blind (IRC)	Unclear	Unclear	Open-label	Unclear
Cross-over permitted	Yes	No	No	No	No
Primary outcome	PFS (assessed by the investigator)	PFS, OS	PFS	PFS	PFS
Secondary outcomes	PFS (assessed by IRC), RR, MRD, EFS, TTNT, OS, AEs, and patient-reported outcomes	RR, Safety, QoL, Withdrawals	RR, PFS, OS, Safety, DOR, TTR	RR, OS, Safety, Withdrawals	Safety
Patient population: previous treatment	Previously untreated and inappropriate for fludarabine-based therapy	Previously untreated	Unclear	No previous chemotherapy	Both previously untreated & previously treated patients
Patient population: age	30 years - 90 years Median: 73	65 years – 78 years Median: 70, 71	31 years – 88 years Median: 64, 62, 63	35 years – 86 years Median: 59, 60	44 years - 91 years Median: 75, 73
Patient population: CLL stage	• Binet stage A, B, and C	• Binet stage A, B, and C	• Binet stage unclear • Rai Stage 0, I, II, III and IV	• Binet stage unclear • Rai Stage 0, I, II, III and IV	• Binet stage A, B, and C
Patient population: comorbidities	Yes • CIRS score >6 and /or Creatinine clearance of 30 to 69 ml per minute 82% of patients had more than three coexisting conditions, and 27% had at least one coexisting condition that was not well controlled at baseline	Unclear	Unclear	Unclear	Not reported
Study duration	Median follow up: 18.6 – 23.2 depending on study arm	Median follow-up: 182 weeks	Median duration: 398.67 weeks	Median follow-up: 24.6 months	Not reported

AEs: Adverse Events; CIRS: Cumulative Illness Rating Scale; CLL: Chronic Lymphocytic Leukaemia; CR: Complete Response; DOR: Duration of Response; ECOG: Eastern Cooperative Oncology Group; EFS: Event-free Survival; IRC: Independent Review Committee; MRD: Minimal Residual Disease; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-free Survival; QoL: Quality of Life; RCT: Randomised Controlled Trial; RR: Response Rate; TTNT: Time to Next Treatment; TTR: Time to Relapse; USA: United States of America

Table 55 Summary of the trials used to conduct the indirect comparison III; taken from Table B24, p94 Roche's submission

	CLL207FMP	HOVON68	Mulligan 2014	Nikitin 2013	PALG-CLL3
Primary study reference	Lepretre 2012 (78)	Geisler 2011 (140)	Mulligan 2014 (130)	Nikitin 2013 (196)	Robak 2010 (170)
Publication type	Journal article	Conference proceeding	Journal article	Conference proceeding	Journal article
Intervention	Alemtuzumab + Fludarabine + Cyclophosphamide (N=83)	Alemtuzumab + Fludarabine + Cyclophosphamide (N=129)	Cladribine (N=72) Fludarabine (N=74)	FCR-lite (N=45)	Fludarabine + Rituximab + Cyclophosphamide (N=276)
Comparator (all active controlled)	Fludarabine + Rituximab + Cyclophosphamide (N=82)	Fludarabine + Cyclophosphamide (N=133)	High dose Chlorambucil (N=77)	Chlorambucil (N=47)	Fludarabine + Cyclophosphamide (N=276)
Location	Non-USA sites	Non-USA sites	USA and non-USA sites	USA and non-USA sites	Not reported
Design	RCT Phase III	RCT Phase III	RCT Phase III	RCT Phase III	RCT Phase III
Method of randomisation	Unclear	Unclear	Unclear	Unclear	Unclear
Method of blinding	Unclear	Unclear	Open-label	Unclear	Open-label but assessor-blind (IRC)
Cross-over permitted	Yes	No	Unclear	Unclear	No
Primary outcome	PFS (at 36 months)	PFS	OR	ORR	PFS
Secondary outcomes	Global RR, CR, OS, EFS, TTNT, Safety and MRD	CR, MRD, OS, Safety	OS, CR, PRR, PFS, OS, Safety, HRQoL	PFS, Safety	ORR< CR, DR, Safety, QoL
Patient population: previous treatment	Previously untreated	Previously untreated high risk CLL patients (17p deletions, 11q deletions, trisomy 12 or unmutated IGH genes)	Previously untreated	Previously untreated	Previously treated CLL
Patient population: age	51 years - 64 years Median: 57	27 years - 75 years Median: 60	56 years –70 years Median: 63, 63, 64	60 years – 84 years Median: 71	35 years – 83 years Median: 62, 63
Patient population:	• Binet stage B and C	• Binet stage A, B, and	• Binet stage A, B, and	• Binet stage A, B, and	• Binet stage A, B, and

CLL stage		C	C • Rai Stage 0, I, II, III and IV	C • Rai Stage 0, I, II, III and IV	C
Patient population: comorbidities	No	Unclear	Unclear	Median CIRS: 8 (1-18)	No
Study duration	Median follow-up: 38 months	Median follow-up: 30 months	Median follow-up: 83 months	Median observation time: 29.8 months	Median follow-up: 25 months

AEs: Adverse Events; CIRS: Cumulative Illness Rating Scale; CLL: Chronic Lymphocytic Leukaemia; CR: Complete Response; DOR: Duration of Response; ECOG: Eastern Cooperative Oncology Group; EFS: Event-free Survival; IRC: Independent Review Committee; MRD: Minimal Residual Disease; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-free Survival; PRR: Partial Response Rate; QoL: Quality of Life; RCT: Randomised Controlled Trial; RR: Response Rate; TTNT: Time to Next Treatment; TTR: Time to Relapse; USA: United States of America

Table 56 Summary of the trials used to conduct the indirect comparison IV; taken from Table B24, p94 Roche's submission

	GCLLSG CLL4	US E2997
Primary study reference	Eichhorst 2006 (132)	Flinn 2007 (218)
Publication type	Journal article	Journal article
Intervention	Fludarabine + Cyclophosphamide (N=141)	Fludarabine + Cyclophosphamide (N=141)
Comparator (all active controlled)	Fludarabine (N=137)	Fludarabine (N=137)
Location	Austria and Germany	USA sites
Design	RCT Phase III	RCT Phase III
Method of randomisation	Adequate	Unclear
Method of blinding	Open-label	Open-label
Cross-over permitted	No	Unclear
Primary outcome	Response to treatment	CRR
Secondary outcomes	CR, PR, PD, OS, PFS, TFS, Safety	OR, OS, PFS, Safety
Patient population: previous treatment	Previously untreated	Previously untreated
Patient population: age	42 years – 65 years Median: 59, 58	33 years – 86 year Median: 61
Patient population: CLL stage	• Binet stage A, B and C • Rai Stage 0, I, II, III and IV	• Rai Stage 0, I, II, III and IV
Patient population: comorbidities	Unclear	Unclear
Study duration	Median follow-up: 22 months	Median follow-up: 2 years

AEs: Adverse Events; CIRS: Cumulative Illness Rating Scale; CLL: Chronic Lymphocytic Leukaemia; CR: Complete Response; DOR: Duration of Response; ECOG: Eastern Cooperative Oncology Group; EFS: Event-free Survival; IRC: Independent Review Committee; MRD: Minimal Residual Disease; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-free Survival; PRR: Partial Response Rate; QoL: Quality of Life; RCT: Randomised Controlled Trial; RR: Response Rate; TTNT: Time to Next Treatment; TTR: Time to Relapse; USA: United States of America

Appendix 3: Utility vignettes in Roche's study

Progression free survival on initial therapy IV treatment

- You are currently undergoing treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, and a fever. The treatment requires you to attend hospital multiple times for short sessions of treatment given through a needle into your vein. You have been told that you are responding to treatment.

- You have no physical problems walking about although due to feeling nauseous and tired, you are sometimes limited in the distance you want to go.

- You are able to wash and dress yourself.

- Due to vomiting and feelings of nausea and tiredness, you are somewhat limited in your ability to do your usual activities. You are also at greater risk of picking up infections such as coughs and colds more easily.

- You experience a reaction when you start treatment which makes you sweat and gives you chills which lasts for a short time during and following treatment.

- You worry about whether your treatment is working and the effect it may have on you and your family.

Progression free survival on initial therapy oral treatment

- You are currently undergoing treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, and a fever. The treatment requires you to take regular tablets. You have been told that you are responding to treatment.

- You have no physical problems walking about although due to feeling nauseous and tired, you are sometimes limited in the distance you want to go.

- You are able to wash and dress yourself.

- You experience sores in your mouth and due to vomiting and feelings of nausea, you are somewhat limited in your ability to do your usual activities. You are also at greater risk of picking up infections such as coughs and colds more easily.

- You worry about whether your treatment is working and the effect it may have on you and your family.

Progression free survival without therapy

- You have previously received treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, and a fever. You have completed an initial course of treatment and have been told that your illness has been brought under control.

- You have no physical problems walking about although you do feel more tired than before you became unwell.

- You are able to wash and dress yourself.

- You are able to carry out your usual activities, but you worry about the risk of picking up infections such as coughs and colds from other people.

- You do not experience any pain or discomfort.

- You worry about your illness coming back which would require you to undergo further treatment. You are concerned as to how this may impact you and your family.

Progression after first line treatment

- You have previously received treatment for a serious illness which affects your blood and bone marrow. The treatment worked initially, but now your illness has worsened and you have been told that your illness requires further treatment.

- The illness also caused you to experience uncomfortable lumps around your neck, and a fever which initially got better with treatment but are now returning and becoming uncomfortable again.

- You have no physical problems walking about although you do feel tired which can limit the distance you want to go.

- You are able to wash and dress yourself.
- You are able to carry out your usual activities, but you worry about the risk of picking up infections such as coughs and colds from other people.
- You experience occasional discomfort in you abdomen and pain from the lumps on your neck.
- You worry about having further treatment for your illness as last time it made you feel unwell. This concern is great because you are aware that your illness came back after your first course of treatment. You worry about how this may affect you and your family.

Progression free survival on second line therapy

- You are currently undergoing a second course of treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, fever and night sweats. The treatment requires you to attend hospital multiple times for short sessions of treatment given through a needle into your vein. You have been told that you are responding to treatment.
- You have no physical problems walking about although due to feeling nauseous and tired, you are limited in the distance you want to go.
- You are able to wash and dress yourself.
- Due to vomiting and feelings of nausea and tiredness, you are somewhat limited in your ability to do your usual activities. You are also at greater risk of picking up severe infections which may result in you being admitted to hospital.
- You experience occasional discomfort in your abdomen and a reaction when you start treatment which makes you sweat and gives you chills which lasts for a short time during and following treatment.
- You worry about whether your treatment is working and the effect this may have on you and your family. This concern is great because you are aware that your illness came back after your first course of treatment. You worry about how this may affect you and your family.

Progression free survival without second line therapy

- You have previously received a second course of treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, fever and night sweats. You have been told that your illness has been bought under control again.

- You have no physical problems walking about although you do feel more tired than before you became unwell.

- You are able to wash and dress yourself.

- You are able to carry out most of your usual activities, but you worry about the risk of picking up severe infections which may result in you being admitted to hospital.

- You do not experience any pain or discomfort.

- You worry about your illness coming back which would require you to undergo a further course of treatment. This concern is causing you a high level of anxiety because you are aware that your illness came back after the first course of treatment which required you to have a second course of treatment. You worry about your illness getting worse again and the effect this may have on you and your family.

Further progression

- You have undergone a second course of treatment for a serious illness which affects your blood and bone marrow. You have been told that your illness is getting worse again despite previous treatments.

- The illness is causing you to experience uncomfortable lumps around your neck, fever, night sweats and feelings of breathlessness. The previous treatments required you to attend hospital multiple times for short sessions of treatment given through a needle into your vein.

- You have no physical problems walking about although due to tiredness, you are limited in the distance you want to go.

- You are able to wash and dress yourself, although this requires more effort than usual because of your tiredness.

- You are able to carry out your usual activities, but you worry about the risk of picking up another severe infection which may result in you being admitted to hospital.
- You experience occasional discomfort in your abdomen.
- You continually worry about your illness getting worse again and the effect this may have on you and your family. You have concerns about the future and how you will cope.

Progression free survival on initial therapy with increased hospital visits

- You are currently undergoing treatment for a serious illness which affects your blood and bone marrow. The illness also caused you to experience uncomfortable lumps around your neck, and a fever. The treatment requires you to attend hospital multiple times for short sessions of treatment given through a needle into your vein. You have to attend the hospital two days in a row for the first treatment. You are at the hospital for a total of 6 hours on each day. You have been told you are responding to treatment.
- You have no physical problems walking about although due to feeling nauseous and tired, you are limited in the distance you want to go.
- You are able to wash and dress yourself.
- Due to vomiting and feelings of nausea and tiredness, you are somewhat limited in your ability to do your usual activities. You are also at greater risk of picking up infections such as coughs and colds more easily.
- You experience a reaction from the treatment which makes you sweat and gives you chills which lasts for two days following treatment.
- You worry about whether your treatment is working and the effect this may have on you and your family.

Relapsed lines of treatment

- You have undergone multiple courses of treatment for a serious illness which affects your blood and bone marrow. You have been told that your illness is getting worse again despite these previous treatments.

- The illness is causing you to experience uncomfortable lumps around your neck, fever, night sweats and feelings of breathlessness. The treatment required you to attend hospital multiple times for short sessions of treatment given through a needle into your vein. Your disease has returned and you have now been told that there is no further treatment available which could cure it.

- You have some physical problems walking about and mainly due to tiredness and breathlessness, you are limited in the distance you want to go.

- You require minor assistance to wash and dress yourself.

- You are able to carry out your usual activities, but you regularly pick up severe infections which result in you being admitted to hospital.

- You experience occasional discomfort in your abdomen.

- You worry about your illness getting worse and the effect this may have on you and your family, especially as your life span is limited

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